Chronic Obstructive Pulmonary Disease (COPD)

This document is a compilation of 12 reports related to the chronic obstructive pulmonary disease (COPD) evidentiary framework, which are also published individually. Each report retains its original pagination, table of contents, and reference list. The compilation contains the following titles:

1. Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
2. Influenza and Pneumococcal Vaccinations for Patients with Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
3. Smoking Cessation for Patients with Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
4. Community-Based Multidisciplinary Care for Patients with Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
5. Pulmonary Rehabilitation for Patients with Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
6. Long-term Oxygen Therapy for Patients with Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
7. Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients with Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
8. Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients with Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
9. Hospital-at-Home Programs for Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
10. Home Telehealth for Patients with Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
11. Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
12. Experiences of Living and Dying with COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

March 2012

Ontario
Health Quality Ontario
Qualité des services de santé Ontario

Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework

OHTAC COPD Collaborative

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 2, pp. 1–97, March 2012

OHTAC COPD Collaborative

Project Lead
BR McCurdy

Medical Advisory Secretariat (MAS)
BR McCurdy, M Bornstein, J Franek, K Kaulback, S Sehatzadeh, N Sikich, M Thabane, the COPD Working Group, and L Levin

Centre for Health Economics and Policy Analysis (CHEPA) at McMaster University
M Giacomini, D DeJean, D Simeonov, A Smith

Program for Assessment of Technology in Health (PATH) Research Institute
K Chandra, G Blackhouse, K Campbell, R Goeree

Toronto Health Economics and Technology Assessment (THETA) Collaborative
AS Brooker, SM Carcone, W Witteman, M Krahn

Suggested Citation

This report should be cited as follows:
OHTAC COPD Collaborative. Chronic obstructive pulmonary disease (COPD) evidentiary framework. Ont Health Technol Assess Ser [Internet]. 2012 March;12(2):1-97. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Framework_March.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to: MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit:
http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

6MWT	6 Minute Walking Test
AECOPD	Acute exacerbation of COPD
ARI	Acute respiratory illness
BIA	Budget impact analysis
BiPAP	Bilevel positive airway pressure
CAP	Community-acquired pneumonia
CEA	Cost-effectiveness analysis
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval(s)
CRQ	Chronic Respiratory Questionnaire
ED	Emergency department
FEV_1	Forced expiratory volume in 1 second
FHT	Family Health Team
FVC	Forced vital capacity
FY	Fiscal year
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HaH	Hospital-at-home
HRQOL	Health-related quality of life
HTA	Health technology assessment
IC	Intensive counselling
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
LOS	Length of stay
LTOT	Long-term oxygen therapy
MAS	Medical Advisory Secretariat
MCID	Minimal clinically important difference
MDC	Multidisciplinary care
NPPV	Noninvasive positive pressure ventilation
NRT	Nicotine replacement therapy
OHTAC	Ontario Health Technology Advisory Committee
PaO_2	Partial pressure of oxygen
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
RR	Relative risk
SC	Smoking cessation

SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
SR	Systematic review
UMC	Usual medical care
VAP	Ventilator-associated pneumonia
WMD	Weighted mean difference

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective

The objective of this report series is to create an evidentiary base and economic analysis that will guide investment in the treatment of chronic obstructive pulmonary disease (COPD) in a way that optimizes patient outcomes and system efficiencies. This evidentiary platform concerning the effectiveness and cost-effectiveness of treatment strategies for patients with COPD will be used to build a provincial COPD strategy.

Clinical Need and Target Population

COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response by the lungs to noxious particles or gases. (1;2) The airflow limitation is caused by small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), both of which contribute to the disease to varying degrees, depending on the person. Chronic inflammation causes structural changes in the lungs and narrowing of the small airways. Inflammatory processes also cause destruction of the lung parenchyma, which leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil. These changes diminish the ability of the airways to remain open during expiration. (1)

The most common symptoms of COPD include chronic and progressive breathlessness, cough, sputum production, wheezing, and chest congestion. (1;3) In addition to the airflow restriction and changes to the lung, COPD is associated with systemic effects and comorbidities. (1;2) Systemic effects include weight loss, nutritional abnormalities and malnutrition, and skeletal muscle dysfunction. (1) Common comorbidities are ischemic heart disease, osteoporosis, respiratory infection, bone fractures, depression and anxiety, diabetes, sleep disorders, anemia, glaucoma and cataracts, and cancer. (1;2)

Natural History of COPD

COPD is a progressive disease. The rate of progression varies and may occur over several years or several decades, depending on factors such as continued exposure to noxious particles (e.g., tobacco smoke). (1;3) There are several systems for classifying the severity of COPD; one of the most widely used is the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging criteria, which are based on postbronchodilator spirometry (forced expiratory volume in 1 second [FEV_1]). In the GOLD system there are 4 stages, which range from mild to very severe (Table 1). (1)

Table 1: GOLD Staging Criteria for COPD*

Stage	Severity	FEV_1/FVC	FEV_1	Symptoms
I	Mild	< 0.70	$FEV_1 \geq 80\%$ predicted	Symptoms may or may not be present Possible symptoms include chronic cough and sputum production
II	Moderate	< 0.70	$50\% \leq FEV_1 < 80\%$ predicted	Shortness of breath on exertion Cough and sputum production are sometimes present
III	Severe	< 0.70	$30\% \leq FEV_1 < 50\%$ predicted	Greater shortness of breath, reduced exercise capacity, fatigue, and repeated exacerbations
IV	Very severe	< 0.70	$FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure	Respiratory failure, which may also lead to cor pulmonale

*Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.
Source: Global Initiative for Chronic Obstructive Lung Disease, 2010. (1)

The disease course varies, but typically patients fluctuate between stable disease and acute exacerbations, which become more common as the disease progresses. Acute exacerbations are periods when symptoms worsen. There is debate about the best definition for exacerbations; a consensus definition developed by GOLD defines an acute exacerbation as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication." (1) Patients may also experience a variety of other symptoms, such as worsening exercise tolerance, fatigue, malaise, and decreased oxygen saturation. (4) After an acute exacerbation, the individual may not recover to his/her previous level of airflow limitation, and this permanent loss of lung function contributes to the progressive nature of the disease. (3)

Two-thirds of exacerbations are caused by either an infection of the tracheobronchial tree or air pollution, but the cause is unknown in the remaining cases. (1;3) Risk factors for exacerbations include disease severity, winter months, and a previous exacerbation in the past 8 weeks. (4;5) The frequency of exacerbations varies by disease severity. Using data from the ISOLDE Study, the European Respiratory Society Study on COPD, and the Copenhagen City Lung Study, Donaldson et al (4) found that patients with severe disease (GOLD stage III) experienced an average of 3.43 exacerbations per year, while patients with moderate disease (GOLD stage II) experienced an average of 2.68 exacerbations per year.

Epidemiology of COPD

Prevalence

Estimates of COPD prevalence vary depending on the methods and diagnostic criteria used to identify cases. Many of the prevalence estimates are also believed to be underestimates due to underdiagnosis and underrecognition of COPD and to limited diagnoses of mild cases, as individuals often do not require health care services until they reach the moderate to severe stages of the disease. (1;6)

Based on the Canadian Community Health Survey, in 2007 about 4.4% of Canadians self-reported that they had been diagnosed with COPD by physicians. (7) Based on Ontario administrative data sets, Gershon et al (8) estimated the 2007 age- and sex-standardized prevalence of COPD in Ontario to be 9.5%. The prevalence of COPD has increased over time; Gershon et al (8) found a 23% increase in the prevalence rate between 1996 and 2007 (1996, 7.8%; 2007, 9.5%), and this corresponds to an increase of

64.8% in the number of adults with COPD. The aging population alone does not entirely account for this increase. (8)

Gershon et al (8) also found the prevalence of COPD to be higher in men than in women: in 2007, the age- and sex-standardized prevalence was 9.0% in women and 10.3% in men; however, prevalence is increasing faster in women than in men, with a 33.4% increase in the age-standardized prevalence rate in women, compared with a 12.9% increase in men ($P < 0.001$). Prevalence also varies by age group, as shown in Figure 1.

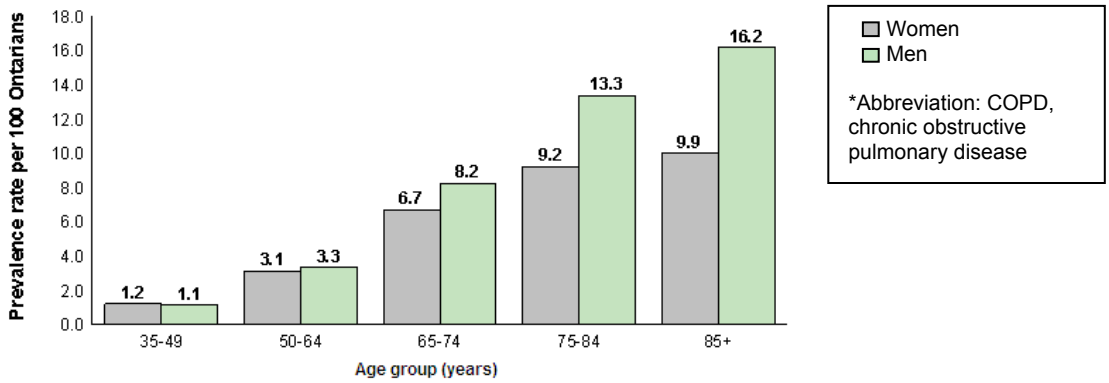


Figure 1: Prevalence of COPD in Ontario in 2006/2007 (Adults Aged 35 Years and Older)*

Source: Institute for Clinical Evaluative Sciences, 2011. (9)

Incidence

Based on Ontario administrative data sets, the 2007 age- and sex-standardized incidence of COPD in Ontario was 8.5 cases per 1,000 adults. (8) Gershon et al (8) showed that the incidence rate has been declining since 1996, when it was 11.8 cases per 1,000 adults. The age-standardized incidence rate is higher in males than in females (9.4 cases per 1,000 adults vs. 7.8 cases per 1,000 adults, respectively); however, the incidence rate has been declining faster in males than females (% decline since 1996, 32.3% vs. 24.7%, respectively). (8)

Risk Factors for COPD

The most common risk factor for COPD—and the primary cause of COPD in 80% to 90% of cases—is exposure to tobacco smoke. (7) There are numerous other risk factors, however, including exposure to occupational dusts and chemicals (including vapours, irritants, and fumes), indoor air pollution (e.g., from burning biomass fuels for heating and cooking in confined spaces in developing countries), outdoor air pollution, genetics, lung growth and development, oxidative stress, respiratory infections and previous tuberculosis, and asthma. The quality and strength of evidence supporting these risk factors vary, with the strongest evidence being for tobacco smoke, occupational exposures, indoor air pollution, and $alpha_1$-antitrypsin deficiencies. (1;10;11)

Diagnosis of COPD

The GOLD guidelines recommend that any individual with breathlessness, chronic cough, or sputum production—especially those with risk factors (such as cigarette smokers)—be evaluated for COPD. (1) Spirometry, the best standardized, objective measurement for airflow limitation, should be used to confirm all COPD diagnoses. (12) Spirometry (or pulmonary function tests) include the forced vital capacity (FVC, volume of air forcibly exhaled from the point of maximal inspiration) and the FEV_1 (volume of air exhaled during the first second of the FVC measurement). (1) During a test, patients

breathe into a mouthpiece attached to a spirometer. The results are compared with standard scores; with reference values based on age, height, sex, and race; and with results presented as a percentage of the predicted value. (1)

Apart from spirometry, other tests may be conducted to help assess severity of disease and provide additional information necessary for treatment. These tests include bronchodilator reversibility testing, chest x-ray, and arterial blood gas measurements. (1;12)

Both over- and underdiagnosis of COPD are possible issues. Overdiagnosis can occur when the diagnosis is based solely upon an individual's medical history and physical examination and is not confirmed by spirometry. (3) Underdiagnosis can occur due to underrecognition of COPD by both clinicians and patients. (1;6)

Management of COPD

COPD management and treatment is a staged process depending on the severity of the disease, with new treatments/management strategies introduced as needed. It begins with avoiding risk factors (e.g., vaccinations, smoking cessation, etc.), and as the disease progresses, introducing additional treatments and medications (e.g., drug therapy, pulmonary rehabilitation, oxygen therapy, etc.). (1;2) More detailed information regarding many of these treatment and management strategies is provided in this report.

Impact of COPD

First and foremost, COPD has a considerable impact on the person with the disease. This impact varies and is influenced not just by the degree of airflow limitation, but also by the severity of symptoms, including breathlessness, decreased exercise capacity, systemic effects, and comorbidities. (1) These symptoms can have a substantial impact on people living with the disease: based on the 1998/1999 National Population Health Survey, 51% of Canadians with COPD reported that their disease restricted their activity at home, at work, or in other activities. (13) In addition, people with moderate to severe COPD typically experience 1 or more acute exacerbations per year. These exacerbations impact health-related quality of life (HRQOL) and lung function; may require hospitalization and invasive treatment such as invasive mechanical ventilation (IMV); and increase the risk of mortality.

COPD is the fourth leading cause of death in Canada and is expected to be the third leading cause of death by 2020. (14;15) The 2007 age- and sex-standardized mortality rate[1] in Ontario was 4.3%, which translates to 32,156 deaths. (8)

Apart from its impact on individual patients, COPD has a substantial effect on the health system. COPD is a leading cause of health care utilization, both globally and in Canada. In 1997, COPD was the fourth most common cause of hospitalization among Canadian men and the sixth most common among Canadian women. (13) The age- and sex-standardized average hospitalization rate from 1996 to 1999 was 632 hospitalizations per 100,000 adults in Ontario. (13) Furthermore, acute exacerbations of COPD are a leading cause of emergency department (ED) visits and hospitalizations, particularly in the winter.

The economic burden of COPD is high. The Canadian component of a large-scale international survey, Confronting COPD in North America and Europe, showed an annual direct cost of almost $2,000 (Cdn) per patient for COPD-related primary and secondary care visits, treatment, and laboratory tests. When combined with indirect costs accounting for lost productivity, the total annual cost was $3,195.52 (Cdn) per patient. (6) Of the direct costs, 60% were accounted for by unscheduled care visits, including primary care provider or specialist visits, hospitalizations, and ED visits. (6) Several studies in the United States

[1] Based on all-cause mortality data from Ontario administrative health data sets. (8)

have shown that per capita spending for COPD-related illness or patients with COPD are 2.5 to 2.7 times higher than for those without COPD. (1)

Project Scope

Technologies Under Review

After an initial review of health technology assessments (HTAs) and systematic reviews about COPD and consultations with experts in Ontario, the following COPD treatment strategies were selected for review: vaccinations, smoking cessation, community-based multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy (LTOT), noninvasive positive pressure ventilation (NPPV), hospital-at-home for the treatment of acute exacerbations of COPD, and home telehealth. In addition, a review of the qualitative literature examined patient, caregiver, and health care provider perspectives on living and dying with COPD.

Influenza and Pneumococcal Vaccinations

Similar to other chronic diseases, people with COPD are at increased risk of contracting both influenza and pneumonia. Both influenza and pneumonia can lead to acute exacerbations of COPD, a major cause of morbidity and mortality in COPD patients. Influenza and pneumococcal vaccinations may decrease the risk of infections and subsequent acute exacerbations in COPD patients.

Smoking Cessation

Tobacco smoke is the main risk factor for COPD and COPD-associated morbidity. Smoking cessation is the process of discontinuing the practice of inhaling a smoked substance. Smoking cessation strategies include both pharmacological and nonpharmacological (behavioural or psychosocial) approaches. The basic components of smoking cessation interventions include simple advice, written self-help materials, individual and group behavioural support, telephone quitlines, nicotine replacement therapy (NRT), and antidepressants. Since addiction to nicotine is a chronic relapsing condition that usually requires several attempts to achieve success, cessation support is usually tailored to individual needs with the recognition that, in general, the more intensive the support the greater the chance of success.

Community-Based Multidisciplinary Care

The term *multidisciplinary* refers to multiple disciplines on a care team, and the term *interdisciplinary* refers to multidisciplinary teams functioning in a coordinated and collaborative manner. There is consensus that a group of multidisciplinary professionals is necessary for optimum specialist management of a chronic illness. However, there is little evidence to guide the decision as to which professionals might be needed to optimize a multidisciplinary team.

Pulmonary Rehabilitation

Pulmonary rehabilitation refers to a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Pulmonary rehabilitation is recommended as the standard of care for treating and rehabilitating patients with COPD who remain symptomatic despite treatment with bronchodilators.

Exercise training is the cornerstone of pulmonary rehabilitation programs and may include both aerobic and strength training. Other components may include psychological support, patient education, nutritional counselling, occupational therapy, medication information, and smoking cessation.

Long-Term Oxygen Therapy

Patients with severe or very severe COPD may also experience hypoxemia (low blood oxygen levels). Severe hypoxemia is defined as partial pressure of oxygen (PaO_2) in arterial blood of less than or equal to

55 mm Hg; moderate hypoxemia is defined as a PaO_2 between 56 mm Hg and 65 mm Hg. (16) Oxygen is a treatment option for COPD patients with hypoxemia because these individuals may have difficulty obtaining sufficient oxygen from the air, and providing oxygen corrects the deficiency of oxygen in arterial blood and prevents tissue hypoxia. LTOT is the extended use of oxygen for 15 hours per day or more. Potential safety concerns include accelerating a fire source such as a lit cigarette, falling over tubing, underusing oxygen, and patients with type 2 respiratory failure using high doses of oxygen, which would further elevate their tissue carbon dioxide levels.

Noninvasive Positive Pressure Ventilation

Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. NPPV can be used to treat both acute hypercapnic respiratory failure secondary to acute exacerbations of COPD and chronic respiratory failure in patients with severe COPD. NPPV provides ventilatory support through a facial or nasal mask and reduces inspiratory work. NPPV can often be used intermittently for short periods of time to treat respiratory failure, which allows patients to continue to eat, drink, talk, and participate in their own treatment decisions. In addition, patients do not require sedation, airway defence mechanisms and swallowing functions are maintained, trauma to the trachea and larynx are avoided, and the risk of ventilator-associated pneumonia (VAP) is reduced. Common complications are damage to facial and nasal skin, higher incidence of gastric distension with aspiration risk, sleeping disorders, and conjunctivitis. In addition, NPPV does not allow direct access to the airway to drain secretions, requires patients to cooperate, and has the potential to cause discomfort; compliance and tolerance may be low.

In addition to treating acute and chronic respiratory failure, NPPV can be used to wean patients from IMV through the gradual removal of ventilation support until the patient can breathe spontaneously. Finally, it has been proposed that NPPV can help prevent extubation failure by preventing the recurrence of acute respiratory failure after extubation and/or to treat respiratory failure when it recurs, thereby avoiding the need for reintubation.

Hospital-at-Home Programs

Hospital-at-home programs are services that provide patients with active treatment by health care professionals in the patient's home for a condition that otherwise would require short-term acute hospital inpatient care. In general, when patients are enrolled in hospital-at-home programs for COPD exacerbations, they receive home visits by specialist nurses who monitor their symptoms, alter their treatment plans if needed, and in some programs, provide additional care such as pulmonary rehabilitation, patient and caregiver education, smoking cessation counselling, and support services. Patients remain the legal and medical responsibility of the hospital while being treated at home. The alternative to hospital-at-home programs for these patients is inpatient hospital care.

Home Telehealth

Given the chronic nature of COPD and the need for continuous patient management, home telehealth technologies are increasingly being used to treat outpatients. This review evaluated 2 types of telehealth used for COPD patients: home telemonitoring and telephone-only support.

Home telemonitoring is defined as the use of medical devices to remotely collect a patient's vital signs and/or other biological health data and transmit these data to a monitoring station for a health care provider to interpret and respond to. Telephone-only support is disease management support given by a health care provider to a patient in his/her residence via telephone or videoconferencing technology, without transmitting patient biological data. There are 4 broad functions of home telehealth interventions for COPD patients:

- to monitor vital signs or biological health data (e.g., oxygen saturation)
- to monitor symptoms, medication, or other nonbiological endpoints (e.g., exercise adherence)

- to provide information, education, and/or other support services (such as reminders to exercise or positive reinforcement)
- to establish a communication link between patient and health care provider

Technologies Not Reviewed

A number of important technologies related to COPD were not included in this review. These include COPD prevention (see previous Medical Advisory Secretariat review on smoking cessation in the general population (17)), screening/early detection, drugs, and surgical interventions. A comprehensive provincial framework on COPD must also take these important topics into consideration.

COPD Prevention

Although the scope of the current project did not include prevention, one of the most important components of COPD prevention is smoking cessation. A 2010 Medical Advisory Secretariat review examined smoking cessation in the general population and provides information on the most effective strategies. The full report is available at:
http://www.hqontario.ca/en/mas/mas_ohtas_tech_smoking_20100120.html (17)

The following points are key findings from this analysis:

- The evidence suggests that pharmacotherapy, physician advice to quit, nursing interventions, hospital-based interventions, and proactive telephone counselling are effective and cost-effective in the short term.
- There is poor quality data around other population-based smoking cessation strategies, including mass media campaigns, community interventions, quit-and-win contests, access to a quitline, and interventions for university and college campuses, making evaluation of their effectiveness and cost-effectiveness difficult.
- Based on pooled summary estimates of effect and safety data, the most effective strategies are taking varenicline or bupropion or using NRTs, followed by physician advice to quit and nursing interventions in nonhospitalized smokers without cardiovascular disease. (17)

Apart from smoking, other risk factors for COPD include indoor (e.g., second-hand smoke) and outdoor air pollutants and occupational exposures to dust, vapours, and fumes. (10;11) COPD prevention initiatives should take these additional risk factors into consideration.

Screening/Early Detection of COPD

Underdiagnosis of COPD

People with known risk factors for COPD, such as smoking, are potential targets for screening and early intervention, and yet COPD is commonly believed to be underdiagnosed. Based on the Canadian Community Health Survey, in 2007 about 4.4% of Canadians self-reported having been diagnosed with COPD. (7) However, studies have shown that this figure is an underestimate of the true prevalence of COPD. For example, the Burden of Lung Disease (BOLD) study conducted spirometry testing (the reference standard for diagnosis of COPD) on patients identified through population sampling from 12 cities, including Vancouver. (18) Overall, the prevalence of COPD stage II or higher was 10.1% ± 4.8% (standard error). In Vancouver, the prevalence of COPD was 9.3% in men and 7.3% in women. (18) Similarly, a longitudinal cohort study using Ontario health administrative data showed an age- and sex-standardized prevalence of COPD in Ontario of 9.5% in 2007. (8)

In a study from Ontario, Hill et al (19) examined patient charts to determine over- and underdiagnosis of COPD. The study examined the charts of patients with a smoking history of at least 20 pack-years and spirometric evidence of COPD, and then matched each patient to 3 patients who did not have spirometric

evidence of COPD. Of 382 patients examined, 230 patients had no COPD based on both spirometric results and no diagnosis of COPD on their charts. Of the 152 patients with COPD, 58 (38%) were correctly diagnosed (diagnosis of COPD on chart matching positive spirometry result), 49 (32%) were undiagnosed (no diagnosis of COPD on chart but positive spirometry result), and 45 (30%) were overdiagnosed (diagnosis of COPD on chart but negative spirometry result). (19) These results suggest that both over- and underdiagnosis of COPD may be an issue.

Benefits of Screening for COPD

Given the evidence of COPD underdiagnosis, screening/early detection to identify individuals with COPD may improve their results and health system outcomes by providing treatment that affects morbidity and mortality rates.

In 2008, the Agency for Healthcare Research and Quality (AHRQ) published a review of the evidence on screening for COPD using spirometry. (20) The AHRQ analysis examined English-language literature published up to January 2007 that addressed 8 questions. The questions and a brief summary of the main findings are shown in Table 2.

Table 2: Summary of Evidence from AHRQ Review on Screening for COPD Using Spirometry*

Question	Studies Identified	Summary Results
Does screening for COPD with spirometry reduce morbidity and mortality?	0 RCTs	No evidence identified
What is the prevalence of COPD in the general population? Do risk factors reliably discriminate between high-risk and average-risk populations?	Population-based surveys	Prevalence 4.5%–21.1% depending on definition of COPD
What are the adverse effects of screening for COPD with spirometry?	3 small studies performed in pulmonary function laboratories	Physically safe; some false-positive test results occurred in asymptomatic people
Do individuals with COPD detected by screening spirometry have improved smoking cessation rates compared with usual smokers?	8 RCTs, 2 SRs; only 2 RCTs evaluated independent motivational effect of spirometry	Spirometry did not increase smoking cessation rates; further studies may be needed
Does pharmacological treatment, oxygen therapy, or pulmonary rehabilitation for COPD reduce morbidity and mortality?	43 RCTs, 10 MAs	Pharmacological treatments reduced exacerbations in those with symptomatic severe COPD and had a small effect on all-cause mortality Oxygen therapy reduced mortality in patients with resting hypoxemia Pulmonary rehabilitation improved some health status measures None of the therapies were tested in patients with airflow obstruction who did not recognize or report symptoms
What are the adverse effects of COPD treatments?	12 SRs	Common minor adverse effects included dry mouth, urinary retention, tachycardia, oropharyngeal candidiasis, easy bruising Major adverse effects were rare
Do influenza and pneumococcal immunizations reduce COPD-associated morbidity and mortality?	2 SRs	Influenza vaccination reduced COPD exacerbations occurring > 4 weeks after vaccination Pneumococcal vaccination had no statistically significant impact on health outcomes
What are the adverse effects of influenza and pneumococcal immunizations in patients with COPD?	2 SRs	Local reactions occurred at the injection site

*Abbreviations: AHRQ, Agency for Healthcare Research and Quality; COPD, chronic obstructive pulmonary disease; MA, meta-analysis; RCT, randomized controlled trial; SR, systematic review.
Source: Lin et al, 2008. (18)

Overall, AHRQ concluded that

> screening for COPD using spirometry is likely to identify a predominance of patients with mild-to-moderate airflow obstruction who would not experience additional health benefits if labeled as having COPD. A few individuals with severe airflow obstruction (FEV_1 < 50% of predicted) might benefit from pharmacologic treatments that reduce exacerbations. Hundreds of patients would need to have screening spirometry to identify 1 person with COPD whose incremental health benefit over clinical diagnosis would likely be limited to avoidance of a first exacerbation. (20)

Based on these findings, in 2008 the United States Preventive Services Task Force recommended against screening adults for COPD using spirometry. (21) The recommendation was classified as a level D recommendation (moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits). (21)

The United States Preventive Services Task Force, however, recognized the need for further research in the following areas:

- The efficacy of various treatments for adults with airflow obstruction who do not recognize or report symptoms, for never smokers, and for smokers younger than 40 years of age.
- The effectiveness of primary care screening to detect patients with a clinical diagnosis of severe or very severe COPD.
- The diagnostic accuracy of spirometry performed in primary care compared with specialty care settings.
- The proportion of patients with previously undiagnosed airflow obstruction who present with a first COPD exacerbation without a clinical diagnosis of COPD. (21)

Since 2008, additional evidence may be available in these areas of uncertainty. Furthermore, based on expert opinion, treatment options and particular medications have improved over the past 5 to 10 years and may lead to greater benefits or additional health benefits.

COPD Medications

A crucial component of COPD treatment is medication. Numerous drugs are involved in the treatment of COPD, including long- and short-acting inhaled bronchodilators (anticholinergics and $beta_2$-agonists), inhaled or oral corticosteroids, methylxanthines, prophylactic antibiotics, mucolytics, and respiratory stimulants. In addition, there are many drug combinations, including combinations of short- and long-acting bronchodilators, combinations of classes of bronchodilators, and combinations of bronchodilators and corticosteroids or bronchodilators and methylxanthines.

The Medical Advisory Secretariat evaluates only nondrug health technologies, so a review of drug therapy for COPD was not included in this project.

Surgical Interventions

Lung volume reduction surgery, bullectomy, and lung transplantation are surgical options that exist for end-stage COPD. These surgical options are invasive and may lead to morbidity and mortality, so only patients with very severe COPD that is not controlled with medical treatment are considered candidates. (22)

Lung volume reduction surgery can be used to treat patients with severe emphysema in which diseased and functionless lung tissue is removed to help improve the functioning of the remaining lung. A 2009 Cochrane Collaboration systematic review by Tiong et al (23) evaluated lung volume reduction surgery

for diffuse emphysema. The conclusions from this systematic review were that 90-day mortality was significantly higher in those who received lung volume reduction surgery compared with usual care, but for those who survived longer than 90 days, improvements in lung function, quality of life, and exercise capacity were more likely than for those who received usual care. A subgroup analysis suggested that patients with very impaired lung function and poor diffusing capacity and/or homogeneous emphysema were at high risk for surgical mortality. (23)

Bullectomy can be used to treat COPD patients with a substantial air-filled bulla. The giant bulla is removed to help improve the functioning of the surrounding lung tissue that is being compressed by the bulla. (22;24) The published evidence for bullectomy is based on case series with incomplete follow-up and using a variety of surgical methods. Snider's review of 22 retrospective case series found that bullectomy is most effective in patients with bullae that are larger than one-third of a hemithorax and compress the adjacent lung tissue, and where FEV_1 is less than 50% predicted. Postoperative mortality ranged from 0% to 22.6%. (24;25)

Finally, single- or double-lung transplantation is an option. COPD is one of the most common indications for lung transplantation worldwide. (24;26) Long-term survival data from the Registry of the International Society for Heart & Lung Transplantation found 80% survival at 1 year, 50% at 5 years, and 35% at 10 years. (27)

Methods

This section describes the methods used to scope the mega-analysis; to conduct the systematic reviews of the clinical literature, the economic analysis, and the systematic review of the qualitative literature; and to contextualize the evidence.

A. Mega-Analysis

Project Scope

An initial scoping phase was undertaken to identify any technologies relevant to COPD that impact patient and/or health system outcomes. The scoping process involved identifying and reviewing health technology assessments and systematic reviews of COPD treatment through keyword searches on PubMed and several health technology assessment and systematic review websites (the Wiley Cochrane Library, the Centre for Reviews and Dissemination/International Agency for Health Technology Assessment, and the National Institute for Health and Clinical Excellence). In addition, preliminary searches were conducted in OVID MEDLINE and OVID EMBASE (see Appendix 1 for the search strategies). A number of topics related to COPD were identified during the literature search:

- drug therapy for stable COPD and acute exacerbations
- hospital-at-home programs for acute exacerbations (early discharge and admission avoidance programs)
- invasive ventilation
- long-term oxygen therapy
- mucous clearing techniques (including mucolytics, chest physiotherapy, and intrapulmonary percussive ventilation)
- multidisciplinary care
- noninvasive ventilation for acute and chronic respiratory failure
- nutritional supplementation
- palliative care
- pulmonary rehabilitation (for stable COPD and following acute exacerbations)
- pulmonary rehabilitation maintenance programs
- smoking cessation
- surgery (lung volume reduction surgery, bullectomy, and lung transplantation)
- telemedicine
- vaccinations

Ontario experts in COPD and the members of the Ontario Health Technology Advisory Committee (OHTAC) provided input into the project scope and which topics to include in the analysis.

Disaggregation of Technologies

After the scope of the project was determined, each topic was systematically reviewed in the published literature. Common patient/clinical and health system outcomes of interest were determined a priori so that, where possible, common outcomes were available to compare across technologies. The following outcomes were examined:

- complications

- dyspnea
- emergency department visits
- exercise capacity
- health-related quality of life
- hospital admissions or readmissions
- hospital length of stay
- lung function
- mortality
- physician or clinic visits

To accompany the systematic review of the literature, a decision-analytic economic model was developed (methods detailed below). Systematic reviews that yielded high, moderate, or low quality evidence on lung function (measured using FEV_1), mortality, and/or hospital admissions were used to populate the economic model. Technologies with outcomes unsuited to the decision-analytic economic model or that had very low quality evidence were not included in the economic model.

Reaggregation

Evidence of effectiveness was combined with evidence of cost-effectiveness, economic feasibility, and information on societal and ethical values obtained from the qualitative literature (methods detailed below) for each of the technologies.

B. Systematic Reviews of Clinical Effectiveness and Safety

For each of the systematic reviews, a literature search was performed using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, the Wiley Cochrane Library, EBSCO Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Centre for Reviews and Dissemination database to identify potential studies. The publication search dates varied by review but typically ranged over 5 to 10 years of literature (specific details are available in the individual reports). Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the systematic search.

The inclusion and exclusion criteria listed below were used for all analyses. Some analyses utilized additional criteria specific to the topic of interest, which are detailed in the individual reports.

Research Methods

Inclusion Criteria

- English-language full-text reports
- HTAs, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and observational studies[2]
- studies performed exclusively using patients with a diagnosis of COPD or studies performed using patients with a mix of conditions if results were reported for COPD patients separately
- patients with stable COPD and/or acute exacerbations of COPD as appropriate for the technology

Exclusion Criteria

- < 18 years of age
- animal studies
- duplicate publications
- grey literature

Statistical Methods

When possible, results were pooled using Review Manager Version 5.1. (28) Continuous data were pooled to calculate relative risks (RR) using the Mantel–Haenszel test and a random effects model. Dichotomous data were pooled to calculate weighted mean differences using the inverse variance method and a random effects model. When data could not be pooled, the results were summarized descriptively. Analyses using data from RCTs were conducted using intention-to-treat protocols. *P* values less than 0.05 were considered statistically significant. When possible, clinical significance was defined when the point estimate was greater than or equal to the minimal clinically important difference (MCID). A priori subgroup analyses were planned for many of the analyses based on appropriate differences for each technology. A full description of the method used for each review is available in each individual report.

Quality of Evidence

The quality of each included study was assessed taking into consideration the following study design characteristics:

- adequate allocation concealment
- randomization (study must include a description of the randomization procedure used and must be a proper method)
- power/sample size (adequate sample size based on a priori calculations and underpowered studies were identified, when possible, using post hoc sample size power calculations)
- blinding (if double blinding is not possible, a single blind study with unbiased assessment of outcomes was considered adequate for this criterion)
- < 20% withdrawals/dropouts
- intention-to-treat analysis conducted and done properly (withdrawals/dropouts considered in analysis)
- other criteria as appropriate for the particular research question and study design

[2] Observational studies were included only in those reviews where the RCT evidence did not include results for important outcomes: that is, the LTOT and home telehealth reviews.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (29) as presented below:

- Quality refers to criteria such as the adequacy of allocation concealment, blinding, and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group (29), the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

C. Economic Evaluation

The aim of this evaluation was to assess the cost-effectiveness and impact on the health system of the reviewed COPD treatment strategies.

Cost-Effectiveness Analysis

A cost-utility analysis was conducted using a Markov model. Starting cohorts reflected the various patient populations from the trials of the strategies analyzed. Using clinical parameters and summary estimates of relative risks of (re)hospitalization, mortality, and abstinence from the Medical Advisory Secretariat systematic reviews, incremental cost-effectiveness ratios (ICERs)—that is, costs per quality-adjusted life-year (QALY)—were estimated for each strategy.

Only those technologies for which the systematic reviews yielded hospitalization or mortality data could be included in the model. Furthermore, only those technologies that had high, moderate, or low quality evidence (based on the GRADE criteria) were included. Technologies with very low quality evidence and low quality evidence with nonsignificant results were not included in the model; the estimates of effect were too uncertain to provide useful results. Finally, technologies that were not effective based on the clinical evidence were also not included in the economic model. Given these criteria, the following treatment strategies were included in the model:

- smoking cessation programs (intensive counselling, NRT, intensive counselling plus NRT, and the antidepressant bupropion) in moderate COPD in an outpatient setting
- multidisciplinary care teams in moderate to severe COPD in an outpatient setting
- pulmonary rehabilitation following acute exacerbations in moderate to severe COPD (within 1 month of discharge)
- LTOT in severe hypoxemia in COPD in an outpatient setting
- ventilation (NPPV in acute respiratory failure due to an acute exacerbation in severe COPD in an inpatient setting and NPPV for weaning COPD patients from IMV in an inpatient setting)

Perspective

The cost-effectiveness analysis (CEA) was taken from the perspective of a publicly funded health care system. Costs from this perspective include drugs covered by the provincial formularies, inpatient costs described by Ontario case costing, and physician fees for services covered by provincial fee schedules. Indirect costs, such as productivity losses, were not considered in the analysis; these were assumed to be minimal considering that the patient population in question is mostly over 65 years of age as reflected in the mean ages from the trials investigated. Costs to family members were beyond the scope of this analysis.

Modelling

Because COPD is a progressive disease, a Markov model was used. The structure of the model, including the transitions between health states, is presented in Figure 2. The circles in the diagram represent different health states. The arrows show the possible patient transitions in a given model cycle. The circular arrows represent cycling within a health state until transition to the next state.

The model comprises different health states based upon the GOLD COPD severity classification. Patients are assigned different costs and utilities depending on the severity of their health during each model cycle. In addition to moving between health states, patients are at risk of acute exacerbations of COPD in each model cycle. During each cycle, patients can have no acute exacerbation, a minor acute exacerbation, or a major exacerbation. For the purpose of the model, a major COPD exacerbation is defined as one requiring hospitalization. Patients are assigned different costs and utilities in each model cycle depending on whether they experience an exacerbation and on the severity of the exacerbation.

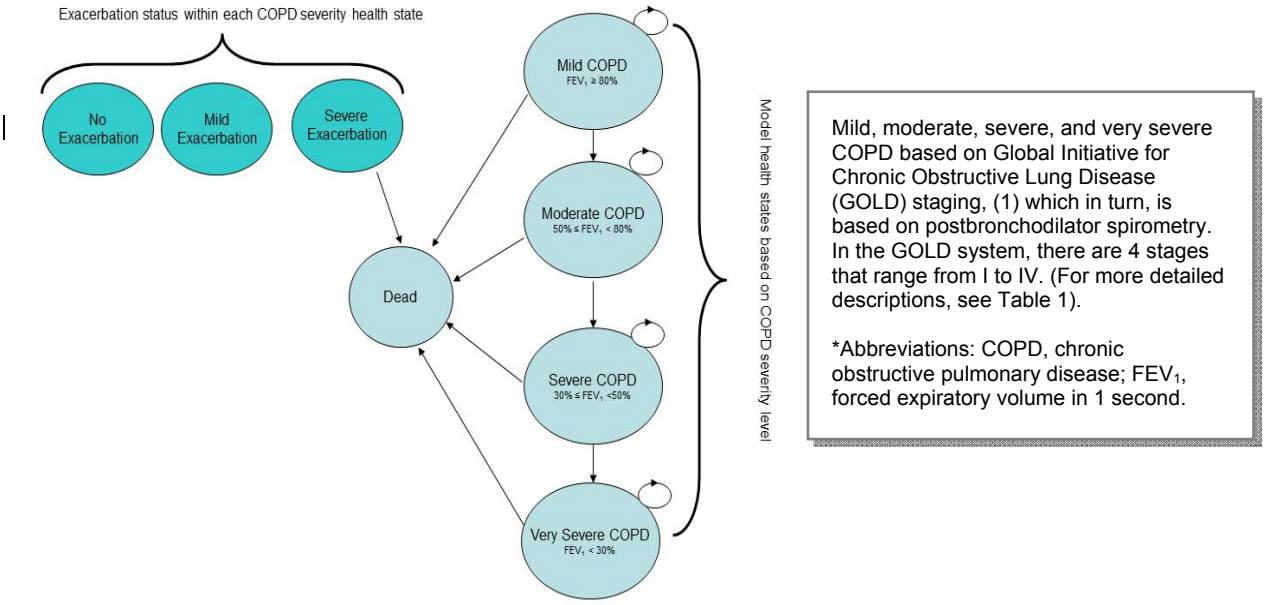


Figure 2: COPD Model Structure*

Discounting and Time Horizon

An annual discount rate of 5% was applied to costs and QALYs. The time horizon of the model was set to lifetime.

Variability and Uncertainty

Variability and uncertainty in the Markov model were assessed using 1-way and probabilistic sensitivity analyses. Program costs of multidisciplinary care and pulmonary rehabilitation following acute exacerbations were varied in 1-way analyses. Model parameter uncertainty was assessed using probabilistic sensitivity analysis by assigning distributions around the point estimate, and results were presented in the form of probability of cost-effectiveness by ceiling ratio: that is, willingness-to-pay values.

Generalizability

The findings of this economic analysis cannot be generalized to all patients with COPD. The findings may, however, be used to guide decision-making about the specific patient populations addressed in the trials.

Budget Impact Analysis

A budget impact analysis (BIA) was also conducted to project potential incremental costs or potential resources already being incurred in Ontario through the various programs offered in the province. Several assumptions were made to calculate potentially impacted populations for the various strategies investigated. Using provincial data and expert opinion, health system impacts were calculated for each strategy.

Further details of the economic analysis can be found in an associated economic report in this series titled *Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model*.

D. Review of Qualitative Literature

Review of Perspectives on Living and Dying with COPD

Literature searches for studies published between January 1, 2000, and November 2010 were performed on November 29, 2010, using OVID MEDLINE; on November 26, 2010, using ISI Web of Science; and on November 28, 2010, using EBSCO Cumulative Index to Nursing and Allied Health Literature (CINAHL). Titles and abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. One additional report, highly relevant to the synthesis, appeared in early 2011 during the drafting of this analysis and was included post hoc.

Inclusion Criteria

English-language full-text reports

- published from January 1, 2000, through November 2010
- primary qualitative empirical research (using any descriptive or interpretive qualitative methodology, including the qualitative component of mixed-methods studies) and secondary syntheses of primary qualitative empirical research
- studies addressing any aspect of the experience of living or dying with COPD, from the perspective of persons at risk, patients, health care providers, or informal carers; studies addressing multiple conditions were included if COPD was addressed explicitly

Exclusion Criteria

- studies addressing topics other than the experience of living or dying with COPD, from the perspective of persons at risk, patients, health care providers, or informal carers

- studies labelled "qualitative" but not using a qualitative descriptive or interpretive methodology (e.g., case studies, experiments, or observational analysis using qualitative categorical variables)
- quantitative research (i.e., using statistical hypothesis testing, using primarily quantitative data or analyses, or expressing results in quantitative or statistical terms)
- studies that did not pose an empirical research objective or question, or involve the primary or secondary analysis of empirical data

Outcomes of Interest

- qualitative descriptions and interpretations (narrative or theoretical) of personal and social experiences of COPD

Further details of the qualitative analysis can be found in an associated report in this series titled *Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature*.

E. Contextualization of the Evidence

A COPD Expert Advisory Panel was convened by the Ontario Health Technology Advisory Committee (OHTAC) to assist with contextualizing the results of the systematic reviews and economic analyses. The roles of the panel were as follows:

- to provide direction to the Medical Advisory Secretariat on the scope of the project, including relevant background knowledge, grey literature, and relevant subgroup analyses for the evidence review of COPD interventions;
- to provide direction on the relevant outcome measures of effectiveness for COPD interventions to help guide the parameters of the systematic review;
- to review the systematic evidence-based analyses of the effectiveness of COPD interventions, comment on the accuracy of the interpretation of evidence, and identify any omissions of evidence in the analyses; and
- to identify any health system, societal, ethical, or economic issues that were relevant to evaluating the effectiveness of these interventions.

Results of the Evidence-Based Analyses

This section provides a summary of the findings for each of the individual evidence-based reviews. Further details can be found in the individual reports in this COPD series.

1. Influenza and Pneumococcal Vaccinations

Background

Influenza Vaccine

Rates of serious illness due to influenza viruses are high among older people and patients with chronic conditions such as COPD. Complications of influenza infection include viral pneumonia, secondary bacterial pneumonia, and other secondary bacterial infections, such as bronchitis, sinusitis, and otitis media. In viral pneumonia, patients develop acute fever and dyspnea, and may also show signs and symptoms of hypoxia. The incidence of secondary bacterial pneumonia is most common in the elderly and those with underlying conditions such as congestive heart disease and chronic bronchitis.

Healthy people usually recover quickly from influenza. However, influenza is associated with higher risks in the very young or very old and in those with underlying medical conditions such as COPD, heart disease, diabetes, and cancer. It may lead to hospitalization and, in some cases, death. In addition, an influenza infection can exacerbate COPD symptoms or an underlying heart disease.

Every year, the World Health Organization convenes technical meetings in February and September to recommend the selection of virus strains for the seasonal flu vaccine based on the type of influenza viruses that were circulating the previous year.

Pneumococcal Vaccine

The rate of pneumococcal pneumonia in developed countries is still not known due to the lack of accurate diagnostic tests. In the United States Veterans' Administration Trial, the incidence of pneumococcal pneumonia per 1,000 person years in people aged 55 years and older was 1.7 in those with no underlying disease, 3.4 in those with 1 underlying disease, and 15 in those with 3 underlying diseases.

People with impaired immune systems are susceptible to pneumococcal infection. Young children, elderly people, and patients with underlying medical conditions—including COPD or heart disease, HIV infection, sickle cell disease, and splenectomy—are at higher risk for acquiring pneumococcal pneumonia.

Recommendations for pneumococcal vaccination target most people who are at high risk for invasive pneumococcal disease. However, the use of pneumococcal vaccines in the elderly or high-risk populations is still controversial and has been the subject of many meta-analyses and systematic reviews.

The Centers for Disease Control and Prevention recommends using the 23-valent pneumococcal polysaccharide vaccine in all adults aged 65 years and older and in those adults aged 19 to 64 years of age with underlying medical conditions that put them at greater risk for serious pneumococcal infection and medical conditions, including chronic lung diseases such as COPD, emphysema, and asthma.

Research Questions

- What is the effectiveness of the influenza vaccination and the pneumococcal vaccination compared with no vaccination in COPD patients?

- What is the safety of these 2 vaccines in COPD patients?
- What is the budget impact and cost-effectiveness of these 2 vaccines in COPD patients?

Included Studies

As shown in Figure 3, of the 1,286 citations identified, 2 RCTs met the inclusion/exclusion criteria: 1 for influenza vaccination and 1 for pneumococcal vaccination.

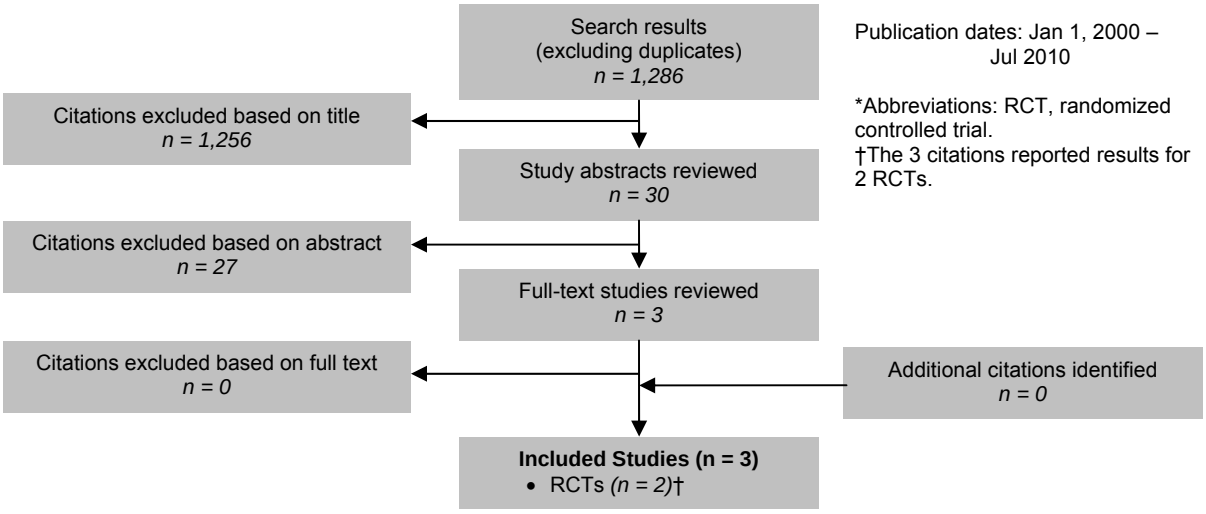


Figure 3: Influenza and Pneumococcal Vaccinations for COPD Citation Flow Chart*

The 2 RCTs[3] included a total of 721 participants. The sample size ranged from 125 to 596 people, and the mean age of the patients was between 61 and 76 years. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, both studies included people with severe COPD.

The setting for both studies was a single university hospital. In 1 study the control arm received a placebo injection, and in the other study the control arm received no vaccine or a placebo injection.

The individual quality of both studies was high.

Results

Influenza Vaccination

Influenza-Related Acute Respiratory Illness

Influenza vaccination was associated with significantly fewer episodes of influenza-related acute respiratory illness (ARI) (RR, 0.24; 95% confidence interval [CI], 0.09–0.67; $P = 0.007$).
GRADE: high

When subgrouped by severity of COPD, the incidence density of influenza-related ARIs was significantly reduced in the severe COPD group (RR, 0.1; 95% CI, 0.003–1.1; $P = 0.04$), but the difference was not significant in the mild and moderate subgroups.

The Kaplan–Meier survival analysis showed a significant difference between the vaccinated and placebo groups in the probability of not acquiring an influenza-related ARI ($P = 0.003$).

[3] Two of the RCTs reported results from the same study; these papers were treated as 1 publication.

Vaccine Effectiveness
Overall, the vaccine was 76% effective. For the categories of mild, moderate, and severe COPD, effectiveness was 84%, 45%, and 85%, respectively.
GRADE: high

Hospitalizations
A subgroup analysis examined the number of patients with influenza-related ARIs that required hospitalization versus those who were treated in the outpatient setting. This subgroup analysis showed a nonsignificant reduction in hospitalizations due to influenza-related ARIs in the vaccinated group compared with the placebo group (RR, 0.41; 95% CI, 0.08–2.02; $P = 0.27$).
GRADE: low

Mechanical Ventilation
A subgroup analysis examined the number of patients with influenza-related ARIs that required treatment with mechanical ventilation during hospitalization. This subgroup analysis showed a nonsignificant reduction in the need for mechanical ventilation in the vaccinated group compared with the placebo group (RR, 0.15; 95% CI, 0.01–2.75; $P = 0.2$).
GRADE: low

Safety/Complications
The most common adverse reactions in the vaccine group were swelling, itching, and pain on contact at the vaccine site, but these symptoms did not require specific treatment and usually lasted less than 48 hours. The incidence of local adverse reactions (27% vs. 6%; $P = 0.002$), and the incidence of swelling and itching specifically ($P = 0.04$), were significantly higher in the vaccinated group compared with the placebo group.

Observed systemic reactions were headache, myalgia, fever, and skin rash. There was no significant difference in systemic reactions between the vaccinated group and the placebo group (76% vs. 81%; $P = 0.5$).
GRADE: low

Economic Model
The influenza vaccination analysis could not be included in the economic model, because the appropriate inputs were not reported in the published literature.

Experiences Concerning Influenza Vaccination (Qualitative Review)
The literature search identified 24,906 citations, of which 218 full-text studies were reviewed. However, none of these studies related to influenza vaccinations.

Pneumococcal Vaccination
Incidence/Episodes of Pneumonia
The Kaplan–Meier survival analysis showed no significant differences in time to first episode of community-acquired pneumonia (CAP) of pneumococcal or unknown etiology between the vaccinated group and the placebo group (log-rank test = 1.15; $P = 0.28$).
GRADE: high

There were no significant differences in the incidence of global pneumonia (12.7% vs. 12.4%), episodes of global pneumonia (14.4% vs. 15%), or first episodes of CAP (11.1% vs. 11.8%) between the vaccinated group and the placebo group. There was, however, a significant difference in the incidence of pneumococcal pneumonia (0% vs. 1.68%; log-rank test 5.03; $P = 0.03$).
GRADE: high

Subgroup analyses of age and severity of COPD (based on FEV_1) were performed. Significant reductions in episodes of CAP (pneumococcal and unknown etiology combined) were observed for those less than 65 years of age (RR, 0.24; 95% CI, 0.07–0.80; $P = 0.02$); those with severe COPD ($FEV_1 < 40\%$) (RR, 0.52; 95% CI, 0.27–1.01; $P = 0.05$); and those who fit into both subgroups (i.e., less than 65 years of age and severe COPD) (RR, 0.09; 95% CI, 0.01–0.65; $P = 0.02$). No significant differences were observed for those who were older than 65 years of age (RR, 1.14; 95% CI, 0.62–2.07; $P = 0.67$) and those with mild-moderate COPD ($FEV_1 \geq 40\%$) (RR, 1.11; 95% CI, 0.53–2.32; $P = 0.78$).

Hospitalizations
There was no significant difference in the number of episodes of CAP that required hospitalization between the vaccinated group and the placebo group (76% vs. 81%; $P = 0.59$).
GRADE: low

Length of Stay
There was no significant difference in the median length of stay (LOS) between the vaccinated group and the placebo group (9.5 days vs. 12 days; $P = 0.16$).
GRADE: low

Safety
There was no significant difference in the mortality rate between the vaccinated group and the placebo group (about 19% in both groups).
GRADE: low

No patients in either group reported local or systemic reactions to the vaccine.
GRADE: low

Economic Model
The pneumococcal vaccination analysis could not be included in the economic model, because the appropriate inputs were not reported in the published literature.

Experiences Concerning Pneumococcal Vaccination (Qualitative Review)
The qualitative literature search identified 24,906 citations, of which 218 full-text studies were reviewed. However, none of these studies related to pneumococcal vaccinations.

Conclusions

Influenza Vaccine

- High quality evidence showed a significant reduction in episodes of influenza-related ARIs in the vaccinated group compared with the placebo group.
- Low quality evidence showed nonsignificant reductions in influenza-related ARI hospitalizations and the need for mechanical ventilation in the vaccinated group compared with the placebo group.
- Low quality evidence showed a significant increase in local adverse reactions, swelling, and itching in the vaccinated group compared with the placebo group; there was no significant difference, however, in the incidence of systemic reactions between the 2 groups.

Pneumococcal Vaccine

- High quality evidence showed a significant decrease in the incidence of pneumococcal pneumonia in the vaccinated group compared with the placebo group; there were no significant

differences, however, in the incidence of global pneumonia, episodes of global pneumonia, first episodes of CAP, or time to first episode of CAP between the groups.

- Low quality evidence showed no significant differences in hospitalizations due to CAP or hospital LOS between the vaccinated group and the placebo group.
- Low quality evidence showed no local or systemic reactions as a result of the vaccine, and the vaccine had no impact on mortality rates.

2. Smoking Cessation

Background

Smoking cessation is the process of discontinuing the practice of inhaling a smoked substance. Smoking cessation programs primarily target tobacco smoking, but may also encompass other substances that can be difficult to stop due to the strong physical addictions or psychological dependencies resulting from their habitual use. Smoking cessation strategies include both pharmacological and nonpharmacological (behavioural or psychosocial) approaches. The basic components of smoking cessation interventions include simple advice, written self-help materials, individual and group behavioural support, telephone quitlines, NRT, and antidepressants. Since addiction to nicotine is a chronic relapsing condition that usually requires several attempts before achieving success, cessation support is usually tailored to individual needs. Nevertheless, it is recognized that, in general, the more intensive the support, the greater the chance of success. In addition, success at quitting smoking decreases with a lack of motivation to quit; the number of pack-years of smoking greater than 10; a lack of social support (e.g., from family and friends); and the presence of psychiatric disorders (such as depression). Smoking cessation can help to slow or halt the progression of COPD.

Research Question

What is the effectiveness and cost-effectiveness of smoking cessation interventions compared with usual care for patients with COPD?

Included Studies

As shown in Figure 4, of the 1,619 citations identified, 13 studies met the inclusion/exclusion criteria: 1 health technology assessment (HTA), 3 systematic reviews, and 9 RCTs.

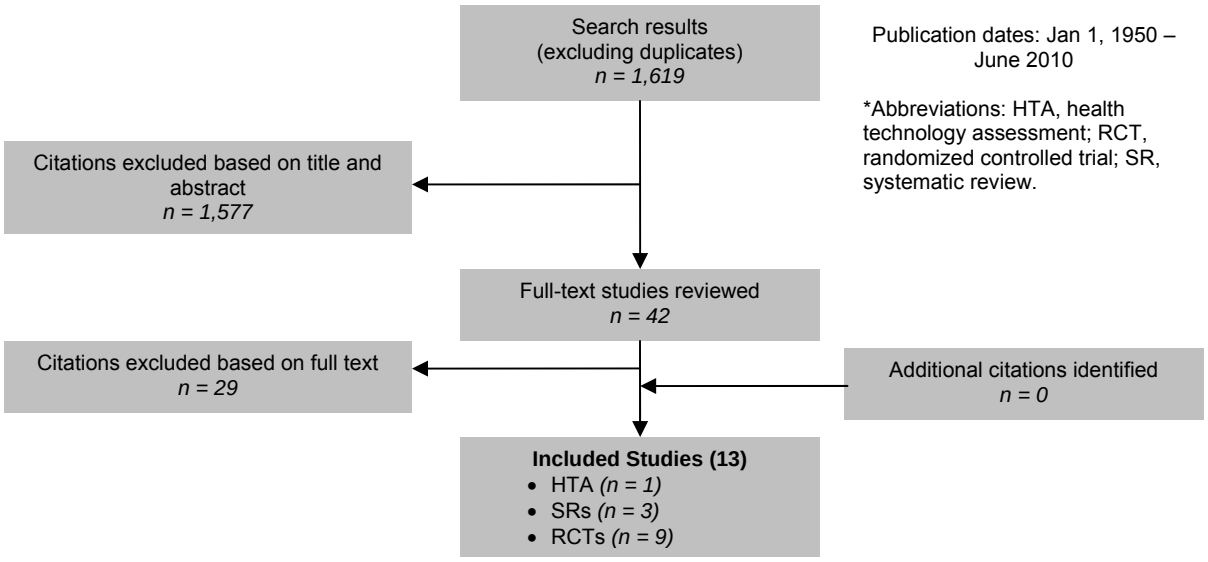


Figure 4: Smoking Cessation for COPD Citation Flow Chart*

The 9 RCTs included a total of 8,291 participants. The sample size ranged from 74 to 5,887 people, and the mean age of the patients was about 55 years. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, 2 studies included people with mild COPD, 3 with mild-to-moderate COPD, 1 with moderate to severe COPD, and 1 with severe to very severe COPD. One study included people at risk of COPD as well as those with mild, moderate, or severe COPD, and the final study did not provide information on the severity of COPD.

Two studies took place in a hospital setting, and the remaining studies in an outpatient setting. Smoking cessation interventions varied across studies and included counselling, pharmacotherapy, or a combination of counselling and pharmacotherapy. The control group received either placebo (for the drug-only trials) or usual care, which was defined as no counselling, pharmacotherapy, or any other type of smoking intervention offered as part of the trial. Since the smoking cessation interventions were very heterogeneous, studies were grouped into categories of similar interventions and pooled if appropriate.

The individual quality of studies was high.

Results

Counselling Versus Usual Care

Two studies that compared counselling and usual care reported abstinence rates. The pooled results showed a statistically significant increase in abstinence in the counselling group compared with the usual care group (RR, 5.85; 95% CI, 3.81–8.97; $P = 0.002$).
GRADE: moderate

When subgrouped by intensity of counselling, there was a statistically significant increase in abstinence in the intensive counselling (≥ 90 minutes) group compared with the usual care group (RR, 7.70; 95% CI, 4.64–12.79; $P < 0.001$); however, the increase was nonsignificant between the minimal counselling (< 90 minutes) group and the usual care group (RR, 1.56; 95% CI, 0.65–3.72; $P = 0.32$). Note that the minimal counselling study was performed in an inpatient setting.

Counselling Plus NRT Versus Usual Care

Three studies that compared counselling plus NRT and usual care reported abstinence rates. The pooled results showed a statistically significant increase in abstinence in the counselling plus NRT group compared with the usual care group (RR, 4.28; 95% CI, 3.51–5.20; $P < 0.001$).
GRADE: moderate

When subgrouped by intensity of counselling, there was a statistically significant increase in abstinence rates in the intensive counselling (≥ 90 minutes) plus NRT group compared with the usual care group (RR, 4.41; 95% CI, 3.60–5.39; $P < 0.001$); however, the increase was nonsignificant between the minimal counselling (< 90 minutes) plus NRT group and the usual care group (RR, 2.11; 95% CI, 0.90–4.91; $P = 0.08$).

Minimal Counselling Plus Antidepressant Versus Usual Care

One study that compared minimal counselling (< 90 minutes) plus antidepressant and usual care reported abstinence rates. The results showed a nonsignificant increase in abstinence rates in the minimal counselling plus antidepressant group compared with the usual care group (RR, 1.91; 95% CI, 0.65–5.61; $P = 0.24$).
GRADE: low

Minimal Counselling Plus NRT Plus Antidepressant Versus Usual Care

One study that compared minimal counselling (< 90 minutes) plus NRT plus antidepressant and usual care reported abstinence rates. The results showed a nonsignificant increase in abstinence rates in the minimal counselling plus NRT plus antidepressant group compared with the usual care group (RR, 2.25; 95% CI, 0.87–5.85; $P = 0.10$).
GRADE: low

NRT Versus Placebo

One study that compared NRT and placebo reported abstinence rates. The results showed a statistically significant increase in abstinence in the NRT group compared with the placebo group (RR, 3.01; 95% CI, 1.02–8.89; $P = 0.05$).
GRADE: moderate

Antidepressant Versus Placebo

Two studies that compared antidepressant and placebo reported abstinence rates. The pooled results showed a statistically significant increase in abstinence in the antidepressant group compared with the placebo group (RR, 2.09; 95% CI, 1.35–3.24; $P < 0.001$).
GRADE: moderate

When subgrouped by type of antidepressant, there was a statistically significant increase in abstinence rates in the bupropion group compared with the placebo group (RR, 2.01; 95% CI, 1.24–3.24; $P = 0.004$); however, the increase was nonsignificant between the nortriptyline group and the placebo group (RR, 2.54; 95% CI, 0.87–7.44; $P = 0.09$).

Economic Model

Comparators and Effect Estimates

The following summary estimates from the systematic review comparing smoking cessation programs versus either usual care or placebo were used in the model to predict long-term outcomes:

- Cessation rates
  - intensive counselling (IC) versus usual care: RR, 7.70 (95% CI, 4.64–12.79; $P < 0.001$)
  - NRT versus placebo: RR, 3.01 (95% CI, 1.02–8.89; $P = 0.05$)
  - IC plus NRT versus usual care: RR, 4.41 (95% CI, 3.60–5.39; $P < 0.001$)
  - bupropion versus placebo: RR, 2.01 (95% CI, 1.24–3.24; $P = 0.004$)

Mortality and lung function benefits were obtained from the Lung Health Study (30), in which data were analyzed comparing sustained quitters and continuing smokers.

- Mortality:
  - quitters: RR, 0.54
  - nonquitters: RR, 1.0
- Lung function (change in FEV_1):
  - year 1: quitters, 4.87 mL; nonquitters, −6.81 mL
  - year 2 and beyond: quitters, −2.86 mL; nonquitters, −6.19 mL

Resource Use and Costs

Pharmacotherapy was costed based on a typical regimen for smoking cessation as per product monographs in the *CPS 2009: Compendium of Pharmaceuticals and Specialties*. Counselling was costed based on expert opinion and physician billing in the 2011 Ontario Schedule of Benefits for Physician Services. The cost per program per patient was calculated to be as follows:

- usual care, $35.40 (Cdn)
- IC, $165.15 (Cdn)
- NRT, $203.24 (Cdn)
- IC plus NRT, $368.49 (Cdn)
- bupropion, $37.92 (Cdn)

CEA Results

All smoking-cessation programs were dominant: that is, they were less expensive and more effective than usual care (usual care was defined as a GP visit).

Using confidence intervals from the systematic review, distributions were assigned to the summary point estimates, and probabilistic sensitivity analyses were run. The probability of smoking cessation programs being cost-effective remained highly probable as the ceiling ratios for willingness to pay increased, since these were dominant strategies.

BIA Results

Ontario pays for intensive counselling through physician billing (Ontario Schedule of Benefits for Physician Services) and for bupropion through the Ontario Drug Benefit formulary. However, NRT is an out-of-pocket expense for smokers. There are 51,029 highly motivated smokers with moderate to severe COPD who could benefit from NRT. Funding NRT could translate to a potential cost to the province of $10 million (Cdn).

Patient Experiences Concerning Smoking Cessation (Qualitative Review)

The qualitative literature search identified 24,906 citations, of which 218 full-text studies were reviewed. Six studies related to COPD patients' attitudes about and experiences with smoking cessation. Findings suggest that patients' beliefs about smoking and COPD causation and exacerbation may differ from those of clinicians, and may be difficult to change. COPD patients may feel guilty about how smoking damages their health, and may suffer stigmatization by others—including health care providers—who also perceive the association.

Some patients may prefer nonsmoking explanations, such as genetics, environment, or occupational risks, for their own COPD. Some patients point to inconsistent patterns between smoking and disease in others as evidence that smoking is not necessarily the cause of their own COPD. Patients with COPD sometimes also have inaccurate information or knowledge about the relationship between smoking and COPD, or even about the benefits of smoking cessation. While clinicians might reinforce the negative effects of smoking to improve patient education, smoking cessation advice may backfire if patients feel stigmatized, blamed, or "preached" at. Such interactions may inadvertently drive smokers away from needed health care.

Patients may experience tangible benefits from continuing to smoke. For some, smoking feels like a "friend" that bolsters a sense of well-being and alleviates anxieties. Some patients even feel that smoking alleviates their COPD symptoms.

Some COPD patients feel motivated to quit smoking to improve their health, or for other reasons such as not wanting to burden others or wanting to see their grandchildren grow up. Smoking cessation is difficult, particularly when attempted without professional help. Some patients find smoking cessation unhelpful when it has no perceptible effect on their disease symptoms.

Conclusions

- Moderate quality evidence showed a statistically significant increase in abstinence rates in the intensive counselling (≥ 90 minutes) group and the intensive counselling (≥ 90 minutes) and NRT group compared with the usual care group.
- Moderate quality evidence showed a statistically significant increase in abstinence rates in the NRT group and the antidepressant bupropion group compared with the placebo group.
- Low quality evidence showed no significant differences between the minimal counselling (< 90 minutes) plus antidepressant group and the minimal counselling plus NRT plus antidepressant group compared with the usual care group.

3. Community-Based Multidisciplinary Care

Background

The term *multidisciplinary* refers to multiple disciplines on a team, and the term *interdisciplinary* refers to a multidisciplinary team functioning in a coordinated and collaborative manner. The consensus is that a group of multidisciplinary professionals is necessary for optimum specialist management of chronic illness. However, there is little evidence to guide the decision as to which professionals might be needed to optimize the care provided by a multidisciplinary team.

Research Question

What is the effectiveness and cost-effectiveness of multidisciplinary care compared with usual care (single-care provider) for the treatment of stable chronic obstructive pulmonary disease (COPD)?

Included Studies

As shown in Figure 5, of the 2,919 citations identified, 6 RCTs met the inclusion/exclusion criteria.

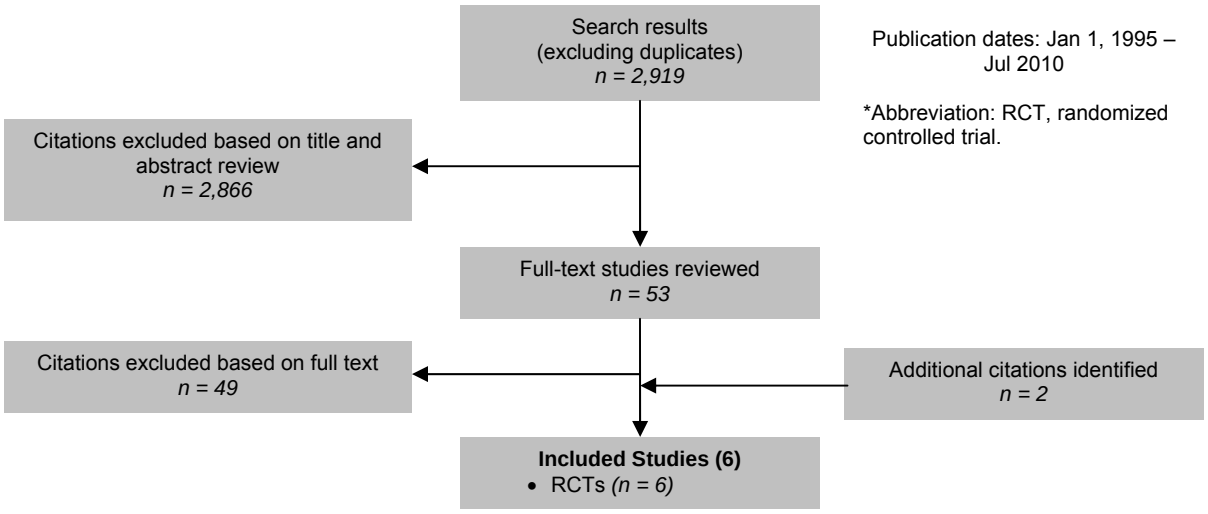


Figure 5: Multidisciplinary Care for COPD Citation Flow Chart*

The 6 RCTs included a total of 1,370 participants. The sample size ranged from 40 to 743 people, and the mean age of the patients was between 66 and 71 years. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, 3 studies included people with severe COPD and 2 with moderate COPD. The information required to classify the population in the sixth study was not available.

All of the 6 studies were conducted in the community, with 3 completed in the United States. Four studies had multidisciplinary care treatment groups that included a physician. All except 1 reported having a respiratory specialist (i.e., respiratory therapist, specialist nurse, or physician) on the multidisciplinary team. The usual care group comprised a single health care practitioner who may or may not have been a respiratory specialist.

The quality of the studies varied. Common methodological issues included lack of blinding, unclear allocation concealment, greater than 20% loss to follow-up, and unclear use of intention-to-treat analysis.

Results

Hospital Admissions

All-Cause

Four studies reported results of all-cause hospital admissions in terms of number of persons with at least 1 admission during the follow-up period. The pooled results showed a statistically significant 25% reduction in all-cause hospitalizations in the multidisciplinary care group compared with the usual care group (RR, 0.75; 95% CI, 0.64–0.87; $P < 0.001$).
GRADE: moderate

COPD-Specific
Three studies reported results of COPD-specific hospital admissions in terms of number of persons with at least 1 admission during the follow-up period. The pooled results showed a statistically significant 33% reduction in all-cause hospitalizations in the multidisciplinary care group compared with the usual care group (RR, 0.67; 95% CI, 0.52–0.87; $P = 0.002$).
GRADE: moderate

Emergency Department Visits
All-Cause
Two studies reported results of all-cause emergency department visits in terms of number of persons with at least 1 visit during the follow-up period. The pooled results showed a statistically nonsignificant reduction in all-cause ED visits in the multidisciplinary care group compared with the usual care group (RR, 0.64; 95% CI, 0.31–1.33; $P = 0.24$).
GRADE: very low

COPD-Specific
Two studies reported results of COPD-specific ED visits in terms of the number of persons with at least 1 visit during the follow-up period. The pooled results showed a statistically significant 41% reduction in COPD-specific ED visits in the multidisciplinary care group compared with the usual care group (RR, 0.59; 95% CI, 0.43–0.81; $P < 0.001$).
GRADE: moderate

Mortality
Three studies reported mortality during the study follow-up period (1 year). The pooled results showed a statistically nonsignificant reduction in mortality in the multidisciplinary care group compared with the usual care group (RR, 0.81; 95% CI, 0.52–1.27; $P = 0.36$).
GRADE: low

Lung Function
Two studies reported results of the percent predicted FEV_1 as a measure of lung function. The multidisciplinary care group showed a statistically significant improvement in lung function for up to 1 year compared with the usual group (weighted mean difference [WMD], 3.05; 95% CI, 0.64–5.46; $P = 0.01$); however, this effect was not maintained at 2 years' follow-up (WMD, 2.78; 95% CI, −1.82 to 7.37; $P = 0.24$).
GRADE: very low

Health-Related Quality of Life
Three studies reported HRQOL results based on the St. George's Respiratory Questionnaire (SGRQ). The studies all showed improvement in the mean change scores (baseline to the end of follow-up) or less deterioration in the multidisciplinary care group compared with the usual care group. The pooled results showed a statistically and clinically[4] significant improvement in the total SGRQ score in the multidisciplinary care group compared with the usual care group (WMD, −4.05; 95% CI, −6.47 to −1.63; $P = 0.001$).
GRADE: low

[4] The minimal clinically important difference (MCID) in the SGRQ is 4 points. (31)

Economic Model

Comparators and Effect Estimates

The following summary estimate from the systematic review comparing multidisciplinary care and usual care was used in the model to predict long-term outcomes: COPD-specific hospitalizations, (RR, 0.67; 95% CI, 0.52–0.87; $P = 0.002$).

Resource Use and Costs

Resources reported in the trials investigated were costed and totalled for each trial. The total costs were then averaged to calculate a cost per patient over a program duration range of 6 to 12 months. Resources could include visits with the general physician, dietitian, social worker, physiotherapist, respiratory nurse, or pharmacist. The cost per program per patient was calculated to be $1,041.03 (Cdn).

CEA Results

Assuming a base case cost of $1,041 (Cdn) per multidisciplinary care program per patient, the incremental cost-effectiveness ratio (ICER) was calculated to be $14,123 (Cdn) per QALY. The cost of the program was varied in a 1-way sensitivity analysis to reflect the variation in resource utilization reported in the literature; the ICER increased to $55,322 (Cdn) per QALY.

Using confidence intervals from the systematic review, distributions were assigned to the summary point estimates and probabilistic sensitivity analyses were run. The probability of multidisciplinary care being cost-effective increased as willingness to pay increased.

BIA Results

Family Health Teams (FHTs) often offer chronic disease management programs, including those for COPD. Data from about half the FHTs was reported to the Ministry of Health and Long-Term Care in fiscal year (FY) 2010. The data suggest that 81,289 patients with COPD are accessing COPD management programs within these FHTs, translating to a potential cost to the province of $85 million (Cdn) in FY 2010. However, this estimate does not accurately reflect the current costs to the province because of lack of report by FHTs, lack of capture of programs outside this model of care by any data set in the province, and because the resource utilization and frequency of visits/follow-up phone calls were based on the findings in the literature rather than the actual FHT COPD management programs in place in Ontario. Therefore, MDC resources being utilized in the province are unknown and difficult to measure.

Patient Experiences Concerning Nurse-Led Multidisciplinary Care (Qualitative Review)

The qualitative literature search identified 24,906 citations, of which 218 full-text studies were reviewed. Three studies related to multidisciplinary team care, specifically nurse-led care, for COPD. Two studies, 1 in the Netherlands and 1 in Sweden, explored patient experiences in the context of multidisciplinary—specifically nurse-led—team care for COPD.

The study from the Netherlands reported that patients valued the extra consultation time with nurse practitioners compared with physicians, as well as the time available for education and explaining educational materials. Patients felt safe under the nurse practitioner's care, but still wanted to maintain their relationship with the specialist physician and be referred smoothly if their care became more complicated. There were mixed views about the appropriate scope of practice for nurse practitioners—some patients favoured a wider scope (e.g., prescribing privileges), while others a narrower scope (e.g., supervision by physicians).

The Swedish study of nurse-led multidisciplinary care for COPD reported that the nurses involved focused their interactions on patients' medical and physical problems and devoted relatively little time to addressing their psychosocial issues or the prospect of acute exacerbations. Nurses tended to inform

patients about self-management and smoking cessation, but tended not to engage in motivational dialogue or articulate an individualized treatment plan with patients.
The third study, from the United Kingdom, found that adopting multidisciplinary care team models for respiratory services involved considerable organizational change. Change could be facilitated by financial incentives (pressures to control costs), teamwork, aligning interests between professionals and administrators, patient involvement, central policy guidance, and adequate support and resources to ensure successful implementation.

Conclusions

- Moderate quality evidence showed that multidisciplinary care significantly improved the following health system outcomes compared with usual care: all-cause and COPD-specific hospital admissions, and COPD-specific ED visits.
- Low quality evidence showed that multidisciplinary care significantly improved HRQOL compared with usual care.
- Very low quality evidence showed that multidisciplinary care significantly improved lung function at 1 year of follow-up, compared with usual care.
- Low and very low quality of evidence showed that multidisciplinary care led to a nonsignificant reduction in mortality and all-cause ED visits, compared with usual care.

4. Pulmonary Rehabilitation

Background

Pulmonary rehabilitation refers to a multidisciplinary program of care for patients with chronic respiratory impairment that is individually designed and tailored to optimize physical and social performance and autonomy. Pulmonary rehabilitation is recommended as the standard of care in the treatment and rehabilitation of patients with COPD who remain symptomatic despite treatment with bronchodilators.

Exercise training is the cornerstone of pulmonary rehabilitation programs and may include both aerobic and strength training. Other components of rehabilitation may include psychological support, patient education, nutritional counselling, occupational therapy, medication information, and smoking cessation.

While pulmonary rehabilitation can be delivered in multiple settings for varying durations, questions remain about the optimal site of rehabilitation delivery, components of rehabilitation programs, duration, target populations, and timing of rehabilitation.

For this review, the Medical Advisory Secretariat focused on pulmonary rehabilitation programs defined according to the Cochrane Collaboration definition from the Cochrane review of pulmonary rehabilitation. This defines pulmonary rehabilitation programs as any inpatient, outpatient, or home-based rehabilitation program lasting at least 4 weeks that includes exercise therapy with or without any form of education and/or psychological support delivered to patients with exercise limitation attributable to COPD.

Research Questions

- What is the effectiveness and cost-effectiveness of pulmonary rehabilitation compared with usual care for patients with stable COPD?
- Does early pulmonary rehabilitation (within 1 month of hospital discharge) in people who had an acute exacerbation of COPD improve outcomes compared with usual care (or no rehabilitation)?
- Do maintenance or postrehabilitation programs for patients with COPD who have completed a pulmonary rehabilitation program improve outcomes compared with usual care?

Included Studies

As shown in Figure 6, of the 3,069 citations identified, 29 met the inclusion/exclusion criteria: 1 HTA, 3 systematic reviews, and 25 RCTs.

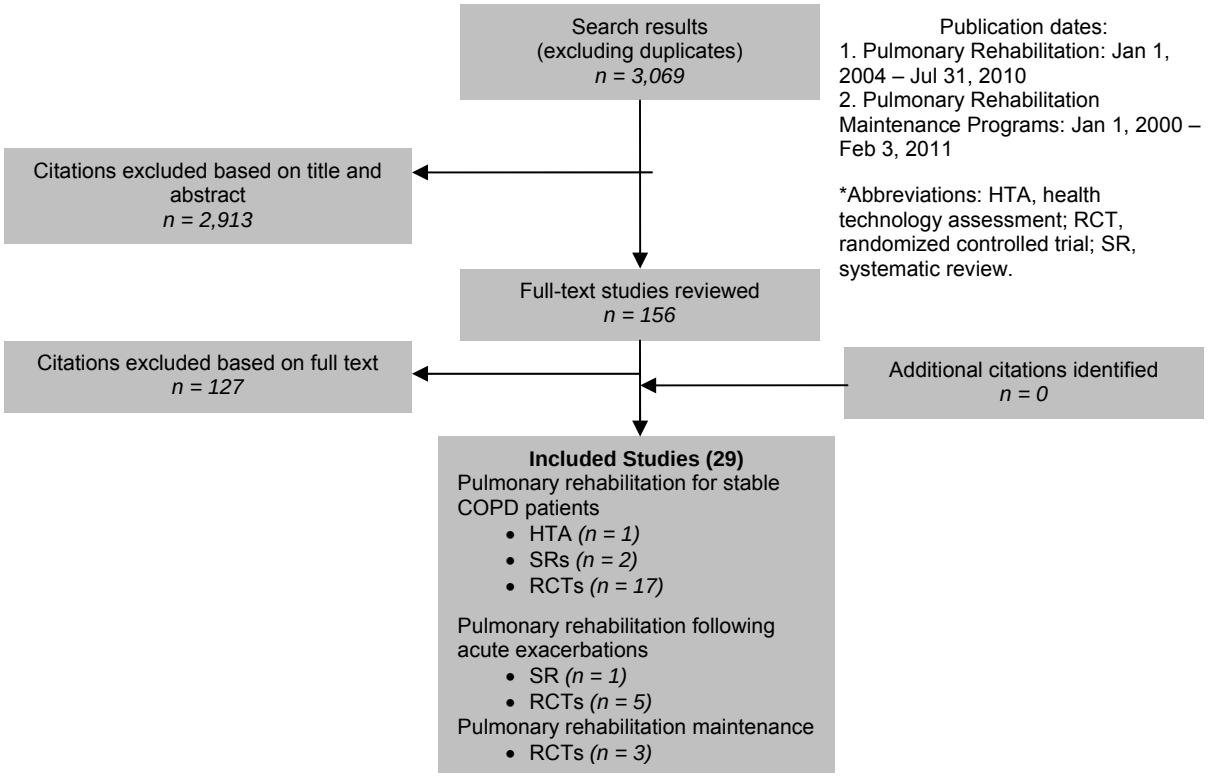


Figure 6: Pulmonary Rehabilitation for COPD Citation Flow Chart*

Results

Pulmonary Rehabilitation for Stable COPD

The 17 RCTs included a total of 1,159 participants. The sample size ranged from 28 to 200 people, and the mean age was 66 years. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, 13 of the studies included people with severe COPD, 3 with moderate COPD, and 1 with very severe COPD.

Pulmonary rehabilitation programs were delivered in a variety of settings; however, the majority of studies (71%) were conducted in a hospital outpatient setting. All the studies used a usual care control group, and 3 of the 17 studies used a wait-list control group. All of the interventions examined in the

studies included a minimum of exercise training. Exercise programs consisted of aerobic training and possibly strength training. Other interventions also included disease education, dietary education/advice, self-care, smoking cessation advice, endurance training, self-management skills, breathing and relaxation exercises, referrals to social services, and psychological support.

The individual quality of the studies varied. Common methodological issues included not conducting analyses using intention-to-treat, lack of blinding, and allocation concealment.

Health-Related Quality of Life
Eight studies reported HRQOL results based on the SGRQ. There was a statistically and clinically[5] significant improvement in HRQOL for the pulmonary rehabilitation group compared with the usual care group based on the Total and Activity scores of the SGRQ.
GRADE: moderate

Eight studies reported HRQOL results based on the Chronic Respiratory Questionnaire (CRQ). There was a statistically and clinically[6] significant improvement in HRQOL for the pulmonary rehabilitation group compared with the usual care group based on all domains of the CRQ.
GRADE: moderate

Exercise Capacity
Fifteen studies reported results of functional exercise capacity assessment based on the 6 Minute Walking Test (6MWT). The pooled results showed a statistically and clinically[7] significant improvement in functional exercise capacity for the pulmonary rehabilitation group compared with the usual care group (WMD, 54.83 m; 95% CI, 35.63–74.03 m; $P < 0.001$).
GRADE: moderate

Economic Model
This analysis could not be included in the economic model, because the appropriate inputs were not reported in the published literature.

Pulmonary Rehabilitation Following Acute Exacerbations of COPD
A total of 276 participants were included in 5 RCTs. The sample size of the studies ranged from 31 to 97 people, and the mean age of the participants was 68 years. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, 3 of the studies included people with severe COPD and 2 included people with moderate COPD.

Pulmonary rehabilitation programs were delivered in a variety of settings. Two studies had outpatient pulmonary rehabilitation programs, 2 studies began with an inpatient program followed by an outpatient program (1 study had a home-based program), and the remaining study had a home-based program for patients who had been admitted to a COPD home from a hospital treatment program. All studies reported a usual care control group. All of the interventions examined in the studies included a minimum of exercise training. Exercise programs consisted of aerobic training, and many also included a strength training component. Other components included in some of the interventions were disease education, dietary education/advice, self-care, smoking cessation advice, endurance training, self-management skills, breathing and relaxation exercises, referrals to social services, and psychological support.

The individual quality of the studies varied. Common methodological issues were unclear randomization and allocation concealment methods, lack of blinding, lack of a priori sample size calculations, and lack of use of intention-to-treat analyses.

[5] The MCID for the SGRQ is 4 points. (31)
[6] The MCID for the CRQ is 0.5 units. (31)
[7] The MCID for the 6MWT is between 25 and 35 metres. (32;33)

Hospital Readmissions

All-Cause

Two studies reported all-cause hospital readmissions. The pooled results showed a nonsignificant reduction in all-cause COPD readmissions in the pulmonary rehabilitation group compared with the usual care group (RR, 0.54; 95% CI, 0.29–1.03; $P = 0.06$).

GRADE: moderate

COPD-Specific

Three of the studies reported COPD-specific readmissions. The pooled results showed a statistically significant reduction in COPD-specific readmissions in the pulmonary rehabilitation group compared with the usual care group (RR, 0.41; 95% CI, 0.18–0.93; $P = 0.03$).

GRADE: moderate

Emergency Department Visits

ED visits were reported in 2 studies. The pooled results showed no statistically significant difference between the 2 groups (RR, 0.53; 95% CI, 0.21–1.32; $P = 0.17$).

Mortality

Mortality was reported in 2 studies. The pooled results showed no statistically significant difference between the 2 groups (RR, 0.60; 95% CI, 0.09–3.88; $P = 0.59$).

Health-Related Quality of Life

Three studies reported HRQOL results based on the SGRQ. There was a statistically and clinically[8] significant improvement in HRQOL, measured by the Total, Impact, and Activity scores, for the pulmonary rehabilitation group compared with the usual care group.

GRADE: moderate

Four studies reported HRQOL results based on the CRQ. There was a statistically and clinically[9] significant improvement in HRQOL, measured by all CRQ domains, all for the pulmonary rehabilitation group compared with the usual care group.

GRADE: moderate

Exercise Capacity

Functional exercise capacity measured by the 6MWT was reported in 2 studies. The pooled results showed a statistically and clinically[10] significant improvement in exercise capacity in the pulmonary rehabilitation group compared with the usual care group (WMD, 203.14 m; 95% CI, 185.17–221.11 m; $P < 0.001$).

GRADE: moderate

Economic Model

Comparators and Effect Estimates

The following summary estimate from the systematic review comparing pulmonary rehabilitation with usual care following acute exacerbations of COPD was used in the economic model to predict long-term outcomes in COPD-specific rehospitalization (RR, 0.41; 95% CI, 0.18–0.93; $P = 0.03$).

Resource Use and Costs

Resources reported in a Toronto-based paper that characterized pulmonary rehabilitation programs in Canada were costed, and the average cost per program per patient was calculated to be $1,527 (Cdn) for

[8] The MCID for the SGRQ is 4 points. (31)
[9] The MCID for the CRQ is 0.5 units. (31)
[10] The MCID for the 6MWT is between 25 and 35 metres. (32;33)

patients benefiting from a pulmonary rehabilitation program following an acute exacerbation for a short-term average duration of 4 weeks. Resources varied by province and setting.

CEA Results

Assuming a base case cost of $1,527 (Cdn) per pulmonary rehabilitation program per patient, the ICER was calculated to be $17,938 per QALY. The cost of the program was varied in a 1-way sensitivity analysis to reflect variation in resource utilization reported in the literature. In response, the ICER increased to $56,270 per QALY.

Using confidence intervals from the systematic review, distributions were assigned to the summary point estimates and probabilistic sensitivity analyses were run. The probability of pulmonary rehabilitation being cost-effective increased as the willingness to pay increased.

BIA Results

Data on COPD-specific hospitalization were obtained from Ontario administrative data sets to calculate the potential impact for patients benefiting from pulmonary rehabilitation programs following an exacerbation. There were 22,485 hospitalizations due to COPD in FY 2009. Based on expert opinion, half of hospitalized patients will access pulmonary rehabilitation at least once, which translates to a potential cost of $17 million (Cdn) for the province.

Pulmonary Rehabilitation Maintenance Programs

A total of 284 patients were included in 3 RCTs. The sample size ranged from 48 to 140 people, and the mean age of the participants was about 67 years. Based on either the GOLD COPD stage criteria or the percent predicted FEV_1, 2 of the studies included people with moderate COPD, and 1 included people with severe COPD.

All of the maintenance programs were delivered in an outpatient setting. All studies reported using a usual care control group. All of the interventions examined in the studies included a minimum of exercise training. Exercise programs consisted of aerobic training, and 2 of the 3 studies included a strength training component. Two of the studies included unsupervised home exercise as part of the interventions. One of the studies also supplemented the exercise training with weekly educational sessions.

The individual quality of the studies was generally poor. Common methodological issues were unclear randomization and allocation concealment methods, lack of a priori sample size calculations, lack of blinding, and lack of use of intention-to-treat analyses.

Hospitalizations and Length of Stay

Two studies reported hospitalizations and LOS, but the results for these 2 outcomes could not be pooled. Over a 12-month follow-up period, there was no difference in the mean number of hospital admissions per patient or the mean number of days spent in hospital per patient between patients in the maintenance group and the usual care group.
GRADE: low

Exercise Capacity

Two studies reported results of functional exercise capacity assessment based on the 6MWT. The pooled results showed a statistically significant improvement in functional exercise capacity for the maintenance group as compared with the usual care group (WMD, 22.93 m; 95% CI, 5.16–40.71 m; $P = 0.01$); however, the result was not clinically significant.[11] A subgroup analysis that examined the study with a maintenance program of higher intensity showed a marginally clinically[11] significant improvement in functional exercise capacity (WMD, 25.88 m; 95% CI, 25.27–26.49 m).
GRADE: low

Health-Related Quality of Life

Two studies reported HRQOL results based on the SGRQ. The results of these studies could not be pooled, as the data were not provided for 1 of the 2 studies. The study that reported results did not find a statistically or clinically[12] significant improvement in HRQOL for patients in the maintenance program compared with the usual care group. The authors of the second study noted that there was no significant difference between the groups.
GRADE: low

Economic Model

This analysis could not be included in the economic model because the appropriate inputs were not reported in the published literature.

Experiences Concerning Pulmonary Rehabilitation (Qualitative Review)

The qualitative literature search identified 24,906 citations, of which 218 full-text studies were reviewed. Fourteen studies related to pulmonary rehabilitation for COPD. The major themes identified are summarized here.

Findings from qualitative studies of patients' attitudes and experiences with pulmonary rehabilitation suggest that pulmonary rehabilitation provides COPD patients with knowledge and techniques to cope with the condition and to control breathing in particular. Better breathing helps patients feel more self-confident and less anxious, and in turn, enables many patients to increase their social participation and activity levels.

Because COPD patients frequently suffer from social isolation, pulmonary rehabilitation provides important opportunities for social interaction. Patients also value enhanced access to health care professionals through their pulmonary rehabilitation programs. Some patients wish for ongoing, rather than time-limited, rehabilitation programs to sustain the benefits and positive experiences.

Obstacles to the pulmonary rehabilitation programs include patients' low expectations, lack of perceived benefits, and expectation of burdensome exercise. The difficulties of living with COPD, such as exacerbations and overall declining health, can present further barriers to participating in pulmonary rehabilitation.

[11] The MCID for the 6MWT is between 25 and 35 metres. (32;33)
[12] The MCID for the SGRQ is 4 points. (31)

Conclusions

Stable COPD

- Moderate quality evidence showed that pulmonary rehabilitation, including at least 4 weeks of exercise training in persons with COPD, led to clinically and statistically significant improvements in HRQOL as measured by CRQ domains and SGRQ domains compared with usual care.
- Moderate quality evidence showed that pulmonary rehabilitation also led to a clinically and statistically significant improvement in functional exercise capacity compared with usual care.

Following Exacerbations

- Moderate quality evidence showed that pulmonary rehabilitation after acute exacerbation (within 1 month of hospital discharge) significantly reduced hospital readmissions and led to statistically and clinically significant improvements in HRQOL compared with usual care.

Maintenance Programs

- Low quality evidence showed no significant differences between pulmonary rehabilitation maintenance programs and usual care for HRQOL, hospital admissions, and LOS in the hospital.
- Low quality evidence showed a statistically but not clinically significant effect of pulmonary maintenance programs on exercise capacity. A subgroup examining the higher quality study with a more intense maintenance program showed a statistically and marginally clinically significant improvement in exercise capacity in the pulmonary maintenance programs group compared with the usual care group.

5. Long-Term Oxygen Therapy

Background

Patients with severe or very severe COPD may experience hypoxemia (low blood oxygen levels). Severe hypoxemia is defined as a PaO_2 less than or equal to 55 mm Hg. Moderate hypoxemia is defined by a PaO_2 between 56 mm Hg and 65 mm Hg. For the purposes of this report, a mild-to-moderate hypoxemia group was created and refers to PaO_2 levels between 56 mm Hg and 74 mm Hg. In patients with hypoxemia, the ventilatory drive is increased to maintain adequate oxygen delivery to tissues. The short-term effects of hypoxemia include greater difficulty breathing, peripheral vascular dilatation with an increase in heart rate and cardiac output, regional pulmonary vasoconstriction, high levels of erythropoietin, and increased hematological viscosity. Prolonged hypoxemia may lead to tissue hypoxia and permanent damage as a result of the adverse effects on organ function and structure.

Oxygen is a treatment option for COPD patients with hypoxemia because these individuals may have difficulty obtaining sufficient oxygen from the air. The provision of oxygen corrects its deficiency in arterial blood and prevents tissue hypoxia.

There are different oxygen sources, including oxygen concentrators, liquid oxygen systems, and oxygen cylinders, each with portable versions. Oxygen is inhaled through a small nasal device or a mask that covers the mouth and nose. Individual needs determine the flow rate, duration of use, method of administration, and oxygen source.

Long-term oxygen therapy, the focus of this analysis, is an extended use of oxygen. Based on Canadian Thoracic Society Guidelines, LTOT of 15 hours per day or more to achieve an oxygen saturation of 90% or more is recommended for patients with stable COPD and severe hypoxemia ($PaO_2 \leq 55$ mm Hg), or

less severe hypoxemia (55 mm Hg < $PaO_2 \leq$ 60 mm Hg) with either bilateral ankle edema, cor pulmonale (right ventricular failure), or hematocrit greater than 56%. In Ontario, oxygen therapy is administered through the Ministry of Health and Long-Term Care's Assistive Devices Program. The eligibility criteria for LTOT in Ontario are consistent with Canadian Thoracic Society guidelines, but also include patients with persistent hypoxemia (PaO_2, 56–60 mm Hg) and exercise-limited hypoxemia documented to improve with supplemental oxygen, or nocturnal hypoxemia, as well as patients with exertional hypoxemia without hypoxemia at rest.

There has been limited work on the safety of oxygen therapy. Use of LTOT in the presence of a fire source, such as a lit cigarette, can accelerate a fire that may lead to facial burns. Other safety hazards include falls related to oxygen tubing and underusing oxygen. As well, patients with type 2 respiratory failure using high doses of oxygen could further elevate their tissue carbon dioxide levels.

Research Question

What is the effectiveness, cost-effectiveness, and safety of LTOT compared with no LTOT in patients with COPD, when stratified by severity of hypoxemia?

Included Studies

In addition to the standard inclusion criteria detailed in the methods section, studies that included COPD patients with hypoxemia were included in this section of the review. As shown in Figure 7, of the 1,096 citations identified, 8 met the inclusion/exclusion criteria: 3 systematic reviews, 3 RCTs, and 2 observational studies.

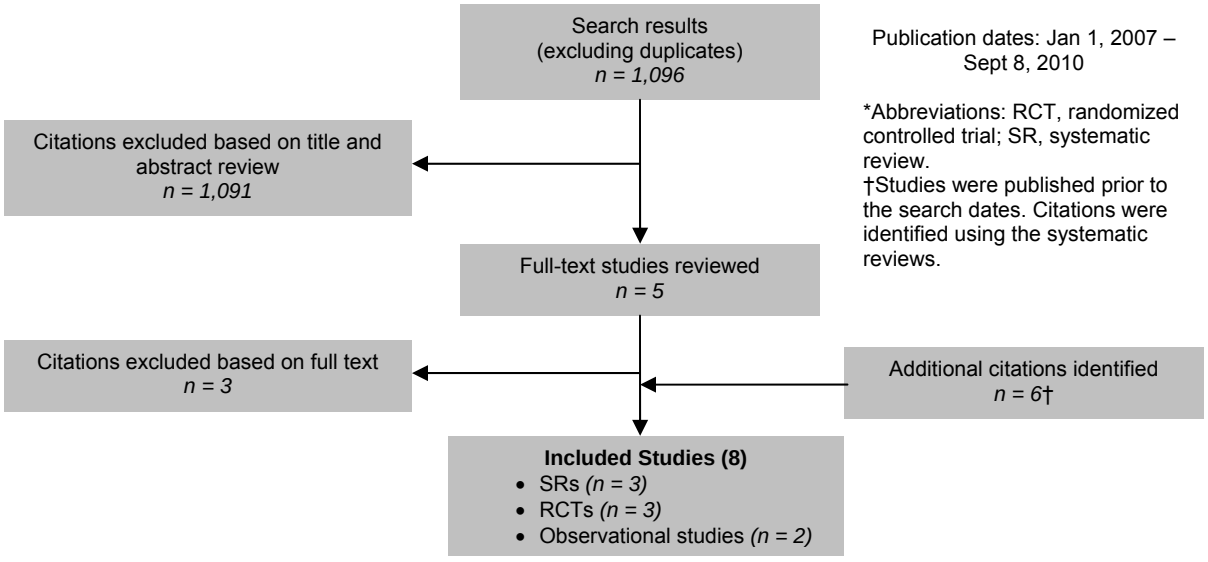


Figure 7: Long-Term Oxygen Therapy for COPD Citation Flow Chart*

Since the RCT evidence did not provide results on health system outcomes, observational studies reporting on health system outcomes were included. In addition to the systematic search described above, a nonsystematic search using MEDLINE was conducted to identify additional citations that examined the impact of LTOT on HRQOL. From this search, an additional 3 prospective observational studies were identified.

The 8 studies included a total of 802 participants. The sample size ranged from 19 to 312 people, and the mean age of the patients was about 64.5 years. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, 3 studies included people with severe COPD and 5 with very severe COPD. The analysis was divided into 2 categories based on the severity of hypoxemia. Studies were classified as either mild-to-moderate hypoxemia (55 mm Hg < $PaO_2 \leq$ 74 mm Hg) or severe hypoxemia ($PaO_2 \leq$ 55 mm Hg). One RCT included patients with mild hypoxemia, 1 with moderate hypoxemia, and 1 with severe hypoxemia. The observational studies, which reported health system outcomes, included patients with severe hypoxemia in the LTOT group and patients with mild hypoxemia in the no LTOT group. Finally, the data on HRQOL from the prospective observational studies included patients with severe hypoxemia.

All 8 studies were conducted in the community with stable COPD patients. Patients in the LTOT group received oxygen therapy for about 15 hours per day (this time may include day and night). The no-LTOT group received usual care.

The individual quality of the studies varied between studies. This analysis included both RCTs and observational studies. Common methodological issues in the RCT evidence were lack of allocation concealment, lack of information on randomization methods, and sparse data. Common limitations in the observational evidence were heterogeneity in the comparison groups and sparse data.

Results

Severe Hypoxemia ($PaO_2 \leq$ 55 mm Hg)

Mortality

One RCT reported mortality. The study showed a borderline significant reduction in mortality in the LTOT group compared with the no-LTOT group (RR, 0.68; 95% CI, 0.46–1.00; P = 0.05).
GRADE: low

Lung Function

One RCT reported lung function measured by FEV_1. The study showed that among survivors, patients on LTOT showed an improvement in FEV_1 compared with no-LTOT therapy (WMD, 0.08 L; 95% CI, 0.04–0.12 L; $P < 0.001$).
GRADE: very low

Health-Related Quality of Life

Three studies reported HRQOL based on the SGRQ and CRQ. The results could not be pooled. The following results are based on before-after comparisons of individuals who were put on LTOT (the original trials were RCTs, but only the LTOT arm was examined for this outcome). One study that reported the SGRQ showed a clinically significantly improvement in the mean change in the SGRQ total score at 2 weeks and 3 months. There were clinically significant improvements in the Impacts domain (2 weeks), Activities and Impacts domains (3 months), and Symptoms and Impacts domains (6 months). Statistical significance was not reported by this study.

Two additional studies reported HRQOL using the CRQ. The first study showed clinically and statistically significant improvements in some CRQ domains for males and females in the short and long term. The second showed statistically significant improvements in CRQ domains and total scores at 2 and 6 months (clinical significance was not defined).
GRADE: low to very low

Hospitalizations

One observational study reported hospitalizations. The study showed an increase in hospitalizations in the LTOT group compared with the no-LTOT group (percentage of patients free of hospitalizations, 38% vs.

77%; $P = 0.01$). In this study, patients in the no-LTOT group had mild-to-moderate hypoxemia, while patients in the LTOT group had severe hypoxemia.
GRADE: very low

Length of Stay
One RCT reported hospital LOS. The study showed no difference between the LTOT and no-LTOT groups (no data reported).
GRADE: low

Economic Model
Comparators and Effect Estimates
The following summary estimate from the systematic review comparing LTOT and no LTOT was used in the model to predict long-term outcomes: mortality (RR, 0.68; 95% CI, 0.46–1.0; $P = 0.05$).

Resource Use and Costs
The Ministry of Health and Long-Term Care Assistive Devices Program supplies LTOT resources and equipment to patients with severe hypoxemia. According to the Assistive Devices Program, the average cost per patient was $2,261 (Cdn) in FY 2006. Resources offered through the program include home assessment, 24-hour emergency service, maintenance and repair, training and education, oxygen supply system, and disposables (i.e., nasal cannula and tubing). This average cost of LTOT to patients with severe hypoxemia was assumed to be an annual incurrence in the model, since patients would be expected to remain indefinitely on LTOT.

CEA Results
Assuming a base case cost of $2,261 (Cdn) per year per patient, the ICER was calculated to be $38,993 (Cdn) per QALY. Using confidence intervals from the systematic reviews, distributions were assigned to the summary point estimates, and probabilistic sensitivity analyses were run. The probability of LTOT being cost-effective increased as the willingness to pay increased.

BIA Results
Data from the Assistive Devices Program suggested that 28,654 patients with severe hypoxemia accessed LTOT in FY 2006, which translates to a cost of $65 million (Cdn) for the province.

Mild-to-Moderate Hypoxemia (55 mm Hg < PaO_2 ≤ 74 mm Hg)
Mortality
Two RCTs reported mortality. The results were not pooled due to differences in the length of the intervention/follow-up (3 years vs. 7 years). At 3 years, there was a nonsignificant increase in mortality between the LTOT and no-LTOT groups (RR, 1.33; 95% CI, 0.36–4.90; $P = 0.66$). At 7 years, there was a nonsignificant increase in mortality in the LTOT group compared with the no-LTOT group (RR, 1.17; 95% CI, 0.84–1.62; $P = 0.35$).
GRADE: low (3 and 7 years)

Lung Function
Two RCTs reported lung function measured by percent predicted FEV_1 among survivors. The results were not pooled due to differences in the length of intervention/follow-up (1 year vs. 7 years). At 1 year, there was a nonsignificant improvement in lung function in the LTOT group compared with the no-LTOT group (WMD, −3.50%; 95% CI, −11.06 to 4.06%; $P = 0.36$). At 7 years, there was a nonsignificant improvement in lung function in the LTOT group compared with the no-LTOT group (WMD, −1.70%; 95% CI, −6.59 to 3.19%; $P = 0.50$).
GRADE: very low

Exercise Capacity
One RCT reported functional exercise capacity measured by endurance time (minutes). The results showed a nonsignificant improvement in the LTOT group compared with the no-LTOT group (WMD, −1.9 minutes; 95% CI, −4.52 to 0.72 minutes; $P = 0.16$).
GRADE: very low

Dyspnea
One RCT reported dyspnea measured using the Borg Scale. The study showed a nonsignificant improvement in the LTOT group compared with the no-LTOT group (WMD, −1.20; 95% CI, −2.51 to 0.11; $P = 0.07$).
GRADE: very low

Economic Model
Due to the low/very low quality of evidence and nonsignificant results, LTOT for mild-to-moderate hypoxemia was not included in the economic model.

Experiences Concerning Oxygen Therapy (Qualitative Review)

The qualitative literature search identified 24,906 citations, of which 218 full-text studies were reviewed. Three studies related to COPD patients', informal caregivers', and health care providers' experiences with oxygen therapy for COPD; 2 relevant themes were identified.

The first theme related to lay beliefs about oxygen therapy. Findings showed that patients gained a sense of independence with use, symptom mastery, improved sleep, and a source of reassurance from the presence of oxygen therapy.

The second theme related to adherence and covered numerous areas, including functional limitation, health benefits, symptom relief, social pressure, and self-management. Increased adherence was associated with:

- modifying the functional limitations of the heavy oxygen equipment;
- the perception of improved health benefits;
- worsening of symptoms;
- symptom relief; and
- social pressures for use (e.g., family, friends, or physician).

Decreased adherence was associated with avoiding the drawbacks of use (e.g., activity modification) and embarrassment. Patients display a series of decision-making steps as they come to terms with their use of oxygen therapy.

Conclusions

Severe Hypoxemia ($PaO_2 \leq 55$ mm Hg)

- Low quality evidence showed a borderline significant reduction in mortality in the LTOT group compared with the no-LTOT group.
- Very low quality evidence showed a significant improvement in FEV_1 in the LTOT group compared with the no-LTOT group.
- Low to very low quality evidence showed a significant improvement in HRQOL as measured by some domains of the SGRQ and the CRQ in the LTOT group compared with the no-LTOT group.
- Low quality evidence showed an increase in hospitalizations in the LTOT group compared with the no-LTOT group, but there was no difference in hospital LOS between the 2 groups.

Mild-to-Moderate Hypoxemia (55 mm Hg < PaO_2 ≤ 74 mm Hg)

- Low quality evidence showed no difference in mortality in the LTOT group compared with the no-LTOT group at 3 and 7 years of follow-up.
- Very low quality evidence showed nonsignificant improvements in percent predicted FEV_1, endurance time, and dyspnea in the LTOT group compared with the no-LTOT group.

6. Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure

Background

Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD. Hypercapnic respiratory failure occurs due to a decrease in the drive to breathe, typically due to increased work to breathe in COPD patients.

There are several treatment options for acute respiratory failure. Usual medical care (UMC)[13] attempts to facilitate adequate oxygenation and treat the cause of the exacerbation. It typically consists of supplemental oxygen, and a variety of medications such as bronchodilators, corticosteroids, and antibiotics. The failure rate of UMC has been estimated to occur in 10% to 50% of cases.

The alternative to UMC is mechanical ventilation, either IMV or noninvasive ventilation. IMV involves sedating the patient, creating an artificial airway through endotracheal intubation, and attaching the patient to a ventilator. While this approach provides airway protection and direct access to drain sputum, it can lead to substantial morbidity and risks, including tracheal injuries and VAP.

While noninvasive ventilation can be done by either positive or negative pressure, noninvasive negative pressure ventilation (such as the iron lung) is no longer in use in Ontario. NPPV provides ventilatory support through a facial or nasal mask and reduces inspiratory work. NPPV can often be used intermittently for short periods of time to treat respiratory failure, allowing patients to continue to eat, drink, talk, and participate in their own treatment decisions. In addition, patients do not require sedation, airway defence mechanisms and swallowing functions are maintained, trauma to the trachea and larynx are avoided, and the risk for VAP is reduced. Common complications with NPPV are damage to facial and nasal skin, higher incidence of gastric distension with aspiration risk, sleeping disorders, and conjunctivitis. In addition, NPPV does not allow direct access to the airway to drain secretions, requires patients to cooperate, and (due to potential discomfort) compliance and tolerance may be low.

In addition to treating acute respiratory failure, NPPV can be used to wean patients from IMV through the gradual removal of ventilation support until the patient can breathe spontaneously. Five percent to 30% of patients have difficulty weaning. Tapering levels of ventilatory support to wean patients from IMV can be achieved using either IMV or NPPV. Use of NPPV helps to reduce the risk of VAP by shortening the amount of time the patient is intubated.

Following extubation from IMV, acute respiratory failure may recur, leading to extubation failure and the need for reintubation, which has been associated with increased risk of nosocomial pneumonia and mortality. To avoid these complications, NPPV has been proposed to help prevent acute respiratory failure from recurring and/or to treat respiratory failure when it recurs, thereby preventing the need for reintubation.

[13] *Usual medical care* is the term used for the medical treatment of patients with acute respiratory failure as an alternative to NPPV. *Usual care* is the generic term for the comparison group in other analyses.

Research Questions

- What is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of acute hypercapnic respiratory failure due to acute exacerbations of COPD compared with:
  - usual medical care, and
  - IMV?
- What is the effectiveness, cost-effectiveness, and safety of NPPV compared with IMV in COPD patients after IMV for the following purposes:
  - weaning COPD patients from IMV,
  - preventing acute respiratory failure in COPD patients after extubation from IMV, and
  - treating acute respiratory failure in COPD patients after extubation from IMV?

Included Studies

As shown in Figure 8, of the 2,585 citations identified, 31 met the inclusion/exclusion criteria: 14 systematic reviews and 17 RCTs.

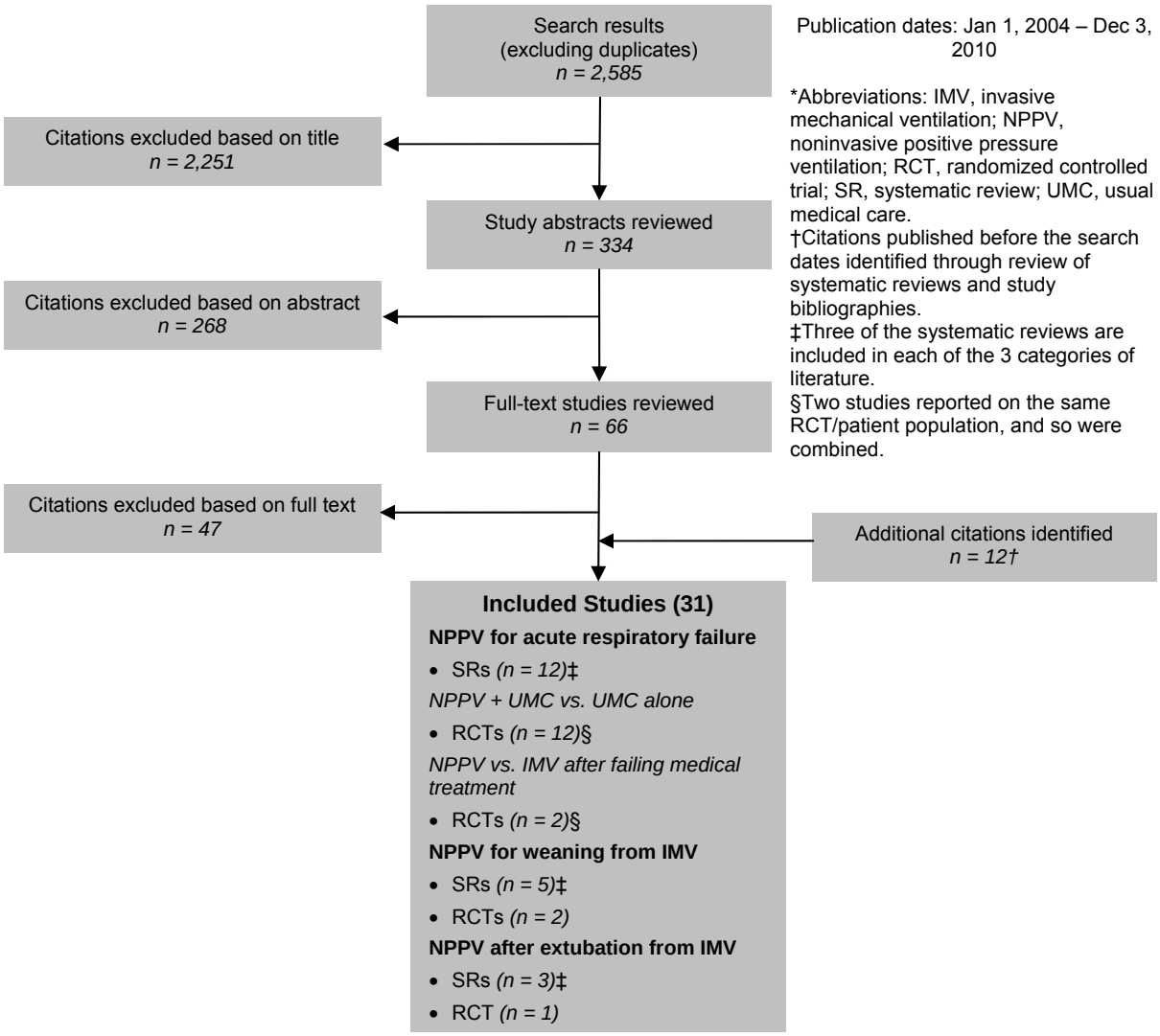


Figure 8: NPPV for Acute Respiratory Failure Citation Flow Chart*

Results

NPPV for Acute Respiratory Failure Due to Acute Exacerbations of COPD

Thirteen[14] RCTs evaluating the effectiveness of NPPV for the treatment of acute respiratory failure due to acute exacerbations of COPD were identified. The following comparisons were examined:

- NPPV plus UMC versus UMC alone (11 RCTs)
- NPPV versus IMV (2 RCTs)

NPPV plus UMC Versus UMC for First-Line Treatment

The 11 RCTs included a total of 1,000 participants. The sample size ranged from 23 to 342 people, and the mean age of the patients ranged from 60 to 72 years. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, 4 of the studies included people with severe COPD; inadequate information was available to classify the remaining 7 studies by COPD severity. The severity of the respiratory failure was classified into 4 categories using the study population mean pH level as follows: mild ($pH \geq 7.35$), moderate ($7.30 \leq pH < 7.35$), severe ($7.25 \leq pH < 7.30$), and very severe ($pH < 7.25$). Based on these categories, 3 studies included patients with a mild respiratory failure, 3 with moderate respiratory failure, 4 with severe respiratory failure, and 1 with very severe respiratory failure.

The studies were conducted either in the intensive care unit (ICU) (3 of 11 studies) or general or respiratory hospital wards (8 of 11 studies) with patients in the NPPV group receiving bilevel positive airway pressure (BiPAP) ventilatory support, although 1 study used pressure support ventilation and 1 used volume cycled ventilation. Patients received ventilation through nasal, facial, or oronasal masks. All studies specified a protocol or schedule for NPPV delivery, but this varied substantially across the studies. For example, some studies restricted the amount of ventilation per day (e.g., 6 hours per day) and the number of days it was offered (e.g., maximum of 3 days), whereas other studies provided patients with ventilation for as long as they could tolerate it and recommended it for much longer periods of time (e.g., 7–10 days). These differences are an important source of clinical heterogeneity between studies. In addition to NPPV, all patients in the NPPV group also received usual medical care. Usual medical care varied between studies, but common interventions included supplemental oxygen, bronchodilators, corticosteroids, antibiotics, diuretics, and respiratory stimulators.

The individual quality of the studies varied. Common methodological issues included lack of blinding, allocation concealment, and small sample sizes.

Need for Endotracheal Intubation

Eleven studies reported the need for endotracheal intubation. The pooled results showed a significant reduction in the need for endotracheal intubation in the NPPV plus UMC group compared with the UMC group (RR, 0.38; 95% CI, 0.28–0.50; $P < 0.001$). When subgrouped by severity of respiratory failure, the results remained significant for the mild, severe, and very severe respiratory failure groups.
GRADE: moderate

Inhospital Mortality

Nine studies reported inhospital mortality. The pooled results showed a significant reduction in inhospital mortality in the NPPV plus UMC group compared with the UMC group (RR, 0.53; 95% CI, 0.35–0.81; $P = 0.003$). When subgrouped by severity of respiratory failure, the results remained significant for the moderate and severe respiratory failure groups.
GRADE: moderate

[14] Fourteen papers were identified; however 2 of the trials reported results for 1 study but different outcomes. These 2 papers have been treated as 1 study.

Hospital Length of Stay

Eleven studies reported hospital LOS. The pooled results showed a significant decrease in mean LOS for the NPPV plus UMC group compared with the UMC group (WMD, −2.68 days; 95% CI, −4.41 to −0.94 days; $P = 0.002$). When subgrouped by severity of respiratory failure, the results remained significant for the mild, severe, and very severe respiratory failure groups.

GRADE: moderate

Complications

Five studies reported complications. Common complications in the NPPV plus UMC group included pneumonia, gastrointestinal disorders or bleeds, skin abrasions, eye irritations, gastric insufflations, and sepsis. Similar complications were observed in the UMC group, including pneumonia, sepsis, gastrointestinal disorders or bleeds, pneumothorax, and complicated endotracheal intubations. Many of the more serious complications in both groups occurred in patients who required endotracheal intubation. Three of the studies compared complications in the NPPV plus UMC group and UMC groups. While the data could not be pooled, overall the NPPV plus UMC group experienced fewer complications than the UMC group.

GRADE: low

Tolerance/Compliance

Eight studies reported patient tolerance or compliance with NPPV. NPPV intolerance ranged from 5% to 29%. NPPV tolerance was generally higher for patients with more severe respiratory failure. Compliance with the NPPV protocol was reported by 2 studies, which showed compliance decreases over time, even over short periods, such as 3 days.

Economic Model

Comparators and Effect Estimates

The following summary estimate from the systematic review comparing NPPV plus UMC with UMC was used in the model to predict long-term outcomes: inpatient mortality (RR, 0.53; 95% CI, 0.35–0.81; $P = 0.003$).

Resource Use and Costs

The Ontario Case Costing Initiative collects cost data for acute inpatient, day surgery, and ambulatory care cases from participating hospitals. This provides a standard data set for hospitalization costs in Ontario. Cost per diem or per average LOS can be obtained by most responsible diagnosis and principal procedure. Codes were identified through Canadian Institute for Health Information reference, and cost per diem for noninvasive ventilation in COPD was obtained. The cost for UMC for a COPD hospitalization was obtained from Canadian literature. The following estimates were used:

- NPPV, $864 per diem
- UMC, $1,009 per diem

Based on average LOSs reported in the trials, total costs for the hospitalization episode of each arm were calculated.

CEA Results

The NPPV plus UMC strategy was dominant; that is, it was cheaper and more effective, as reflected by the clinical evidence of significant inhospital days avoided.

BIA Results

Based on expert opinion, 15% of the patient population at risk is eligible for ventilation and 50% will choose to be ventilated. These estimates suggest that 11,163 patients can benefit from NPPV, which translates into a cost savings to the province from the hospital perspective of $42 million (Cdn).

NPPV Versus IMV

A total of 205 participants were included in 2 studies. The sample sizes were 49 and 156 people. The mean age of the patients was 71 to 73 years in 1 study, and the median age was 54 to 58 years in the other. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, patients in 1 study had very severe COPD. The COPD severity could not be classified in the second study. Both studies included patients with very severe respiratory failure (mean pH < 7.23). One study enrolled patients with acute respiratory failure due to acute exacerbations of COPD who had failed medical therapy. The patient population was not clearly defined in the second study, and it was not clear whether patients had to have failed medical therapy before entry into the study.

Both studies were conducted in the ICU. Patients in the NPPV group received BiPAP ventilatory support through nasal or full facial masks. Patients in the IMV group received pressure support ventilation.

Common methodological issues included small sample size, lack of blinding, and unclear methods of randomization and allocation concealment. Due to uncertainty about whether both studies included the same patient population and substantial differences in the direction and significance of the results, the results of the studies were not pooled.

Mortality

Both studies reported ICU mortality. Neither study showed a significant difference in ICU mortality between the NPPV and IMV groups; 1 study, however, showed a higher mortality rate in the NPPV group (21.7% vs. 11.5%; *P* value not reported), while the other study showed a lower mortality rate in the NPPV group (5.1% vs. 6.4%; $P = 0.93$). One study reported 1-year mortality and showed a nonsignificant reduction in mortality in the NPPV group compared with the IMV group (26.1% vs. 46.1%; $P = 0.24$).
GRADE: low to very low

Intensive Care Unit Length of Stay

Both studies reported LOS. The results were inconsistent. One study showed a statistically significant shorter LOS in the NPPV group compared with the IMV group (mean [standard deviation (SD)] = 5.00 [1.35] days vs. 9.29 [3.00] days; $P < 0.001$), whereas the other showed a nonsignificantly longer LOS in the NPPV group compared with the IMV group (mean [SD] = 22 [19] days vs. 21 [20] days; $P = 0.86$).
GRADE: very low

Duration of Mechanical Ventilation

Both studies reported the duration of mechanical ventilation (including both invasive and noninvasive ventilation). The results were inconsistent. One study showed a statistically significant shorter duration of mechanical ventilation in the NPPV group compared with the IMV group (mean [SD] = 3.92 [1.08] days vs. 7.17 [2.22] days; $P < 0.001$), whereas the other showed a nonsignificantly longer duration of mechanical ventilation in the NPPV group compared with the IMV group (mean [SD] = 16 [19] days vs. 15 [21] days; $P = 0.86$).
GRADE: very low

Complications

Both studies reported VAP and tracheotomies. Both studies showed a reduction in VAP in the NPPV group compared with the IMV group, but the results were significant in only 1 study (13% vs. 34.6%; $P = 0.07$ and 6.4% vs. 37.2%; $P < 0.001$). Similarly, both studies showed a reduction in tracheotomies in the NPPV group compared with the IMV group, but the results were significant in only 1 study (13% vs. 23.1%; $P = 0.29$; and 6.4% vs. 34.6%; $P < 0.001$).
GRADE: very low

Other Outcomes

One of the studies followed patients for 12 months, at the end of which patients in the NPPV group had a significantly lower rate of needing *de novo* oxygen supplementation at home. In addition, the IMV group experienced significant increases in functional limitations due to COPD, while no increase was seen in the NPPV group. Finally, no significant differences were observed for hospital readmissions, ICU readmissions, and patients with an open tracheotomy between the NPPV and IMV groups.

Economic Model

Due to the low/very low quality of evidence and inconsistent results that could not be pooled, these results were not included in the economic model.

NPPV for Weaning COPD Patients from IMV

The 2 RCTs included a total of 80 participants. The sample sizes were 30 and 50 people, and the mean age of the patients ranged from 58 to 69 years. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, both studies included patients with very severe COPD. Both studies also included patients with very severe respiratory failure (mean pH < 7.23). COPD patients receiving IMV were enrolled in the study if they failed a spontaneous breathing test (T-piece weaning trial), so they could not be directly extubated from IMV.

Both studies were conducted in the ICU. Patients in the NPPV group were weaned using either BiPAP or pressure support ventilation NPPV through a face mask, while patients in the IMV weaning group received pressure support ventilation. In both cases, weaning was achieved by tapering the ventilation level slowly.

The individual quality of the studies varied. Common methodological problems included unclear randomization methods and allocation concealment, lack of blinding, and small sample size.

Mortality

Both studies reported mortality. The pooled results showed a significant reduction in ICU mortality in the NPPV group compared with the IMV group (RR, 0.47; 95% CI, 0.23–0.97; $P = 0.04$).
GRADE: moderate

Intensive Care Unit Length of Stay

Both studies reported LOS. The pooled results showed a nonsignificant reduction in ICU LOS in the NPPV group compared with the IMV group (WMD, −5.21 days; 95% CI, −11.60 to 1.18 days; $P = 0.11$).
GRADE: low

Duration of Mechanical Ventilation

Both studies reported the duration of mechanical ventilation (including both invasive and noninvasive ventilation). The pooled results showed a nonsignificant reduction in duration of mechanical ventilation (WMD, −3.55 days; 95% CI, −8.55 to 1.44 days; $P = 0.16$).
GRADE: low

Nosocomial Pneumonia

Both studies reported nosocomial pneumonia. The pooled results showed a significant reduction in nosocomial pneumonia in the NPPV group compared with the IMV group (RR, 0.14; 95% CI, 0.03–0.71; $P = 0.02$).
GRADE: moderate

Weaning Failure
One study reported a significant reduction in weaning failure in the NPPV group compared with the IMV group, but not the data. In this study, 1 of the 25 patients in the NPPV group and 2 of the 25 patients in the IMV group could not be weaned after 60 days in ICU.
GRADE: moderate

Economic Model
Comparators and Effect Estimates
The summary estimate of inpatient mortality (RR, 0.47; 95% CI, 0.23–0.97; $P = 0.04$) from the systematic review comparing NPPV versus IMV was used in the model to predict long-term outcomes.

Resource Use and Costs
The Ontario Case Costing Initiative collects cost data for acute inpatient, day surgery, and ambulatory care cases from participating hospitals. This provides a standard data set for hospitalization costs. Cost per diem or per average LOS can be obtained by most responsible diagnosis and principal procedure. The following per diem estimates for IMV and NPPV in COPD were used:

- IMV, $1,679 per diem
- NPPV, $864 per diem

Based on average LOS reported in the trials, total costs for the hospitalization episode of each arm were calculated.

CEA Results
Weaning with NPPV was a dominant strategy: that is, the strategy is cheaper and more effective than weaning with IMV (as reflected by the reduced inpatient mortality in the study group).

BIA Results
Based on expert opinion, 15% of the patient population at risk is eligible for ventilation. Of those, 50% will choose to be ventilated, and 15% will fail spontaneous breathing tests. Therefore, an estimated 1,435 patients can benefit from weaning with NPPV, which translates into a cost savings to the province from the hospital perspective of $12 million (Cdn).

NPPV After Extubation of COPD Patients from IMV
The literature was reviewed to identify studies that examine the effectiveness of NPPV compared with usual medical care in preventing recurrence of acute respiratory failure after extubation from IMV or treating acute respiratory failure that recurred after extubation from IMV. None of the studies identified included COPD patients only or reported results for preventing acute respiratory failure after extubation for COPD patients separately.

Reintubation
One study discussed the treatment of acute respiratory failure that recurred within 48 hours of extubation from IMV in COPD patients. This study included 221 patients, of whom 23 had COPD. A post hoc subgroup analysis examined the rate of reintubation in the COPD patients only. A nonsignificant reduction in the rate of reintubation was observed in the NPPV group compared with the usual medical care group (7 of 14 patients vs. 6 of 9 patients, $P = 0.67$).
GRADE: low

Economic Model
Due to the low quality of evidence and nonsignificant results, the results on the use of NPPV in COPD patients to treat acute respiratory failure after extubation from IMV were not included in the economic model.

Experiences Concerning Ventilation (Qualitative Review)

The qualitative literature search identified 24,906 citations, of which 218 full-text studies were reviewed. Three studies related to patients' experiences with noninvasive (2 studies) and invasive (1 study) ventilation.

Findings showed both adverse and beneficial effects in COPD patients for both invasive and noninvasive ventilation. Potential adverse effects include patients feeling trapped by the machine, both literally and figuratively; feeling dependent on it; and feeling shut in or suffocated by the mask. Difficulties moving, communicating, and making choices bring further distress.

In terms of advantages, ventilation provides the much-appreciated benefit of improved breathing and regaining strength with time. Patients develop the ability to cope with the mask and machine, just as they regain strength and willpower, realize their situation, and to some extent redefine themselves. Clinicians' presence and encouragement are highly valued and improve the ability to cope.

Other findings were that COPD patients who become candidates for ventilation are quite vulnerable, both mentally and physically (breathless, anxious, incapacitated, exhausted); they typically have little knowledge of ventilation technology before it is offered to them.

The study on invasive ventilation found that patients often experience a period of amnesia after intubation. Following this, patients often experience an awareness of loss of physiological and personal autonomy and a feeling that someone or something is controlling them.

Conclusions

NPPV Plus UMC Versus UMC for First-Line Treatment of Acute Respiratory Failure Due to Acute Exacerbations of COPD

- Moderate quality evidence showed that NPPV plus UMC significantly reduced the need for endotracheal intubation, inhospital mortality, and mean length of hospital stay compared with UMC.
- Low quality evidence showed a lower rate of complications in the NPPV plus UMC group compared with the UMC group.

NPPV Versus IMV for Treatment of Acute Respiratory Failure in Patients Who Have Failed UMC

- Because of inconsistent and low to very low quality evidence, there was insufficient evidence to draw conclusions on the comparison of NPPV versus IMV for patients who have failed medical treatment.

NPPV for Weaning COPD Patients from IMV

- Moderate quality evidence showed that weaning COPD patients from IMV using NPPV results in significant reductions in mortality, nosocomial pneumonia, and weaning failure compared with weaning with IMV.
- Low quality evidence showed a nonsignificant reduction in mean LOS and mean duration of mechanical ventilation in the NPPV group compared with the IMV group.

NPPV for Treatment of Recurrent Acute Respiratory Failure in COPD Patients After Extubation from IMV

- Low quality evidence showed a nonsignificant reduction in rate of reintubation in the NPPV group compared with the UMC group; however, there was inadequate evidence to draw conclusions on the effectiveness of NPPV for the treatment of acute respiratory failure in COPD patients after extubation from IMV.

7. Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure

Background

In addition to its use in acute respiratory failure (described above), NPPV can be used to treat chronic respiratory failure in stable COPD patients.

In Ontario, ventilatory devices and positive airway pressure systems are covered under Respiratory Products by the Ministry of Health and Long-Term Care's Assistive Devices Program. There are no specific guidelines for eligibility, but applicants must be assessed by a medical professional. According to the ventilator equipment pool database, there were 263 patients registered with a primary or secondary diagnosis of chronic bronchitis, emphysema, bronchiectasis, and chronic airway obstruction between 2005 and 2010. This may be an underestimate, because certain diagnoses, such as respiratory failure/respiratory insufficiency or hypoventilation, are not captured in the ventilator equipment pool.

Research Question

What is the effectiveness and cost-effectiveness of NPPV, compared with no ventilation while receiving usual care, for stable COPD patients?

Included Studies

As shown in Figure 9, of the 2,593 citations identified, 10 studies met the inclusion/exclusion criteria: 2 systematic reviews and 8 RCTs.

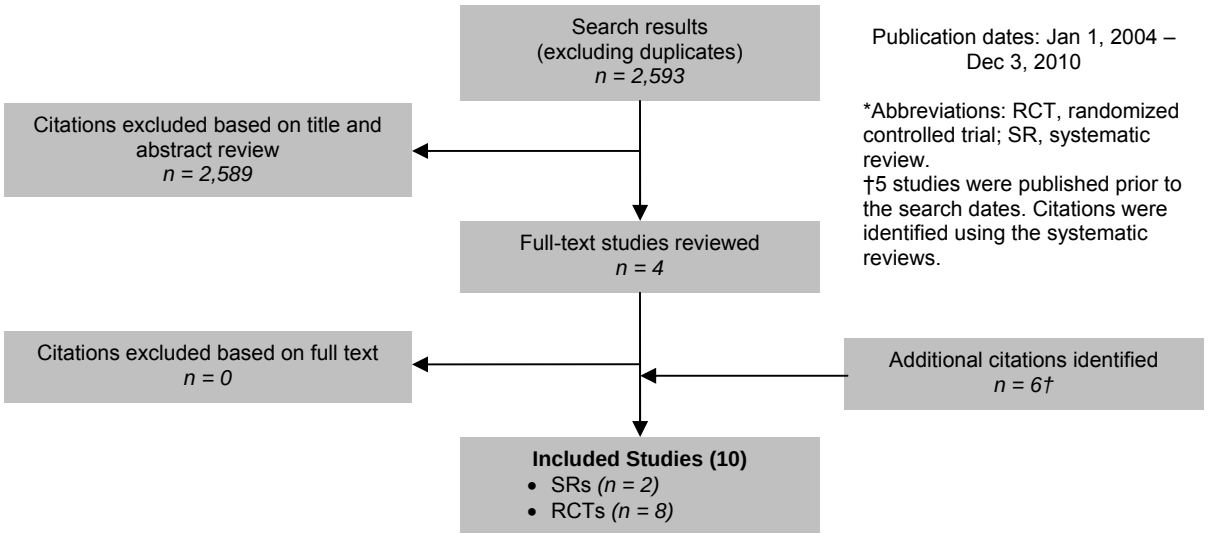


Figure 9: NPPV for Chronic Respiratory Failure Citation Flow Chart*

The 8 RCTs included a total of 403 participants. The sample size ranged from 13 to 144 participants. The mean age of the participants was 67 years of age. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, 3 of the studies included people with severe COPD and 5 included people with very severe COPD.

All of the studies enrolled patients with stable COPD. Six of the trials were conducted in the outpatient setting and 2 in laboratory-based settings. Patients in the NPPV group received BiPAP ventilatory support with inspiratory levels set between 10 and 18 cm H_2O. The amount of ventilation varied, ranging from 2 hours per day to 9 hours during the night. Usual care varied, but often included bronchodilators and LTOT.

The individual quality of the studies varied. Common methodological issues included lack of allocation concealment, lack of information on randomization methods, lack of blinding, limited generalizability (e.g., for studies conducted in a laboratory setting), and sparse data.

Results

Mortality

Three studies reported long-term (≥ 3 months) mortality. The pooled results showed a nonsignificant reduction in mortality in the NPPV group compared with the usual care group (RR, 0.89; 95% CI, 0.69–1.15; $P = 0.39$).
GRADE: moderate

Lung Function

Short term

One study reported mean change in percent predicted FEV_1. The study showed a nonsignificant improvement in percent predicted FEV_1 in the NPPV group compared with the usual care group (WMD, 5.00%; 95% CI, −1.91% to 11.91%; $P = 0.16$).
GRADE: very low

Long term

Two studies reported mean change in percent predicted FEV_1. The pooled results showed a nonsignificant improvement in the NPPV group compared with the usual care group (WMD, 1.05%; 95% CI, −2.17% to 4.27%; $P = 0.52$).
GRADE: moderate

Exercise Capacity

Short term

Three studies reported functional exercise capacity assessment based on the 6MWT. The pooled results showed a clinically and statistically significant improvement in the NPPV group compared with the usual care group (WMD, 49.72 m; 95% CI, 2.93–96.51 m; $P = 0.04$).
GRADE: low

Long term

One study reported functional exercise capacity assessment based on the 6MWT. The study showed a nonsignificant decrease in exercise capacity in the NPPV group compared with the usual care group (WMD, −3.00 m; 95% CI, −52.55 m to 46.55 m; $P = 0.91$).
GRADE: moderate

Dyspnea

Four studies reported dyspnea. The results could not be pooled because different measures and characterizations of breathlessness were reported. Overall, there was a beneficial effect of NPPV as measured by the Borg Scale and Medical Research Council Score.
GRADE: low

Health-Related Quality of Life

Two studies reported HRQOL based on the SGRQ. The results of these studies could not be pooled because of insufficient data in the published reports. Overall, data on which to base a conclusion on the impact of NPPV on HRQOL were insufficient.
GRADE: n/a

Hospitalizations

Two studies reported short-term and long-term hospitalizations. Overall, there was no significant difference between the NPPV and usual care groups.
GRADE: moderate

Economic Model

Due to the lack of evidence of clinical effectiveness of NPPV in chronic respiratory failure in stable COPD, the results were not included in the economic model.

Experiences Concerning Ventilation (Qualitative Review)

The qualitative review of literature on noninvasive ventilation was not separated by acute or chronic respiratory failure. Thus, the results on patients' perspectives on noninvasive ventilation are the same as those summarized in Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure (see page 61 of this report).

Conclusions

- Moderate quality evidence showed nonsignificant differences in mortality, lung function after 3 months, functional exercise capacity (6MWT) after 3 months, and hospitalizations between the NPPV and usual care groups.
- Low quality evidence showed clinically and statistically significant improvements in functional exercise capacity (6MWT) for the first 3 months of treatment and a beneficial impact on dyspnea in the NPPV group compared with the usual care group.
- There was insufficient evidence to draw conclusions about the impact of NPPV on HRQOL.

8. Hospital-at-Home Programs for Acute Exacerbations of COPD

Background

Hospital-at-home programs are services that provide patients with active treatment by health care professionals in the patient's home for a condition that otherwise would require acute hospital inpatient care for a limited time period. Based on the programs described in the literature, when enrolled in hospital-at-home programs for COPD exacerbations, patients receive visits in their home from medical professionals (typically specialist nurses) who monitor the patients, alter their treatment plans if needed, and in some programs, provide additional care such as pulmonary rehabilitation, patient and caregiver education, smoking cessation counselling, and support services.

There are 2 types of hospital-at-home programs: admission avoidance and early discharge. In admission avoidance, after being assessed in the ED, patients are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home, where they will receive visits from medical professionals. Alternatively, in some programs patients may be referred directly to admission avoidance by their general practitioner, rather than first going to the ED. In early discharge, after being assessed in the ED, patients are admitted to the hospital where they receive the initial phase of their treatment, following which they are discharged early into hospital-at-home before the exacerbation has resolved. In both cases, once the exacerbation has resolved, the patient is discharged from the hospital-at-home program and no longer receives visits at home.

Hospital-at-home programs differ from other home care programs in 2 ways. First, they deal with patients who require higher-acuity care; in this case, patients have severe acute exacerbations of COPD and would otherwise require hospitalization for the treatment of their exacerbation. Second, hospitals retain the medical and legal responsibility for patients (at least in the models for COPD that have existed to date). Furthermore, patients requiring home care services may require these services for long periods of time or indefinitely, whereas patients in hospital-at-home programs require and receive the services for a limited period of time only (e.g., only until the acute exacerbation has resolved).

Hospital-at-home care is not appropriate for all patients with acute exacerbations of COPD. Those patients with less severe exacerbations who can be managed without admission to hospital are not eligible for hospital-at-home care. This includes patients who do not present to the ED for their exacerbation or those who can be discharged with some changes in medication only. Furthermore, some patients require admission to the hospital and cannot be safely treated in a hospital-at-home program, whether for medical reasons (e.g., diminished consciousness) or lack of/poor social support at home.

The proposed potential benefits of hospital-at-home for exacerbations of COPD include decreased health care resource utilization and decreased costs by avoiding hospital admissions and/or reducing LOS in the hospital; increased HRQOL for patients and their caregivers; and reduced risk of hospital-acquired infections in this susceptible, elderly, sick patient population.

Research Question

What is the effectiveness, cost-effectiveness, and safety for hospital-at-home care compared with inpatient hospital care of acute exacerbations of COPD?

Included Studies

As shown in Figure 10, of the 3,142 citations identified, 13 studies met the inclusion/exclusion criteria: 1 HTA, 5 systematic reviews, and 7 RCTs.

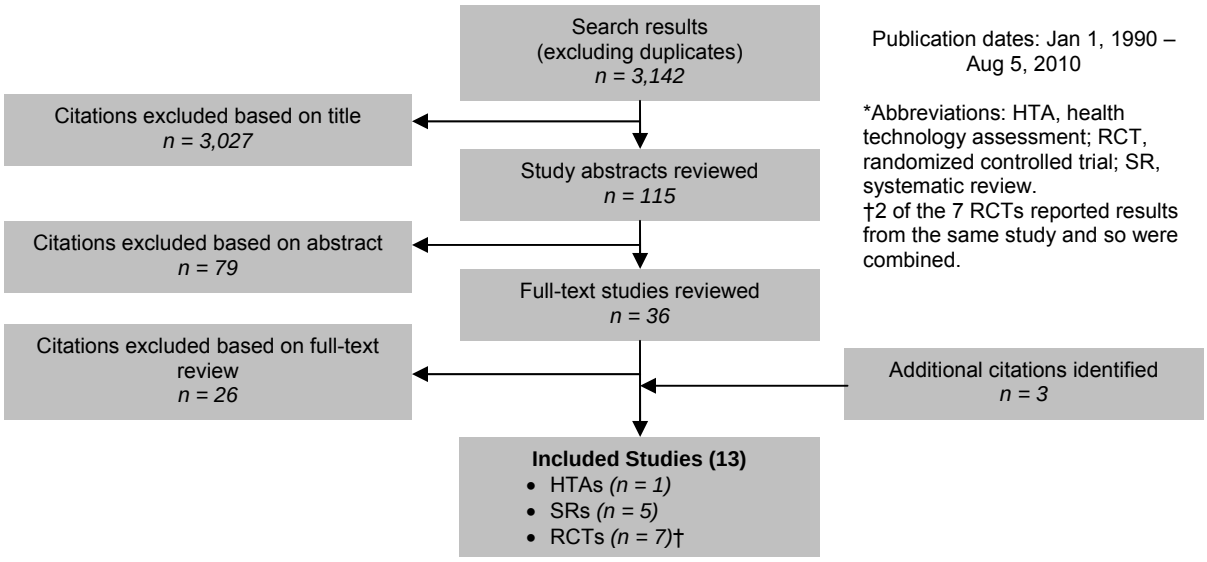


Figure 10: Hospital-at-Home for Acute Exacerbations Citation Flow Chart*

The 6 RCTs[15] included a total of 611 patients. Sample size ranged from 32 to 184 people. The mean age of the participants ranged from about 66 to 80 years of age. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, 3 of the studies included people with severe COPD. The other 3 studies could not be classified by severity of disease, as the necessary information was not provided.

Three studies used early discharge programs, 2 used admission avoidance programs, and 1 used both types of programs. The setting for hospital-at-home programs differed between study arms. In all studies, the control arm received care in the hospital. In the admission avoidance studies, patients in the hospital-at-home group received care in the home; in the early discharge studies, patients received some of their care in the hospital followed by early discharge and care in the home. Hospital-at-home programs varied between low-intensity programs (2 studies), in which patients were primarily monitored and received changes to medications as needed, and high-intensity programs (3 studies) that included additional care in the home such as pulmonary rehabilitation, social support services, COPD education, and smoking cessation counselling. One study did not provide adequate information for classification. Nurses made the home visits in all the studies, but in 1, doctors also made visits to the patients' homes. The control group received usual care in hospital for the treatment of acute exacerbations of COPD.

The individual quality of the studies varied. Common methodological issues included not conducting analyses using intention-to-treat, lack of blinding and allocation concealment, and small sample sizes.

Results

Mortality

Six studies reported mortality from 2 to 6 months of follow-up. The pooled results showed a nonsignificant reduction in mortality in the hospital-at-home group compared with the inpatient hospital group (RR, 0.68; 95% CI, 0.41–1.12; $P = 0.13$). Subgroup analyses showed a significant reduction in mortality at 2 months of follow-up (RR, 0.32; 95% CI, 0.11–0.93; $P = 0.04$) and for the early discharge programs (RR, 0.33; 95% CI, 0.13–0.85; $P = 0.02$), but nonsignificant results for all other subgroups (3

[15] Two of the 7 RCTs reported the results for the same study and so were combined.

and 6 months of follow-up [$P = 0.91$ and $P = 0.47$, respectively], admission avoidance programs [$P = 0.63$] and high-intensity [$P = 0.71$] and low-intensity [$P = 0.26$] programs).
GRADE: very low

Hospital Readmissions
Six studies reported hospital readmissions during follow-up. The pooled results showed a nonsignificant reduction in hospital readmissions in the hospital-at-home group compared with the inpatient hospital group (RR, 0.90; 95% CI, 0.70–1.16; $P = 0.41$). Subgroup analyses showed a significant reduction at 6 months of follow-up (RR, 0.59; 95% CI, 0.40–0.87; $P = 0.009$), but no other significant differences.
GRADE: low

Two studies showed an increase in mean days to readmission in the hospital-at-home group, which was significant in 1 of the studies (29.6 days vs. 25.6 days and mean [SD] 75 [55] days vs. 37 [29] days).

Thirteen to 50% of readmissions occurred early—that is, during the time that the patient was receiving visits in the home—with a weighted mean of 24.6%. However, not all readmissions occurred due to worsening of the patients' condition.

Lung Function
Three studies reported lung function. The results could not be pooled because of different outcomes and methods of measurement. The studies that compared the mean change in FEV_1 found no significant differences between the hospital-at-home and inpatient hospital groups.
GRADE: very low

Health-Related Quality of Life
Five studies reported HRQOL results using a variety of measures, including the SGRQ, CRQ, and the Geriatric Depression Scale. Overall, no significant differences were observed between the hospital-at-home and inpatient groups, with the exception of a significant improvement in the Geriatric Depression Scale and the Nottingham Health Profile score in the hospital-at-home group compared with the inpatient group in 1 of the studies. In 4 of the 5 studies, however, HRQOL was compared between baseline and end of follow-up, rather than during the time of the hospital-at-home or inpatient care program, and it may have been more appropriate to measure HRQOL results during the actual program.
GRADE: very low

Length of Stay
Six studies reported LOS, but the results could not be pooled due to differences in measurement. Three studies reported longer LOS in the hospital-at-home group, 1 reported a shorter LOS in the hospital-at-home group, and 1 reported similar LOS. Many of the hospital-at-home programs did not visit patients every day, which may inflate the LOS in these groups.
GRADE: very low

Patient Preference
One study reported patient and caregiver preference with the care as measured during the hospital-at-home and inpatient care. Patients receiving hospital-at-home care significantly preferred hospital-at-home care to inpatient care compared with patients receiving inpatient care (96.3% of patients in the hospital-at-home group preferred hospital-at-home care vs. 59.3% of patients in the inpatient hospital group preferred hospital-at-home care; $P = 0.001$). The same trend was observed for caregivers. These results, however, do not provide information on patients' preference for hospital-at-home care before they have been enrolled in a program.
GRADE: very low

Satisfaction with Care

Three studies measured patient satisfaction with care and 1 measured caregiver satisfaction with care. Overall, satisfaction with care was very high for patients and caregivers in both hospital-at-home and inpatient care groups, and none of the studies observed a significant difference between the 2 groups.
GRADE: very low

Transfer to Long-Term Care

One study reported the number of patients who require transfer from home to long-term care after the acute exacerbation. A nonsignificant reduction in transfers to long-term care was observed in the hospital-at-home group compared with the inpatient care group (0 of 52 patients vs. 6 of 52 patients).
GRADE: very low

Eligibility for Hospital-at-Home Programs

Hospital-at-home programs are not appropriate for all patients with acute exacerbations of COPD. Eligibility criteria varied by study, but common reasons for excluding patients were absence of or poor home/social support, severe acidosis or alkalosis, severe comorbidities (e.g., cancer, dementia, renal failure, etc.), and acute chest radiograph changes. Overall, between 20.7% and 36.7% of patients who presented to EDs with acute exacerbations of COPD were enrolled in the included studies, though these estimates may underestimate the true number of eligible patients because of study-specific factors such as small geographic enrolment areas and the requirement to participate in a RCT.

Economic Model

Due to the low/very low quality of evidence and nonsignificant results, the hospital-at-home analysis was not included in the economic model.

Experiences with Hospital-at-Home Programs (Qualitative Review)

The qualitative literature search identified 24,906 citations of which 218 full-text studies were reviewed. Three studies related to early discharge or hospital-at-home programs in COPD patients. All 3 studies were conducted in primary care organizations in the United Kingdom. Several key themes emerged. First, COPD patients may often be unaware of early discharge schemes. Second, patients may be afraid of being discharged too early, whether they are part of an early discharge program or not. They may want—but nevertheless find it difficult—to negotiate the timing of their own hospital discharge. Third, transportation and medical dispensing can complicate discharge planning. Fourth, patients' feelings about being at home varies: some may be glad to be home in familiar surroundings and appreciate responsive help via the telephone, but many find it difficult to resume necessary activities at home and fear future exacerbations or being alone. Some patients appreciate nurse home visits, while others find them unnecessary. Finally, patients may be averse to seeking medical help for problems that arise after going home, for fear of bothering health care providers or being readmitted to the hospital or in the hope that a problem will resolve itself.

Conclusions

- Low quality evidence showed no significant differences in hospital readmissions between the hospital-at-home and inpatient care groups, but days to hospital readmission were increased in the hospital-at-home group compared with the inpatient care group.
- Very low quality evidence showed no significant differences in mortality, HRQOL, or patient and caregiver satisfaction with care between the hospital-at-home and inpatient care groups.
- There was insufficient evidence to determine the impact of hospital-at-home compared with inpatient care on lung function and LOS.

9. Home Telehealth

Background

Definitions for telehealth vary. For the purposes of this review, the following were used:

- *Telemedicine* (or telehealth) refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services. While telemedicine is often associated with direct patient clinical services, *telehealth* is often associated with a broader definition of remote health care and perceived to be more focused on other health-related services.
- *Telemonitoring* (or remote monitoring) refers to using medical devices to remotely collect a patient's vital signs and/or other health data and transmit those data to a monitoring station for interpretation by a health care provider.
- *Telephone-only support* refers to disease/disorder management support provided by a health care provider to a patient's residence via telephone or videoconferencing technology without transmitting patient biological data.
- *Telenursing* generally refers to the regular, in-person visit of a health care provider, typically a nurse, to a patient's residence to provide clinical care or professional education. Because of the resource requirements, telenursing is generally not feasible from a population perspective and is therefore not discussed further in this review.

In terms of telemonitoring, 2 types of devices are used: i) *upload devices* are wireless or modem-compatible devices that can measure biological information and directly upload the data either automatically or through patient assistance via landline or wireless transmission; and ii) *entry devices* are devices (either landline-based or wireless) or websites through which patients enter biological health data that was measured by a distinct measurement device. The monitoring of patient data by a health care practitioner can occur either in real time (i.e., real-time monitoring or synchronous monitoring) or can be stored and viewed at a later time (i.e., store-and-forward monitoring or asynchronous monitoring).

Because of the chronic nature of COPD and the subsequent need for continuous patient management, home telehealth technologies are increasingly being used to help outpatients maintain their independence and continue living in their own homes while ensuring their symptoms, vital signs, medication, education, and other management-related factors are monitored and/or managed and/or improved. There are 4 broad functions of home telehealth interventions for COPD:

- to monitor vital signs or biological health data (e.g., oxygen saturation);
- to monitor symptoms, medication, or other nonbiological endpoints (e.g., exercise adherence);
- to provide information (education) and/or other support services (such as reminders to exercise or positive reinforcement); and
- to establish a communication link between patient and health care provider.

These functions often require distinct technologies, although some devices can perform a number of these functions.

Research Questions

- What is the effectiveness, cost-effectiveness, and safety of home telemonitoring compared with usual care for patients with COPD?
- What is the effectiveness, cost-effectiveness, and safety of telephone-only support programs compared with usual care for patients with COPD?

Included Studies

As shown in Figure 11, of the 759 citations identified, 9 studies met the inclusion/exclusion criteria: 1 HTA, 1 systematic review, 5 RCTs, and 2 clinical controlled trials.

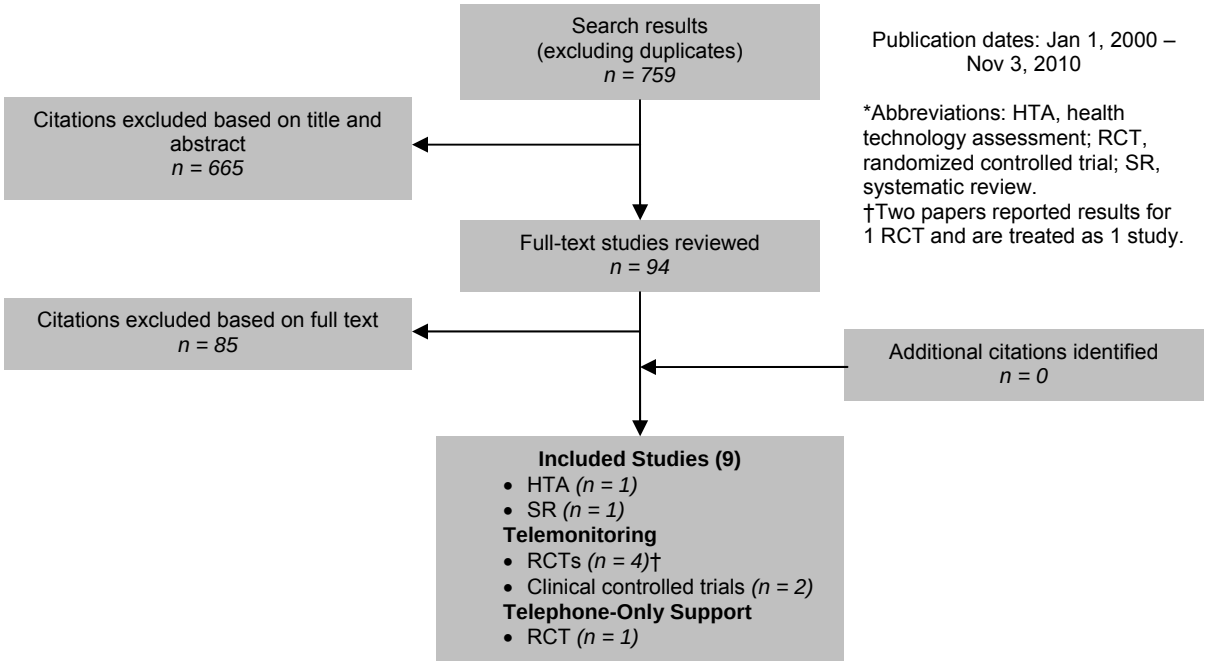


Figure 11: Telehealth for COPD Citation Flow Chart*

Results

Home Telemonitoring

The 5[16] trials (3 RCTs and 2 clinical controlled trials) included a total of 310 patients. The sample size ranged from 29 to 101 people. The mean age of the study participants ranged from 61 to 75 years. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, trials varied in terms of disease severity of COPD participants. Two trials included patients with severe or very severe COPD, 1 included patients with moderate or severe COPD, 1 included patients with severe COPD only, and 1 included patients with moderate COPD only.

In the RCTs, the patients were randomized to receive either home telemonitoring or usual care, and in the clinical controlled trials, the patients or health care centres were non-randomly assigned to home telemonitoring or usual care. Three trials initiated telemonitoring following discharge from hospital, 1 following a pulmonary rehabilitation program, and 1 during management of patients at an outpatient clinic.

The home telemonitoring intervention involved measuring biological data such as oxygen saturation (i.e., pulse oximetry), FEV_1, peak expiratory flow, and temperature. The telemonitoring devices varied: 3 of the 5 trials used an electronic health hub that performed multiple functions beyond the monitoring of biological parameters (e.g., it may have an electronic questionnaire for measuring symptoms), 1 trial used a pulse oximeter device connected to a modem, and 1 trial had patients measure and forward data to a

[16]2 of the 5 total RCTs reported results of the same parent study and so were combined.

nurse during televideo consultations. Usual care varied considerably between studies but often included follow-up care by a patient's treating physician.

There was considerable clinical heterogeneity between trials in study design, methods, and intervention/control. The individual quality of the studies varied between studies. Common methodological issues included a lack of blinding, unplanned subgroup analyses, differences in important baseline variables between intervention and control, and a potential lack of power.

Hospitalizations

All-Cause

Four studies reported hospitalizations. Since hospitalizations were defined and measured differently across the trials, the data could not be pooled. The results were inconsistent. Three studies showed a nonsignificant reduction in hospitalizations for the home telemonitoring group compared with the usual care group; 2 studies, however, showed a significant reduction in hospitalizations.[17] The study that was powered to assess hospitalizations did not find a significant difference between the 2 groups.

COPD-Specific

One trial reported COPD-specific hospitalizations. This study showed a nonsignificant reduction in hospitalizations in the home telemonitoring group compared with the usual care group (mean number of hospitalizations over 6 months: 0.20 vs. 0.35; $P = 0.16$). This study was powered to assess this outcome.
GRADE: very low (COPD-specific and all-cause hospitalizations combined)

Time Free of Hospitalizations

Two studies reported time free of hospitalizations as a secondary outcome. The results could not be pooled. The RCT showed a significant increase in time free of hospitalizations in the home telemonitoring group compared with the usual care group based on a Kaplan–Meier survival analysis adjusting for using home mechanical ventilation ($P < 0.001$). The clinical controlled trial also showed a protective benefit in the home telemonitoring group based on a multivariate Cox regression model adjusted for a number of factors including age and current smoking status (hazard ratio, 0.25; 95% CI, 0.09–0.60; $P < 0.05$).
GRADE: low

Mortality

One study evaluated mortality. The RCT showed no significant difference in mortality between the home telemonitoring group and usual care ($P = 0.148$), but no data were provided.
GRADE: low

Health-Related Quality of Life

Two studies reported the results of HRQOL. The results could not be pooled. One study showed a statistically and clinically significant improvement in mean change in total score for the SGRQ in the home telemonitoring group compared with the usual care group. While the mean change in SGRQ domain scores were also improved in the home telemonitoring group compared with usual care, these differences were not statistically significant. The second study showed no significant differences in HRQOL between the groups as measured by mean change in the total SGRQ score, hospital anxiety score, and EQ-5D. This study, however, was not powered to assess HRQOL.
GRADE: low

[17] One study reported hospitalizations in 2 ways: proportion of patients with at least 1 hospitalization and mean number of hospitalizations over 6 months follow-up. These 2 results are counted separately here.

Length of Stay
Two studies reported hospital LOS as a secondary outcome. The results could not be pooled. Neither study showed a significant difference in median days in hospital between the home telemonitoring and usual care groups.
GRADE: low

Exacerbations
Two studies reported exacerbations as a secondary outcome. The results could not be pooled. The clinical controlled trial showed no significant difference in number of exacerbations ($P > 0.05$) between the home telemonitoring and usual care groups. The RCT showed a longer time until first exacerbation in a Kaplan–Meier survival analysis adjusting for using home mechanical ventilation in the home telemonitoring group compared with the usual care group ($P < 0.001$).
GRADE: low

Emergency Department Visits
Three studies reported ED visits as a secondary outcome. The results could not be pooled. Two studies showed no difference between the home telemonitoring and usual care groups for median ED visits per patient or total ED visits. One study showed that compared with usual care, the home telemonitoring group was more likely to have a longer time until first ED visit in a Kaplan–Meier survival analysis adjusting for using home mechanical ventilation ($P < 0.001$).
GRADE: low

Patient Satisfaction
Four studies reported patient satisfaction. Overall, these studies showed that participants generally felt safer or more secure when using home telemonitoring, perceived that the intervention was beneficial, and reported being satisfied with the equipment.
GRADE: n/a[18]

Economic Model
Due to low/very low quality evidence and nonsignificant results for the model inputs, home telemonitoring was not included in the economic model.

Telephone-Only Support
A total of 60 patients were included in the 1 RCT identified for telephone-only support. The mean age of the participants was 73.6 years. Patients of all severities of COPD were enrolled in the study. Participants were recruited from the medical department of an acute-care hospital in Hong Kong. They began receiving follow-up after they had been discharge from hospital with a diagnosis of COPD. The telephone support consisted of 2 telephone calls between 10 and 20 minutes long, the first occurring between days 3 and 7 and the second between days 14 and 20. These calls were led by a nurse and involved a structured, individualized educational and supportive program that focused on 3 components: assessment, management options, and evaluation. The usual care group did not receive telephone follow-up.

Health-Related Quality of Life
The study measured HRQOL using the Chinese Self-Efficacy Scale and showed significant improvements in the overall score, as well as in the Physical Exertion and Weather or Environment domains, in the telephone-only support group compared with the usual care group. In a multiple regression model, the conditions of telephone follow-up (β, 0.33; 95% CI, 0.19–0.48; $P = 0.001$), attendance at a pulmonary rehabilitation program (β, 0.44; 95% CI, 0.6–0.72; $P = 0.003$), smoking (β, 0.34; 95% CI, 0.09–0.57; $P =$

[18] Outcomes of patient satisfaction were sparsely reported and their method of assessment varied widely, making it impossible to apply GRADE.

0.009), and health care use (β, 0.27; 95% CI, −0.07 to 0.47; $P = 0.008$) were significant factors in predicting patient self-efficacy.
GRADE: low

Hospitalizations
There was no significant difference between the telephone-only support and usual care groups when comparing mean hospitalizations per patient during the study and follow-up period ($P = 0.20$).
GRADE: low

Length of Stay
There was no significant difference in the mean LOS for hospital readmissions between the telephone-only support and usual care groups ($P = 0.40$).
GRADE: low

Emergency Department Visits
There was a significant reduction in the mean number of ED visits in the telephone-only support group compared with the usual care group (mean [SD], 0.1 [0.3] vs. 0.4 [0.7]; $P = 0.03$).
GRADE: low

Economic Model
Due to the low quality of evidence and nonsignificant results for the model inputs, telephone-only support was not included in the economic model.

Experiences Concerning Home Telehealth (Qualitative Review)

The literature search identified 24,906 citations, of which 218 full-text studies were reviewed. Eight studies related to home telehealth. Included studies were heterogeneous with regard to the study population and the type and application of telehealth technology offered to patients. Only 2 studies focused exclusively on patients with COPD; the remainder included patients with other complex chronic conditions as well as COPD. The types of technologies studied included telephone help lines, automated telephone services (for medication reminders or health-related weather warnings), videophones, and remote diagnostic monitoring. The primary focus of the qualitative review was 5 studies that examined patients' and health care providers' experiences with remote diagnostic monitoring technology. The main themes identified in these studies are summarized here.

Remote diagnostic monitoring can improve self-management, autonomy, and feelings of security for some patients, which may reduce health care visits and the burdensome process of travelling for care. Although patients may accept the technology in their homes, some patients may find the equipment difficult to use or accommodate.

Health care providers recognize potential benefits in terms of reduced need for clinical visits, better continuity of care, and enhanced collaboration between health care providers, but they also have reservations about possible negative changes to their duties and roles, with potentially new sources of legal liability if the technology interferes with optimal care.

Targeting patients for telehealth care poses challenges for both secondary prevention (population health) and equity, as current practices (i.e., setting up the technology for high-risk patients post hospital discharge) tend to miss patients at earlier disease stages, as well as those who do not speak English.

Conclusions

Home Telemonitoring

- Low quality evidence showed that the time free of exacerbations, time free of hospitalizations, and time to ED visits were significantly improved in the home telemonitoring group compared with the usual care group. However, no significant differences were observed in terms of the number of exacerbations and ED visits.
- Low to very low quality evidence showed conflicting results for HRQOL and hospitalizations, with some studies showing significant benefits in the home telemonitoring group compared with the usual care group, and other studies showing no significant differences between the 2 groups.
- Low quality evidence showed no significant differences in mortality and LOS between the home telemonitoring and usual care groups.
- There is substantial clinical heterogeneity between the trials, and since home telemonitoring is largely dependent on local information technologies, infrastructure, and personnel, the generalizability of these findings may be low.

Telephone-Only Support

- Low quality evidence showed a significant reduction in ED visits and a significant improvement in HRQOL measured by the Chinese Self-Efficacy Scale for the telephone-only support group compared with the usual care group.
- Low quality evidence showed no significant differences in hospitalizations and hospital LOS between the telephone support group and the usual care group.
- Due to concerns regarding the generalizability of these results, additional research is required.

10. Experiences of Living and Dying with COPD

Qualitative empirical studies (from social sciences and clinical and related fields) offer important insights into how many COPD patients experience their condition, their needs, and health care and interventions. Before diagnosis, patients experience the suboptimal health that clinicians might call "early COPD," but patients know as their own "normal," and not necessarily an illness. Many patients initially misunderstand terms such as *COPD*, *chronic obstructive pulmonary disease*, or *exacerbation*. Some people with COPD prefer fuller prognostic information, while others fear and avoid it. Smokers may not readily understand or agree with the idea that smoking caused or worsens their COPD. Those who believe the causal link may feel regret or shame. Some feel stigmatized by care providers who seem to blame them, and avoid health care for this reason. The diagnosis and nature of the condition come into focus over time, with personal experience and piecemeal information from various sources.

COPD patients experience alternating good days and bad days. A roller coaster pattern of ups and downs becomes apparent, and COPD becomes a way of life. Patients use many means—social, psychological, medical, organizational—to control what they can, and to cope with what they cannot. Economic hardship, comorbidities, language barriers, or low health literacy can make coping more difficult. For smokers, medical advice to quit can conflict with smoking as a tool for coping with the stress of living with COPD. A patient's sense of what is normal, as well as his/her tolerance of health problems and interventions, evolves with the progression of the disease.

Patients may not always attribute repeated exacerbations to advancing disease, but rather, as temporary setbacks caused by activities, environmental factors, faltering self-management, or infection. Although some exacerbations may create episodes of great dependency, patients may not expect a decline to total dependency over time. Dependency is challenging and disruptive, and patients often yearn for others to

"be there" for them during crises. However, informal social support and formal social services are difficult to establish around intermittent and emergent needs. Many aspects of the COPD experience—physical, pragmatic, social, and emotional—isolate patients from others while also increasing their need for social support. These same challenges can impair patients' access to, or rapport with, their health care providers.

The experience of chronic COPD challenges bodily integrity, self-confidence, and self-esteem. Many patients describe feeling powerless, helpless, hopeless, sad, frustrated, angry, anxious, or irritable. The incapacitation of COPD threatens one's very identity, and many patients grieve for their lost roles, activities, and productivity. They may seek new sources of meaning in their lives. Late in the disease, the severity, duration, or frequency of bad days leads patients to recognize a permanent decline in health. Even so, patients may still envision death from COPD to be off in the distant, unpredictable future. They hope to recover from each exacerbation, but also fear dying from suffocation or breathlessness during these crises. Palliative end-of-life care may not be anticipated prior to referral for such care. A palliative care referral can convey the demoralizing message that providers have "given up."

Family caregivers' challenges often echo COPD patients' own challenges, including anxiety, uncertainty about the future, helplessness, powerlessness, depression, difficulties maintaining employment, loss of mobility and freedoms, strained relationships, and growing social isolation. They too ride an "emotional roller coaster" over the course of the disease, with its evolving demands on care giving.

11. Preference for Ventilation among COPD Patients

Background

HTAs are increasingly considering patient values and preferences. Incorporating systematic reviews on patient preferences is one way of achieving this goal. To explore the feasibility of such an approach, we conducted a systematic review of patient preferences for ventilation among patients with COPD.

Study Objectives

- to explore and discuss the feasibility of including systematic literature reviews on patient preferences within HTAs
- to develop an appropriate search strategy for finding quantitative research on patient preferences
- to summarize the literature on patient preferences for ventilation among COPD patients
- to discuss the advantages and disadvantages of including patient preference data within HTAs

Methods

Databases were searched for studies published in English from 1990 through March 4, 2011. Two independent reviewers identified studies based on title and abstract. Full articles were retrieved if a decision could not be made based on the abstracts.

Inclusion Criteria

- study participants met criteria for COPD
- results for COPD were reported separately
- at least 1 of the study interventions included IMV and/or NPPV for the treatment of COPD
- patient preferences were reported
- the study was quantitative

- the study was not based on a quality of life indicator

Results

Preferences for IMV

The proportion of COPD patients who reported a willingness to use IMV varied considerably across studies, as estimates ranged from about 12% to 77%. Studies that used decision aids to elicit preferences or that emphasized IMV as an indefinite life support rather than as a temporary modality produced lower estimates (< 50%).

Preferences for NPPV

The proportion of COPD patients who expressed a willingness to try NPPV varied from 67% to 96%.

Satisfaction With IMV and NPPV

Two studies explored the experiences of COPD patients who had received ventilation. However, both of these had very small sample sizes (n = 9 and n = 11).

Predicting Ventilation Preferences

The results from this systematic review indicate that it is difficult to predict which COPD patients are likely to choose ventilation. Study results revealed no consistent association between patient preferences and covariates such as age, sex, education, marital status, FEV_1, depression index, or quality-of-life scores.

Patient Preferences Vary by Context

Patient preferences can vary depending on how the intervention is presented and described to the patient. One study showed how preferences for NPPV ranged from 76% to 96%, depending on whether the patient was provided with a verbal description, a photograph, or a demonstration. Another study showed how patient preferences can vary when they were asked about their choices under different hypothetical health states. Rejection of IMV was 31% for COPD patients' current health state, but ranged from 84% to 94% when they were asked about IMV under situations of permanent coma, dementia, or being bed-bound.

Conclusions

- A significant proportion of COPD patients were willing to forgo a potentially life-saving intervention, particularly when it was framed as an indefinite procedure.
- COPD patients who were willing to forgo either IMV or NPPV could not be reliably predicted by known covariates (such as age, quality of life).
- COPD patient preferences for ventilation were not stable, but varied depending on how the intervention was described. Many COPD patients also altered their preferences when asked to consider ventilation under different hypothetical health states.
- A systematic review of the patient preference literature offers many insights. However, the process is time-consuming due to the heterogeneity of study designs, outcomes measures, and terminology.

Summary of Results

Based on the results from the systematic reviews and economic model, the Ontario Health Technology Advisory Committee identified 10 treatment strategies for which there was adequate clinical/patient, health system, and cost-effectiveness evidence to make recommendations. For the remaining 8 treatment strategies, there was substantial uncertainty regarding the clinical/patient and health system outcomes due to low or very low quality of evidence. The mean ICER and the budget impact for each of these 8 strategies are unknown; the strategies were not included in the economic model due to the quality of evidence. The clinical and economic results are summarized below in Table 3.

Table 3: Summary of Findings by Topic and Research Question*

Intervention	Comparator	Study Population	No. Studies (N)	Summary Findings	GRADE Quality of Evidence
INFLUENZA VACCINATIONS					
Research Question: What is the effectiveness, safety, and cost-effectiveness of **influenza** vaccination compared with no vaccination in COPD patients?					
Influenza vaccine	Placebo	COPD patients	1 (125)	Influenza vaccination significantly reduced the risk of influenza-related ARIs compared with placebo.	HIGH
				Influenza vaccination had no significant impact on influenza-related ARI hospitalizations and the need for mechanical ventilation compared with placebo.	LOW
				Influenza vaccinations significantly increased local adverse reactions, but there was no significant difference in systemic reactions compared with placebo.	LOW
				Economic model Excluded from model as appropriate inputs were not available in the literature.	n/a
PNEUMOCOCCAL VACCINATIONS					
Research Question: What is the effectiveness, safety, and cost-effectiveness of **pneumococcal** vaccination compared with no vaccination in COPD patients?					
Pneumococcal vaccine	Placebo	COPD patients	1 (596)	Pneumococcal vaccination significantly reduced the risk of pneumococcal pneumonia compared with placebo, but there was no significant difference in incidence of global pneumonia, episodes of global pneumonia, first episode of CAP, or time to first episode of CAP between the groups.	HIGH
				Pneumococcal vaccination had no significant impact on hospitalizations due to CAP, hospital LOS, mortality, or local or systemic adverse reactions compared with placebo.	LOW
				Economic model Excluded from model as appropriate inputs were not available in the literature.	n/a
SMOKING CESSATION					
Research Question: What is the effectiveness and cost-effectiveness of smoking cessation interventions compared with usual care for patients with COPD?					
SC counselling	Usual care	COPD patients who smoke	2 (501)	Intensive SC counselling (≥ 90 minutes) significantly increased abstinences rates compared with usual care, but there was no significant difference in abstinence between the minimal counselling (< 90 minutes) and usual care groups.	MODERATE

Intervention	Comparator	Study Population	No. Studies (N)	Summary Findings	GRADE Quality of Evidence
SC counselling plus pharmacology (NRT and/or antidepressant)	Usual care	COPD patients who smoke	5 (6,802)	Intensive SC counselling (≥ 90 minutes) plus NRT significantly increased abstinences rates compared with usual care, but there was no significant difference in abstinence between the minimal counselling (< 90 minutes) plus NRT and usual care groups, the minimal counselling plus antidepressant and usual care groups, and the minimal counselling plus NRT plus antidepressant and usual care groups.	MODERATE (intensive SC counselling plus NRT) LOW (all other comparisons)
NRT	Placebo	COPD patients who smoke	1 (183)	NRT significantly increased abstinence rates compared with placebo.	MODERATE
Antidepressant	Placebo	COPD patients who smoke	2 (596)	Bupropion significantly increased abstinence rates compared with placebo; however, nortriptyline had no significant impact on abstinence compared with placebo.	MODERATE
				Economic model 1. Mean ICER: dominates (compared with usual care [or placebo where noted], the following interventions were cheaper and less costly: intensive counselling, NRT [compared with placebo], intensive counselling plus NRT, and bupropion [compared with placebo]) 2. Net Budget Impact for NRT: $10 million (Cdn)	n/a
MULTIDISCIPLINARY CARE					
Research Question: What is the effectiveness and cost-effectiveness of multidisciplinary care compared with usual care (single-care provider) for the treatment of stable COPD?					
MDC (2 or more providers)	Usual care (1 provider)	Patients with stable COPD	6 (1,370)	MDC significantly improved all-cause and COPD-specific hospitalizations and COPD-specific ED visits compared with usual care.	MODERATE
				MDC significantly improved HRQOL compared with usual care.	LOW
				MDC significantly improved lung function at 1 year compared with usual care.	VERY LOW
				MDC had no significant impact on mortality and all-cause ED visits compared with usual care.	LOW / VERY LOW
				Economic model 1. Mean ICER: $14,000 ($0–$55,000)† (Cdn) per QALY 2. Net Budget Impact: Unknown‡	n/a
PULMONARY REHABILITATION					
Research Question 1: What is the effectiveness and cost-effectiveness of pulmonary rehabilitation compared with usual care for patients with **stable** COPD?					

Intervention	Comparator	Study Population	No. Studies (N)	Summary Findings	GRADE Quality of Evidence
PR	Usual care	Patients with stable COPD	17 (1,159)	PR clinically and statistically significant improved HRQOL and functional exercise capacity (6MWT) compared with usual care.	MODERATE
				Economic model Excluded from model as appropriate inputs were not available in the literature.	n/a
Research Question 2: Does early pulmonary rehabilitation (within 1 month of hospital discharge) in **people who had an acute exacerbation of COPD** improve outcomes compared with usual (or no rehabilitation)?					
PR	Usual care	Patients within 1 month of discharge from hospital due to acute exacerbations of COPD	5 (276)	PR within 1 month of hospital discharge after an acute exacerbation of COPD significantly reduced hospital readmissions and resulted in clinically significant improvements in HRQOL and functional exercise capacity compared with usual care.	MODERATE
				Economic model 1. Mean ICER: $18,000 ($0–$56,000)† per QALY 2. Net Budget Impact: 1 time access, $17.2 million; repeat: $17.2 million	n/a
Research Question 3: Do **maintenance** or post-rehabilitation programs for people with COPD who have completed a pulmonary rehabilitation program improve outcomes compared with usual care in people with COPD?					
PR maintenance	Usual care	Patients after discharge from a pulmonary rehab program	3 (295)	PR maintenance programs had no significant impact on HRQOL, hospital admissions and LOS in the hospital compared with usual care.	LOW
				PR maintenance programs resulted in statistically significant but not clinically significant improvements in exercise capacity compared with usual care.	LOW
				Economic model Excluded from model as appropriate inputs were not available in the literature.	n/a
LONG-TERM OXYGEN THERAPY					
Research Question 1: What is the effectiveness, cost-effectiveness, and safety of LTOT compared with no LTOT in COPD patients with **severe hypoxemia**?					
LTOT (> 15 hours/day)	No LTOT therapy, usual care	COPD patients with severe hypoxemia	4 (263)	LTOT resulted in a borderline significant reduction in mortality compared with no LTOT.	LOW
				LTOT significantly improved FEV_1 and HRQOL compared with no LTOT.	LOW/VERY LOW
				LTOT resulted in increased hospitalizations§ but no difference in hospital LOS compared with no LTOT.	LOW

Intervention	Comparator	Study Population	No. Studies (N)	Summary Findings	GRADE Quality of Evidence
				Economic model 1. Mean ICER: $39,000 per QALY 2. Net Budget Impact: Funded by the MOHLTC ($65 million in fiscal year 2010)	n/a
Research Question 2: What is the effectiveness, cost-effectiveness, and safety of LTOT compared with no LTOT in COPD patients with **mild-to-moderate hypoxemia**?					
LTOT (> 15 hours/day)	No LTOT, usual care	COPD patients with mild-to-moderate hypoxemia	4 (539)	LTOT had no significant impact on mortality compared with no LTOT.	LOW
				LTOT had no significant impact on lung function (% predicted FEV_1), endurance time, or dyspnea compared with no LTOT.	VERY LOW
				Economic model Excluded from the economic model because of very low quality of evidence for model input (FEV_1).	n/a
NPPV FOR THE TREATMENT OF ACUTE RESPIRATORY FAILURE DUE TO ACUTE EXACERBATIONS OF COPD					
Research Question 1a: What is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of acute hypercapnic respiratory failure due to acute exacerbations of COPD compared with UMC?					
NPPV + UMC	UMC	COPD patients with acute respiratory failure due to AECOPD	11 (1,000)	NPPV significantly reduced the risk of endotracheal intubation and IMV, inhospital mortality, and mean hospital LOS compared with UMC.	MODERATE
				NPPV resulted in fewer complications compared with UMC.	LOW
				Economic model 1. Mean ICER: dominates (NPPV + UMC less costly and more effective than UMC alone) 2. Net Budget Impact: $42 million cost saving (hospital perspective)	n/a
Research Question 1b: What is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of acute hypercapnic respiratory failure due to acute exacerbations of COPD for patients who **failed medical treatment** compared with IMV?					
NPPV	IMV	COPD patients with acute respiratory failure who failed medical treatment‖	2 (205)	At this time, the data could not be pooled and the results were conflicting.	LOW/VERY LOW
				No conclusions can be drawn regarding the comparative effectiveness of NPPV and IMV for this patient population.	n/a
				Economic model Excluded from the economic model due to conflicting results in the clinical evidence.	n/a

Intervention	Comparator	Study Population	No. Studies (N)	Summary Findings	GRADE Quality of Evidence
Research Question 2a: What is the effectiveness, cost-effectiveness and safety of NPPV compared with IMV for **weaning COPD patients from IMV**?					
NPPV	Pressure support IMV	COPD patients being invasively ventilated who failed T-piece weaning trials	2 (80)	NPPV resulted in significant reductions in mortality, nosocomial pneumonia, and weaning failure compared with pressure support IMV.	MODERATE
				NPPV had no significant impact on LOS in the ICU and duration of mechanical ventilation compared with pressure support IMV.	LOW
				Economic model 1. Mean ICER: dominates (NPPV for weaning less costly and more effective than IMV for weaning) 2. Net Budget Impact: $12 million cost saving (hospital perspective)	n/a
Research Question 2b: What is the effectiveness, cost-effectiveness, and safety of NPPV compared with UMC for the **prevention** of acute respiratory failure in COPD patients **after they have been extubated from IMV**?					
NPPV	UMC	COPD patients after they have been extubated from IMV	0 (0)	No evidence was identified to evaluate the use of NPPV after extubation of COPD patients from IMV.	n/a
				Economic model Excluded from economic model due to lack of evidence.	n/a
Research Question 2c: What is the effectiveness, cost-effectiveness, and safety of NPPV compared with IMV for the **treatment** of acute respiratory failure in COPD patients **after they have been extubated from IMV**?					
NPPV	IMV	COPD patients who develop respiratory failure within 48 hours of extubation from IMV	1 (23)	NPPV had no significant impact on the reintubation rate based on a post hoc subgroup analysis of 23 patients with COPD.	LOW
				At this time, there is inadequate evidence to reach conclusions on the comparative effectiveness of NPPV and UMC for the treatment of COPD patients who have developed acute respiratory failure following extubation from IMV.	n/a
				Economic model Excluded from economic model due to lack of evidence.	n/a
NPPV FOR THE TREATMENT OF CHRONIC RESPIRATORY FAILURE IN STABLE COPD					
Research Question: What is the effectiveness and cost-effectiveness of NPPV compared with no ventilation while receiving usual care for stable COPD patients with **chronic respiratory failure**?					
NPPV	Usual care	Stable COPD patients with chronic respiratory failure	8 (403)	NPPV had no significant impact on mortality, lung function after 3 months, functional exercise capacity (6MWT) after 3 months, and hospitalizations compared with usual care.	MODERATE

Intervention	Comparator	Study Population	No. Studies (N)	Summary Findings	GRADE Quality of Evidence
				NPPV clinically and statistically significantly improved functional exercise capacity (6MWT) during the first 3 months of treatment and had a beneficial impact on dyspnea compared with usual care.	LOW
				Economic model Excluded from economic model due to lack of clinical effectiveness.	n/a
HOSPITAL-AT-HOME PROGRAMS FOR ACUTE EXACERBATIONS OF COPD					
Research Question: What is the effectiveness, cost-effectiveness, and safety of hospital-at-home care compared with inpatient hospital care for acute exacerbations of COPD?					
Early discharge and admission avoidance HaH programs	Inpatient hospital care	COPD patients presenting to the ED with acute exacerbations of COPD that require admission to hospital	6 (611)	HaH had no significant impact on hospital readmissions, but the days to readmission were increased in the HaH group compared with inpatient care.	LOW
				HaH had no significant impact on mortality, HRQOL, and patient/caregiver satisfaction with care compared with inpatient care.	VERY LOW
				Economic model Excluded from economic model due to low/very low quality of evidence and nonsignificant differences between groups.	n/a
HOME TELEHEALTH					
Research Question 1: What is the effectiveness, cost-effectiveness and safety of **home telemonitoring** compared with usual care for patients with COPD?					
Home telemonitoring	Usual care	COPD patients	5 (310)	Home telemonitoring significantly improved time free of exacerbations, time free of hospitalizations, and time to ED visits, but had no significant impact on number of exacerbations or ED visits.	LOW
				The impact of home telemonitoring on HRQOL and hospitalizations could not be determined due to conflicting results in the literature.	LOW/VERY LOW
				Home telemonitoring had no significant impact on mortality and LOS compared with usual care.	LOW
				Economic model Excluded from economic model due to very low quality of evidence for the model inputs and inability to pool data for hospitalizations.	n/a
Research Question 2: What is the effectiveness, cost-effectiveness, and safety of **telephone-only support** programs compared with usual care for patients with COPD?					
Telephone-only support	Usual care	COPD patients	1 (60)	Telephone-only support significantly reduced ED visits and significantly improved HRQOL measured by the Chinese Self-Efficacy Scale compared with usual care.	LOW

Intervention	Comparator	Study Population	No. Studies (N)	Summary Findings	GRADE Quality of Evidence
				Telephone-only support had no significant impact on hospitalizations and hospital LOS compared with usual care.	LOW
				Economic model Excluded from economic model due to the low quality of evidence and nonsignificant difference between groups.	n/a

*Abbreviations: 6MWT, 6 minute walking test; AECOPD, acute exacerbation of COPD; ARI, acute respiratory illness; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; ED, emergency department; FEV_1, forced expiratory volume in 1 second; HaH, hospital-at-home; HRQOL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS; length of stay; LTOT, long-term oxygen therapy; MDC, multidisciplinary care; NPPV, noninvasive positive pressure ventilation; NRT, nicotine replacement therapy; PaO_2, partial pressure of oxygen (in arterial blood); PR, pulmonary rehabilitation; SC, smoking cessation; UMC, usual medical care.

†Ranges reflect the results of the one-way sensitivity analysis that was performed for multidisciplinary care and pulmonary rehabilitation.

‡Based on the most recent FHT data, the costs of MDC programs to manage COPD were estimated at $85 million in FY 2010, with projected future expenditures of up to $51 million for incident cases, assuming the base case cost of program. However, this estimate does not accurately reflect the current costs to the province because of lack of report by FHTs, lack of capture of programs outside this model of care by any data set in the province, and because the resource utilization and frequency of visits/follow-up phone calls were based on the findings in the literature rather than the actual FHT COPD management programs in place in Ontario. Therefore, MDC resources being utilized in the province are unknown and difficult to measure.

§In this study, patients in the LTOT arm had severe COPD, while patients in the no LTOT comparison arm had mild/moderate COPD.

‖While it was clear in 1 study that the patients had first failed usual medical care, this was not clear in the second study although it has been assumed.

Ontario Health Technology Advisory Committee Recommendations

Based on the clinical and economic evidence summarized above, using the Ontario Health Technology Advisory Committee Decision Determinants (1), the Ontario Health Technology Advisory Committee made the following recommendations:

1. The Ontario Health Technology Advisory Committee (OHTAC) recommends that any provincial strategy on chronic obstructive pulmonary disease (COPD) address gaps in patient and public knowledge about this disease and its causes, management, and course. Effective interventions for improving lay understanding of COPD should be identified.*

   *In implementing this recommendation, Health Quality Ontario should communicate regarding the inadequate public recognition of this disease with Public Health Ontario, which is working with Cancer Care Ontario on a blueprint for management of the burden of chronic disease in the province. The under-recognition of COPD extends to health professionals, and this should be communicated to relevant training bodies.

Recommendations Regarding Secondary Prevention

2. OHTAC recommends maximizing the use of pneumococcal and influenza vaccines in patients with COPD, ensuring that vaccination reflects the established guidelines and recommendations for immunization.

   OHTAC recommends that any barriers to making the pneumococcal vaccine easily available through physician offices be removed, thereby making the pneumococcal vaccine more accessible to patients.

   Other opportunities to optimize access to influenza and pneumococcal vaccines, including patients with acute exacerbations of COPD admitted to hospital, should be explored.

3. OHTAC strongly endorses evidence-based strategies aimed at encouraging smoking cessation in patients with COPD.

   Intensive counselling (≥90 minutes) is the most effective and cost-effective strategy, and should continue to be encouraged.

   OHTAC recommends that consideration be made to providing training programs to health care professionals involved in providing intensive counselling.

   OHTAC recommends bupropion or nicotine replacement therapies for smoking cessation.

Recommendations Regarding Stable COPD

4. OHTAC recommends ongoing access to existing community-based multidisciplinary care for the management of moderate to severe stable COPD.

5. OHTAC recommends ongoing access to existing pulmonary rehabilitation for the management of moderate to severe COPD in stable patients.

6. OHTAC recommends that long-term oxygen therapy continue to be provided to COPD patients with severe resting hypoxemia (≤ 55 mmHg).

7. OHTAC does not recommend the use of noninvasive positive pressure ventilation (NPPV) for chronic respiratory failure in stable COPD patients due to its lack of clinical effectiveness.

Recommendations Regarding Acute Exacerbations of COPD

8. OHTAC recommends the use of pulmonary rehabilitation in patients following an acute exacerbation (within 1 month of hospital discharge).

9. OHTAC recommends the use of NPPV as an adjunct to usual medical care as a first-line treatment for patients with acute respiratory failure due to acute exacerbations of COPD who do not require immediate access to invasive mechanical ventilation (IMV). NPPV should be made widely available, with appropriate support systems and human resources for this indication.

10. OHTAC recommends the use of NPPV to wean COPD patients who have failed spontaneous breathing tests following IMV.

11. OHTAC recommends that patient preferences regarding mechanical ventilation be sought prior to acute respiratory decompensation, and should serve as a guide for the provision of this service.

Recommendations Regarding Palliative Care for COPD

12. In making palliative care services available, the fluctuating physical, psychosocial, spiritual, and information needs should be considered, without necessarily forgoing acute care or hope of improvement during and following severe exacerbations.

Recommendations Regarding Opportunities for Further Research

There was insufficient evidence for OHTAC to make recommendations on the following COPD treatment strategies:

- hospital-at-home for the treatment of acute exacerbations
- pulmonary rehabilitation maintenance programs
- home telemonitoring
- telephone-only support
- NPPV versus IMV for the treatment of acute respiratory failure in patients who have failed medical treatment
- NPPV for recurrent respiratory failure (postextubation)
- long-term oxygen therapy for mildto-moderate hypoxemia

13. Due to substantial uncertainty arising from low/very low quality evidence of effectiveness and cost-effectiveness, but the potential for important health system and/or patient/clinical benefits, OHTAC recommends field evaluations for:
    - pulmonary rehabilitation maintenance programs
    - telemonitoring

As regards telemonitoring, OHTAC recommends that an evaluation of the proposed Ministry Telehomecare Expansion Project in partnership with Infoway, the Ontario Telemedicine Network, and the Local Health Integration Networks, which will encompass monitoring of patients with COPD, be undertaken and reported back to OHTAC upon completion.

Prior to expanding access to multidisciplinary care and pulmonary rehabilitation, OHTAC recommends field evaluation to evaluate long-term impacts of effectiveness and cost-effectiveness, optimal delivery of programs, characterization of patients most likely to benefit from these programs, and a survey of existing services.

14. Any primary research endorsed by OHTAC will include outcomes relevant to patient needs and perspectives, including patient preference, if applicable.

Implementation Considerations

In order to optimize the translation of the above recommendations into practice and to ensure high quality care, the formation of a provincial COPD Expert Panel to advise the health system and the Ministry of Health and Long-Term Care through Health Quality Ontario should be considered. This Expert Panel, representing patient and provider interests, should also inform OHTAC in an ongoing way of additional evidentiary requirements to further shape the COPD strategy.

Furthermore, opportunities to align these OHTAC recommendations to current funding strategies should be sought.

Feedback through public engagement expressed interest in pursuing other components of LTOT (oxygen assessment clinics, ambulatory oxygen therapy, and personal oximeters), OHTAC has reflected on this and regards these topics as out of scope of the existing overall mega-analysis on COPD, but these comments have been forwarded to the Assistive Devices Program (ADP). Similarly, through public engagement, OHTAC was made aware of the fact that there is a wide gap between the true costs of LTOT and the current funding level through ADP. This has also been forwarded to ADP.

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbation of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity	The amount of air that can be forcibly exhaled from the lungs after taking

(FVC)	the deepest breath possible.
Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.
Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[19]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.

[19] The mild-to-moderate classification was created for the purposes of the report.

Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.
Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.
Quality-adjusted life-year (QALY)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Editorial Staff

Jan Collins
Joanna Odrowaz
Jeanne McKane

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

Experiences of Living and Dying with COPD Report

This study was funded by the Canadian Institutes of Health Research, Grant # TOO-105430. Deirdre DeJean and Andrea Smith were supported by CIHR Frederick Banting and Charles Best Canada Graduate Scholarships (CGS) Doctoral Awards. We thank the Ontario Ministry of Health and Long-Term Care for its support for the Centre for Health Economics and Policy Analysis (CHEPA) at McMaster University, whose collegial environment made this project possible.

Appendices

Appendix 1: Scoping Search Strategies

Database: Ovid MEDLINE(R) <1996 to June Week 2 2010>
Search Strategy:
---
1 exp Pulmonary Disease, Chronic Obstructive/ (13437)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (14383)
3 (copd or coad).ti,ab. (12702)
4 chronic airflow obstruction.ti,ab. (110)
5 exp Emphysema/ (2872)
6 ((chronic adj2 bronchitis) or emphysema).ti,ab. (8319)
7 or/1-6 (29151)

Database: EMBASE <1980 to 2010 Week 23>
Search Strategy:
---
1 exp chronic obstructive lung disease/ (35645)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (19275)
3 (copd or coad).ti,ab. (15657)
4 chronic airflow obstruction.ti,ab. (453)
5 exp emphysema/ (14476)
6 exp chronic bronchitis/ (6184)
7 ((chronic adj2 bronchitis) or emphysema).ti,ab. (14524)
8 or/1-7 (58190)

References

(1) Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [Internet]. [place unknown]: Global Initiative for Chronic Obstructive Lung Disease, Inc.; 2010 [cited: 2011 Jul 6]. 97 p. Available from: http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf

(2) O'Donnell DE, Hernandez P, Kaplan A, Aaron S, Bourbeau J, Marciniuk D, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease — 2008 update — highlights for primary care. Can Respir J. 2008 Jan;15 Suppl A:1A-8A.

(3) Niewoehner DE. Clinical practice. Outpatient management of severe COPD. N Engl J Med. 2010 Apr 15;362(15):1407-16.

(4) Donaldson GC, Wedzicha JA. COPD exacerbations.1: Epidemiology. Thorax. 2006 Feb;61(2):164-8.

(5) Hurst JR, Donaldson GC, Quint JK, Goldring JJ, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009 Mar 1;179(5):369-74.

(6) Chapman KR, Bourbeau J, Rance L. The burden of COPD in Canada: results from the Confronting COPD survey. Respir Med. 2003 Mar;97 Suppl C:S23-S31.

(7) Public Health Agency of Canada. COPD [Internet]. [Ottawa (ON)]: Public Health Agency of Canada; [updated 2007 Nov 22; cited 2011 Jun 21]. Available from: http://www.phac-aspc.gc.ca/publicat/2007/lbrdc-vsmrc/copd-mpoc-eng.php

(8) Gershon AS, Wang C, Wilton AS, Raut R, To T. Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in Ontario, Canada, 1996 to 2007: a population-based study. Arch Intern Med. 2010 Mar 22;170(6):560-5.

(9) Institute for Clinical Evaluative Sciences. Prevalence rate of chronic obstructive pulmonary disease (COPD) [Internet]. Toronto (ON): Institute for Clinical Evaluative Sciences; [updated 2011; cited 2011 Jun 12]. Available from: http://intool.ices.on.ca/Default.aspx

(10) Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007 Sep 1;370(9589):765-73.

(11) Devereux G. ABC of chronic obstructive pulmonary disease. Definition, epidemiology, and risk factors. BMJ. 2006 May 13;332(7550):1142-4.

(12) National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care [Internet]. London (U.K.): National Clinical Guideline Centre; 2010 [cited: 2011 Jun 6]. 673 p. Available from: http://www.nice.org.uk/nicemedia/live/13029/49425/49425.pdf

(13) Editorial Board for Respiratory Disease in Canada. Respiratory disease in Canada [Internet]. [Ottawa (ON)]: Health Canada; 2001 [cited: 2011 Jun 12]. 118 p. Available from: http://www.phac-aspc.gc.ca/publicat/rdc-mrc01/pdf/rdc0901e.pdf

(14) Statistics Canada. Leading causes of death [Internet]. Ottawa (ON): Statistics Canada; [updated 2007; cited 2011 Jul 7]. Available from: http://www.statcan.gc.ca/daily-quotidien/101130/dq101130b-eng.htm

(15) Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet. 1997 May 24;349(9064):1498-504.

(16) Marciniuk DD, Goodridge D, Hernandez P, Rocker G, Balter M, Bailey P, et al. Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline. Can Respir J. 2011 Mar;18(2):69-78.

(17) Medical Advisory Secretariat. Population-based smoking cessation strategies: a summary of a select group of evidence-based reviews. Ont Health Technol Assess Ser [Internet]. 2010 Jan; 10(1): 1-44. [cited: 2011 Jun 12]. Available from: http://www.hqontario.ca/en/mas/mas_ohtas_tech_smoking_20100120.html.

(18) Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007 Sep 1;370(9589):741-50.

(19) Hill K, Goldstein RS, Guyatt GH, Blouin M, Tan WC, Davis LL, et al. Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. CMAJ. 2010;182(7):673-8.

(20) Lin K, Watkins B, Johnson T, Rodriguez JA, Barton MB. Screening for chronic obstructive pulmonary disease using spirometry: summary of the evidence for the U.S. Preventative Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality; 2008 [cited: 2011 Jun 12]. Report No. 59. Available from: http://www.uspreventiveservicestaskforce.org/uspstf08/copd/copdes.pdf

(21) U.S.Preventative Services Task Force. Screening for chronic obstructive pulmonary disease using spirometry: recommendation statement [Internet]. [updated 2008; cited 2011 Jun 22]. Available from: http://www.uspreventiveservicestaskforce.org/uspstf08/copd/copdrs.htm

(22) Meyers BF, Patterson GA. Chronic obstructive pulmonary disease. 10: Bullectomy, lung volume reduction surgery, and transplantation for patients with chronic obstructive pulmonary disease. Thorax. 2003 Jul;58(7):634-8.

(23) Tiong LU, Gibson PG, Hensley MJ, Hepworth R, Lasserson TJ, Smith B, Davies HRHR. Lung volume reduction surgery for diffuse emphysema. Cochrane Database Syst Rev 2006, Issue 4. Art. No.: CD001001. DOI: 10.1002/14651858.CD001001.pub2.

(24) Benditt JO. Surgical options for patients with COPD: sorting out the choices. Respir Care. 2006 Feb;51(2):173-82.

(25) Snider GL. Reduction pneumoplasty for giant bullous emphysema. Implications for surgical treatment of nonbullous emphysema. Chest. 1996 Feb;109(2):540-8.

(26) Patel N, Criner GJ. Transplantation in chronic obstructive pulmonary disease. COPD. 2006 Aug;3(3):149-62.

(27) Martinez FJ, Chang A. Surgical therapy for chronic obstructive pulmonary disease. Semin Respir Crit Care Med. 2005 Apr;26(2):167-91.

(28) Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen (DK): The Nordic Cochrane Centre, The Cochrane Collaboration; 2011.

(29) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490.

(30) Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005 Feb 15;142(4):233-9.

(31) Puhan MA, Gimeno-Santos E, Scharplatz M, Troosters T, Walters EH, Steurer J. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2011, Issue 10. Art. No.: CD005305. DOI: 10.1002/14651858.CD005305.pub3.

(32) Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schunemann HJ. Interpretation of treatment changes in 6-minute walk distance in patients with COPD. Eur Respir J. 2008;32(3):637-43.

(33) Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. Arch Phys Med Rehabil. 2010 Feb;91(2):221-5.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-7018-3 (PDF)

Ontario
Health Quality Ontario
Qualité des services
de santé Ontario

Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Review

S Sehatzadeh

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 3, pp. 1–64, March 2012

Suggested Citation

This report should be cited as follows:

Sehatzadeh S. Influenza and pneumococcal vaccinations for patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2012 Mar; 12(3) 1-64. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Vaccinations_March.pdf.

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to: MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit:
http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the *Ontario* Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ARI	Acute respiratory illness
CAP	Community-acquired pneumonia
CI	Confidence interval(s)
CDC	Centers for Disease Control and Prevention
CIRID	Centre for Immunization and Respiratory Infectious Diseases
COPD	Chronic obstructive pulmonary disease
FEV_1	Forced expiratory volume in 1 second
H	Hemagglutinin
HI	Hemagglutination inhibition
HR	Hazard Ratio
MAS	Medical Advisory Secretariat
N	Neuraminidase
OR	Odds Ratio
PHAC	Public Health Agency of Canada
PPSV	Pneumococcal polysaccharide vaccine
RCT	Randomized controlled trial
RR	Relative risk
WHO	World Health Organization

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective

The objective of this analysis was to determine the effectiveness of the influenza vaccination and the pneumococcal vaccination in patients with chronic obstructive pulmonary disease (COPD) in reducing the incidence of influenza-related illness or pneumococcal pneumonia.

Clinical Need: Condition and Target Population

Influenza Disease

Influenza is a global threat. It is believed that the risk of a pandemic of influenza still exists. Three pandemics occurred in the 20th century which resulted in millions of deaths worldwide. The fourth pandemic of H1N1 influenza occurred in 2009 and affected countries in all continents.

Rates of serious illness due to influenza viruses are high among older people and patients with chronic conditions such as COPD. The influenza viruses spread from person to person through sneezing and coughing. Infected persons can transfer the virus even a day before their symptoms start. The incubation period is 1 to 4 days with a mean of 2 days. Symptoms of influenza infection include fever, shivering, dry cough, headache, runny or stuffy nose, muscle ache, and sore throat. Other symptoms such as nausea, vomiting, and diarrhea can occur.

Complications of influenza infection include viral pneumonia, secondary bacterial pneumonia, and other secondary bacterial infections such as bronchitis, sinusitis, and otitis media. In viral pneumonia, patients develop acute fever and dyspnea, and may further show signs and symptoms of hypoxia. The organisms involved in bacterial pneumonia are commonly identified as *Staphylococcus aureus* and *Hemophilus influenza*. The incidence of secondary bacterial pneumonia is most common in the elderly and those with underlying conditions such as congestive heart disease and chronic bronchitis.

Healthy people usually recover within one week but in very young or very old people and those with underlying medical conditions such as COPD, heart disease, diabetes, and cancer, influenza is associated with higher risks and may lead to hospitalization and in some cases death. The cause of hospitalization or death in many cases is viral pneumonia or secondary bacterial pneumonia. Influenza infection can lead to the exacerbation of COPD or an underlying heart disease.

Streptococcal Pneumonia

Streptococcus pneumoniae, also known as pneumococcus, is an encapsulated Gram-positive bacterium that often colonizes in the nasopharynx of healthy children and adults. Pneumococcus can be transmitted from person to person during close contact. The bacteria can cause illnesses such as otitis media and sinusitis, and may become more aggressive and affect other areas of the body such as the lungs, brain, joints, and blood stream. More severe infections caused by pneumococcus are pneumonia, bacterial sepsis, meningitis, peritonitis, arthritis, osteomyelitis, and in rare cases, endocarditis and pericarditis.

People with impaired immune systems are susceptible to pneumococcal infection. Young children, elderly people, patients with underlying medical conditions including chronic lung or heart disease, human immunodeficiency virus (HIV) infection, sickle cell disease, and people who have undergone a splenectomy are at a higher risk for acquiring pneumococcal pneumonia.

Technology

Influenza and Pneumococcal Vaccines

Trivalent Influenza Vaccines in Canada

In Canada, 5 trivalent influenza vaccines are currently authorized for use by injection. Four of these are formulated for intramuscular use and the fifth product (Intanza®) is formulated for intradermal use.

The 4 vaccines for intramuscular use are:

- Fluviral (GlaxoSmithKline), split virus, inactivated vaccine, for use in adults and children ≥ 6 months;
- Vaxigrip (Sanofi Pasteur), split virus inactivated vaccine, for use in adults and children ≥ 6 months;
- Agriflu (Novartis), surface antigen inactivated vaccine, for use in adults and children ≥ 6 months; and
- Influvac (Abbott), surface antigen inactivated vaccine, for use in persons ≥ 18 years of age.

FluMist is a live attenuated virus in the form of an intranasal spray for persons aged 2 to 59 years. Immunization with current available influenza vaccines is not recommended for infants less than 6 months of age.

Pneumococcal Vaccine

Pneumococcal polysaccharide vaccines were developed more than 50 years ago and have progressed from 2-valent vaccines to the current 23-valent vaccines to prevent diseases caused by 23 of the most common serotypes of *S pneumoniae*. Canada-wide estimates suggest that approximately 90% of cases of pneumococcal bacteremia and meningitis are caused by these 23 serotypes. Health Canada has issued licenses for 2 types of 23-valent vaccines to be injected intramuscularly or subcutaneously:

- Pneumovax 23® (Merck & Co Inc. Whitehouse Station, NJ, USA), and
- Pneumo 23® (Sanofi Pasteur SA, Lion, France) for persons 2 years of age and older.

Other types of pneumococcal vaccines licensed in Canada are for pediatric use. Pneumococcal polysaccharide vaccine is injected only once. A second dose is applied only in some conditions.

Research Questions

1. What is the effectiveness of the influenza vaccination and the pneumococcal vaccination compared with no vaccination in COPD patients?
2. What is the safety of these 2 vaccines in COPD patients?
3. What is the budget impact and cost-effectiveness of these 2 vaccines in COPD patients?

Research Methods

Literature Search

Search Strategy

A literature search was performed on July 5, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment

(INAHTA) for studies published from January 1, 2000 to July 5, 2010. The search was updated monthly through the AutoAlert function of the search up to January 31, 2011. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established. Data extraction was carried out by the author.

Inclusion Criteria

- studies comparing clinical efficacy of the influenza vaccine or the pneumococcal vaccine with no vaccine or placebo;
- randomized controlled trials published between January 1, 2000 and January 31, 2011;
- studies including patients with COPD only;
- studies investigating the efficacy of types of vaccines approved by Health Canada;
- English language studies.

Exclusion Criteria

- non–randomized controlled trials;
- studies investigating vaccines for other diseases;
- studies comparing different variations of vaccines;
- studies in which patients received 2 or more types of vaccines;
- studies comparing different routes of administering vaccines;
- studies not reporting clinical efficacy of the vaccine or reporting immune response only;
- studies investigating the efficacy of vaccines not approved by Health Canada.

Outcomes of Interest

Primary Outcomes

Influenza vaccination: Episodes of acute respiratory illness due to the influenza virus.

Pneumococcal vaccination: Time to the first episode of community-acquired pneumonia either due to pneumococcus or of unknown etiology.

Secondary Outcomes

- rate of hospitalization and mechanical ventilation
- mortality rate
- adverse events

Quality of Evidence

The quality of each included study was assessed taking into consideration allocation concealment, randomization, blinding, power/sample size, withdrawals/dropouts, and intention-to-treat analyses. The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. The following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Summary of Efficacy of the Influenza Vaccination in Immunocompetent Patients With COPD

Clinical Effectiveness

The influenza vaccination was associated with significantly fewer episodes of influenza-related acute respiratory illness (ARI). The incidence density of influenza-related ARI was:

- All patients: vaccine group: (total of 4 cases) = 6.8 episodes per 100 person-years; placebo group: (total of 17 cases) = 28.1 episodes per 100 person-years, (relative risk [RR], 0.2; 95% confidence interval [CI], 0.06–0.70; $P = 0.005$).

- Patients with severe airflow obstruction (forced expiratory volume in 1 second [FEV_1] < 50% predicted): vaccine group: (total of 1 case) = 4.6 episodes per 100 person-years; placebo group: (total of 7 cases) = 31.2 episodes per 100 person-years, (RR, 0.1; 95% CI, 0.003–1.1; $P = 0.04$).

- Patients with moderate airflow obstruction (FEV_1 50%–69% predicted): vaccine group: (total of 2 cases) = 13.2 episodes per 100 person-years; placebo group: (total of 4 cases) = 23.8 episodes per 100 person-years, (RR, 0.5; 95% CI, 0.05–3.8; $P = 0.5$).

- Patients with mild airflow obstruction ($FEV_1 \geq 70\%$ predicted): vaccine group: (total of 1 case) = 4.5 episodes per 100 person-years; placebo group: (total of 6 cases) = 28.2 episodes per 100 person-years, (RR, 0.2; 95% CI, 0.003–1.3; $P = 0.06$).

The Kaplan-Meier survival analysis showed a significant difference between the vaccinated group and the placebo group regarding the probability of not acquiring influenza-related ARI (log-rank test *P* value = 0.003). Overall, the vaccine effectiveness was 76%. For categories of mild, moderate, or severe COPD the vaccine effectiveness was 84%, 45%, and 85% respectively.

With respect to hospitalization, fewer patients in the vaccine group compared with the placebo group were hospitalized due to influenza-related ARIs, although these differences were not statistically significant. The incidence density of influenza-related ARIs that required hospitalization was 3.4 episodes per 100 person-years in the vaccine group and 8.3 episodes per 100 person-years in the placebo group (RR, 0.4; 95% CI, 0.04–2.5; $P = 0.3$; log-rank test *P* value = 0.2). Also, no statistically significant differences between the 2 groups were observed for the 3 categories of severity of COPD.

Fewer patients in the vaccine group compared with the placebo group required mechanical ventilation due to influenza-related ARIs. However, these differences were not statistically significant. The incidence density of influenza-related ARIs that required mechanical ventilation was 0 episodes per 100 person-years in the vaccine group and 5 episodes per 100 person-years in the placebo group (RR, 0.0; 95% CI, 0–2.5; $P = 0.1$; log-rank test *P* value = 0.4). In addition, no statistically significant differences between the 2 groups were observed for the 3 categories of severity of COPD. The effectiveness of the influenza vaccine in preventing influenza-related ARIs and influenza-related hospitalization was not related to age, sex, severity of COPD, smoking status, or comorbid diseases.

Safety

Overall, significantly more patients in the vaccine group than the placebo group experienced local adverse reactions (vaccine: 17 [27%], placebo: 4 [6%]; $P = 0.002$). Significantly more patients in the vaccine group than the placebo group experienced swelling (vaccine 4, placebo 0; $P = 0.04$) and itching (vaccine 4, placebo 0; $P = 0.04$). Systemic reactions included headache, myalgia, fever, and skin rash and there were no significant differences between the 2 groups for these reactions (vaccine: 47 [76%], placebo: 51 [81%], $P = 0.5$).

With respect to lung function, dyspneic symptoms, and exercise capacity, there were no significant differences between the 2 groups at 1 week and at 4 weeks in: FEV_1, maximum inspiratory pressure at residual volume, oxygen saturation level of arterial blood, visual analogue scale for dyspneic symptoms, and the 6 Minute Walking Test for exercise capacity.

There was no significant difference between the 2 groups with regard to the probability of not acquiring total ARIs (influenza-related and/or non-influenza-related); (log-rank test P value = 0.6).

Summary of Efficacy of the Pneumococcal Vaccination in Immunocompetent Patients With COPD

Clinical Effectiveness

The Kaplan-Meier survival analysis showed no significant differences between the group receiving the penumoccocal vaccination and the control group for time to the first episode of community-acquired pneumonia due to pneumococcus or of unknown etiology (log-rank test 1.15; $P = 0.28$). Overall, vaccine efficacy was 24% (95% CI, −24 to 54; $P = 0.33$).

With respect to the incidence of pneumococcal pneumonia, the Kaplan-Meier survival analysis showed a significant difference between the 2 groups (vaccine: 0/298; control: 5/298; log-rank test 5.03; $P = 0.03$).

Hospital admission rates and median length of hospital stays were lower in the vaccine group, but the difference was not statistically significant. The mortality rate was not different between the 2 groups.

Subgroup Analysis

The Kaplan-Meier survival analysis showed significant differences between the vaccine and control groups for pneumonia due to pneumococcus and pneumonia of unknown etiology, and when data were analyzed according to subgroups of patients (age < 65 years, and severe airflow obstruction $FEV_1 < 40\%$ predicted). The accumulated percentage of patients without pneumonia (due to pneumococcus and of unknown etiology) across time was significantly lower in the vaccine group than in the control group in patients younger than 65 years of age (log-rank test 6.68; $P = 0.0097$) and patients with a FEV_1 less than 40% predicted (log-rank test 3.85; $P = 0.0498$).

Vaccine effectiveness was 76% (95% CI, 20–93; $P = 0.01$) for patients who were less than 65 years of age and −14% (95% CI, −107 to 38; $P = 0.8$) for those who were 65 years of age or older. Vaccine effectiveness for patients with a FEV_1 less than 40% predicted and FEV_1 greater than or equal to 40% predicted was 48% (95% CI, −7 to 80; $P = 0.08$) and −11% (95% CI, −132 to 47; $P = 0.95$), respectively. For patients who were less than 65 years of age ($FEV_1 < 40\%$ predicted), vaccine effectiveness was 91% (95% CI, 35– 99; $P = 0.002$).

Cox modelling showed that the effectiveness of the vaccine was dependent on the age of the patient. The vaccine was not effective in patients 65 years of age or older (hazard ratio, 1.53; 95% CI, 0.61–2.17; $P =$

0.66) but it reduced the risk of acquiring pneumonia by 80% in patients less than 65 years of age (hazard ratio, 0.19; 95% CI, 0.06–0.66; $P = 0.01$).

Safety

No patients reported any local or systemic adverse reactions to the vaccine.

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this analysis was to determine the effectiveness of the influenza vaccination and the pneumococcal vaccination in patients with COPD in reducing the incidence of influenza-related illness or pneumococcal pneumonia.

Clinical Need and Target Population

Influenza Disease

Influenza is a global threat. It is believed that the risk of a pandemic of influenza still exists. Three pandemics occurred in the 20th century which resulted in millions of deaths worldwide. (1) The fourth pandemic of H1N1 influenza occurred in 2009 and affected countries on all continents.

Rates of serious illness due to influenza viruses are high among older people and patients with chronic conditions such as COPD. (2) The influenza viruses spread from person to person through sneezing and coughing. Infected persons can transfer the virus even a day before their symptoms start. (3) The incubation period is 1 to 4 days with a mean length of 2 days. (1) Symptoms of influenza infection include fever, shivering, dry cough, headache, runny or stuffy nose, muscle ache, and sore throat. Other symptoms such as nausea, vomiting, and diarrhea can occur.

Complications of influenza infection include viral pneumonia, secondary bacterial pneumonia, and other secondary bacterial infections such as bronchitis, sinusitis, and otitis media. In viral pneumonia, patients develop an acute fever and dyspnea, and may further show signs and symptoms of hypoxia. The organisms involved in bacterial pneumonia are commonly *Staphylococcus aureus* and *Hemophilus influenza*. The incidence of secondary bacterial pneumonia is most common in the elderly and those with underlying conditions such as congestive heart disease and chronic bronchitis. (4)

Healthy people usually recover within one week, but in very young or very old people and those with underlying medical conditions such as COPD, heart disease, diabetes, and cancer, influenza is associated with higher risks and may lead to hospitalization and in some cases death. The cause of hospitalization or death in many cases is viral pneumonia or secondary bacterial pneumonia. (3) Influenza infection can lead to the exacerbation of COPD or an underlying heart disease. (2)

Strains of Influenza Virus

Influenza viruses exist in 3 forms: A, B, and C. Influenza A is generally responsible for epidemics and pandemics while influenza B generally causes milder and less severe outbreaks in smaller communities such as schools or camps. (1) Virus strains are characterized by different hemagglutinin (H) and neuraminidase (N) subclasses. Sixteen H subtypes (H1 to H16) and 9 N subtypes (N1 to N9) have been identified for influenza A viruses. Major shifts in the antigenic profiles of the viruses can cause epidemics. However, minor antigenic shifts can cause less severe outbreaks.

Influenza Ecology

Influenza A viruses are primarily viruses of water-based birds (5) which are natural reservoirs for a variety of H and N combinations. Influenza A viruses infect a wide range of species such as humans, pigs, wild birds, domestic poultry, domestic cats, civets, tigers, seals, aquatic mammals, and horses. (4) Influenza B and C are viruses that affect humans, with only a few reports of sporadic infections in mammalian hosts such as seals, pigs, and dogs. (4;5)

Avian influenza in birds is usually mild or asymptomatic and the virus can be secreted in high titres through the cloacae for a period of up to 30 days. The practice of free-ranging poultry close to the family dwelling facilitates the transfer of the virus to a human.

Influenza Diagnosis

Infection by the influenza virus results in a rise in the serum antibody titre. Demonstration of fourfold or greater rise in the hemagglutination inhibition (HI) antibody titre in the convalescent serum as compared with the acute serum is considered as diagnostic of the infection. (4)

Influenza Vaccination

Influenza vaccination is the primary method of influenza prevention and has been available for about 70 years. (3) It has been shown that during 10 seasons, influenza vaccination significantly reduced the risk of hospitalization for pneumonia or influenza, and the risk of death among community-dwelling elderly persons. Nichol et al (6) have shown that in people with chronic lung diseases, vaccination resulted in a 52% reduction in hospitalizations and a 70% reduction in death rates during influenza seasons. In this study, hospitalization rates for pneumonia and influenza among unvaccinated people were twice as high in the influenza seasons as they were in the interim (non-influenza) periods. During the influenza seasons, those who received the vaccine had fewer hospitalizations for pneumonia and influenza compared with those who were not vaccinated (adjusted risk ratio [RR], 0.48; 95% confidence interval [CI], 0.28–0.82), and they had lower risk for death (adjusted odds ratio [OR], 0.30; 95% CI, 0.21–0.43).

Several studies have shown that antibody response decreases in the elderly compared with young people following subsequent vaccinations. Gardner et al (7) studied antibody responses to annual influenza vaccination over 4 years in a healthy elderly population. In the first year following vaccination, 32% of the persons produced a fourfold rise in antibody titre to any vaccine component included in the vaccine. However, this percentage decreased after subsequent vaccinations with the same component (10% following the second and the third vaccination, 12% following the fourth vaccination, and 6% following the fifth vaccination). However, in any given year, the percentage of people with post vaccination titres greater than or equal to 40 to A/Texas was not less than 50% (first year 84%, second year 50%, third year 84%, fourth year 82%, and fifth year 76%).

Global Prevalence and Incidence of Influenza

During the 20th century there were 3 pandemics of influenza: year 1918, year 1957, and year 1968. The fourth influenza outbreak occurred in 2009. The 1918 pandemic had the highest mortality rate causing approximately 40 million deaths worldwide. In 1957 the appearance of influenza A2 type H2N2 caused over 2 million deaths worldwide. The pandemic that occurred in 1968 was the result of the influenza type H3N2 that emerged in Hong Kong. The avian influenza caused by H5N1 emerged in 1997 and re-emerged in 2004 to 2005. (1)

From April 2009 to January 2010, more than 211 countries and overseas territories reported laboratory confirmed cases of influenza A (H1N1) 2009. Pandemic influenza A (H1N1) 2009 remained predominant while seasonal influenza types A (H1N1), A (H3N2), and B viruses circulated at very low levels in many countries during this period. (8)

A highly pathogenic avian influenza A (H5N1) is present in poultry. Since December 2003, a total of 478 confirmed human cases and 286 deaths due to influenza A (H5N1) have been reported by 15 countries. (8)

In Canada, the national influenza surveillance is coordinated through the Centre for Immunization and Respiratory Infectious Diseases (CIRID) and the Public Health Agency of Canada (PHAC). The Flu Watch program provides a national picture of influenza activities through collecting information from different sources.

Streptococcal Pneumonia

Pathogenic Bacteria

Streptococcus pneumoniae, also known as pneumococcus, is an encapsulated Gram-positive bacterium that often colonizes in the nasopharynx of healthy children and adults. Pneumococcus can be transmitted from person to person during close contact. The bacteria can cause illnesses such as otitis media and sinusitis, and may even become more aggressive and affect other areas of the body such as the lungs, brain, joints, and blood stream. More severe infections caused by pneumococcus are pneumonia, bacterial sepsis, meningitis, peritonitis, arthritis, osteomyelitis, and in rare cases endocarditis and pericarditis.

High Risk Groups

People with impaired immune systems are susceptible to pneumococcal infection. Young children, elderly people, and patients with underlying medical conditions including chronic lung or heart disease, human immunodeficiency virus (HIV) infection, sickle cell disease, and people who have undergone splenectomy are at a higher risk for acquiring pneumococcal pneumonia.

Limitations of Trials of Pneumococcal Vaccine Efficacy

Although randomized controlled trials (RCTs) would provide the most definitive data about vaccine efficacy in the COPD population, identification of an organism-specific effect such as pneumococcal pneumonia, which is difficult to isolate in clinical samples (9), limits the implementation of these trials.

It has been estimated that an RCT would require between 120,000 and 482,000 patients to demonstrate a benefit in a clinically relevant outcome such as pneumococcal pneumonia. (10) These trials are prohibitive in terms of costs and logistics. In addition, conducting a placebo-controlled trial in patients with COPD may raise ethical concerns, as the pneumococcal vaccination of this at risk group is considered to be the standard of care in many countries.

Studies of Pneumococcal Vaccine Efficacy in the General Population

Recommendations for pneumococcal vaccinations target people who are at high risk for invasive pneumococcal disease. However, the use of a pneumococcal vaccine in the elderly or in high risk populations is still controversial and has been the subject of many meta-analyses and systematic reviews. It is not clear whether effectiveness wanes over time and/or with age. Presence of significant heterogeneity between the results of the trials makes it difficult to estimate the true effect of the pneumococcal vaccine in adults. Albeit, it seems that the strongest evidence is for the end point of pneumococcal bacteremia.

Some studies have found that the pneumococcal vaccine was not protective against pneumococcal pneumonia without bacteremia. For example, a large retrospective cohort study of 47,365 participants 65 years of age and older (11) did not find an association between the pneumococcal vaccination and a reduced risk of community-acquired pneumonia (CAP), regardless of the need for hospitalization (hazard ratio [HR], 1.07; 95% CI, 0.99–1.14). However, this study found a significant reduction in the risk of pneumococcal bacteremia (HR, 0.56; 95% CI, 0.33–0.93; $P = 0.03$). Another finding of this study was a higher risk of hospitalization due to pneumonia among those vaccinated (HR, 1.14; 95% CI, 1.02–1.28; $P = 0.02$). The patient population for the above study consisted of members of the Group Health Cooperative, a health maintenance organization in Washington State, and there were significant differences in baseline characteristics of those who received the vaccine and those who did not. For example, significantly more patients in the vaccine group had coronary artery disease, diabetes mellitus, chronic lung failure, and were immunocompromised.

Cornu et al (12) conducted a meta-analysis of the properly conducted RCTs published from 1996 to 2000, comparing pneumococcal polysaccharide vaccine (PPSV) with a placebo in immunocompetent adults. Fourteen trials were identified, which included 48,837 participants. Their findings included a significant

reduction in the incidence of definite pneumococcal pneumonia[1] (OR 0.29; 95% CI, 0.2–0.42) without significant heterogeneity, a significant reduction in presumptive pneumococcal pneumonia[2] (OR 0.6; 95% CI, 0.37–0.96) with significant heterogeneity, and no significant effect on all-cause pneumonia (OR 0.78; 95% CI, 0.58–1.07) with significant heterogeneity. A subgroup analysis of trials conducted in gold miners in South Africa showed a significant reduction in all-cause pneumonia (OR 0.52; 95% CI, 0.43–0.63) without significant heterogeneity. The meta-analysis also found a significant reduction in mortality due to pneumonia (OR 0.68; 95% CI, 0.51–0.92) without significant heterogeneity.

Cornu et al (12) also performed an analysis of a subgroup of patients over 55 years of age. The study could not follow the prior plan for analyzing patients over 65 years of age because the age of the patients was dichotomized differently. They identified 7 trials, representing 7,907 high-risk patients (i.e., patients suffering from diabetes mellitus, chronic renal, hepatic, or respiratory disease, or cancer). Although there was a trend towards a lower risk of definite pneumococcal pneumonia (OR 0.58; 95% CI, 0.18–1.0) and mortality due to pneumonia (OR 0.69; 95% CI, 0.28–1.27), these effects were not statistically significant due to low power for this subgroup analysis and low events rates.

Studies of Pneumococcal Vaccine Efficacy in COPD Patients

A prospective cohort study (13) investigated the clinical effectiveness of the 23-valent pneumococcal vaccine (PPSV23) in older adults (mean age 75 years) with chronic respiratory disease (bronchitis, emphysema, and asthma). A total of 1,298 persons were observed for 3 years (a total of 3,676 person-years). The study found that PPSV23 did not significantly reduce the risk of overall CAP, outpatient CAP, 30-day mortality from CAP, or all-cause mortality. Hospitalization due to overall CAP or due to pneumococcal pneumonia was not significantly different between the 2 groups (Table 1).

Table 1: Results of a Prospective Cohort Study of the Pneumococcal Vaccine in Patients With Respiratory Disease*

	Incidence per 1,000 Person-Years		Age Adjusted HR for All Subjects (95% CI)	*P* Value	Multivariable HR for All Subjects (95% CI)	*P* Value
	Vaccinated	Unvaccinated				
Overall CAP	46.96	45.77	0.93 (0.68–1.28)	0.68	0.77 (0.56–1.07)	0.12
Outpatient CAP	10.53	7.15	1.29 (0.61–2.72)	0.5	1.15 (0.48–2.72)	0.75
Hospitalization for overall CAP	36.43	38.62	0.87 (0.61–1.23)	0.43	0.7 (0.48–1.00)	0.05
Hospitalization for CAP due to Pneumococcal pneumonia	5.26	5.72	0.87 (0.35–2.17)	0.78	0.76 (0.30–1.90)	0.56
30-day mortality due to CAP	6.14	5.72	0.91 (0.35–2.37)	0.84	0.87 (0.33–2.28)	0.78
All-cause mortality	81.19	64.36	1.22 (0.92–1.62)	0.16	1.2 (0.91–1.59)	0.2

* Abbreviations: CI, confidence interval; CAP, community-acquired pneumonia; HR, hazard ratio.
Source: Ochoa-Gondar et al, 2008 (13)

Prevalence and Incidence of Pneumococcal Pneumonia

The rate of pneumococcal pneumonia in developed countries is still not known due to the lack of accurate diagnostic tests. In the United States Veterans' Administration Trial among participants aged 55 years and older, the incidence of pneumococcal pneumonia per 1,000 person-years was 1.7 in people with no

[1]Defined as clinically and radiographically confirmed pneumonia with *S pneumoniae* isolated from a culture of blood or any other usually sterile fluid
[2] Defined as clinically and radiographically confirmed pneumonia with *S pneumoniae* isolated from a culture of sputum or a nasal swab

underlying disease, 3.4 in those with 1 underlying disease, and 15 for those with 3 underlying diseases. (14)

Technology

Current Vaccines

Influenza Vaccine

The selection of influenza viruses for the seasonal influenza vaccine is based on the type of influenza viruses that circulated during the previous year. Every year, the World Health Organization (WHO) convenes at technical meetings in February and September and makes recommendations about the selection of virus strains. The WHO recommended the following strains of viruses for use in the influenza vaccines in the 2010 to 2011 northern hemisphere influenza season: (8)

- A/California/7/2009 (H1N1)-like virus,
- A/Perth/16/2009 (H3N2)-like virus, and
- B/Brisbane/60/2008-like virus.

In Canada, there are currently 5 trivalent influenza vaccines authorized for use by injection (15). Four of these are formulated for intramuscular use and the fifth product (Intanza®) is formulated for intradermal use.

The 4 vaccines for intramuscular use are:

- Fluviral (GlaxoSmithKline), split virus, inactivated vaccine, for use in adults and children ≥ 6 months;
- Vaxigrip (Sanofi Pasteur), split virus inactivated vaccine, for use in adults and children ≥ 6 months;
- Agriflu (Novartis), surface antigen inactivated vaccine, for use in adults and children ≥ 6 months; and
- Influvac (Abbott), surface antigen inactivated vaccine, for use in persons ≥ 18 years of age.

FluMist is a live attenuated virus in the form of a nasal spray for persons aged from 2 to 59 years. Immunization (with current available influenza vaccines) is not recommended for infants less than 6 months of age.

The Public Health Agency of Canada (PHAC) (15) provided recommendations for the use of the influenza vaccine for the following groups of people:

- people at high risk for influenza-related complications or those likely to require hospitalization for the conditions indicated in the report, which includes cardiac or pulmonary disorders[3];
- people capable of transmitting influenza to those at high risk[4];
- people who provide essential community services; and
- people in direct contact during culling operations with poultry infected with the avian influenza.

Special groups considered for influenza vaccination in 2010 to 2011 include:

- persons who are morbidly obese (body mass index ≥ 40),

[3] Details are provided in the PHAC report (15)

[4] Details are provided in the PHAC report (15)

- Aboriginal peoples, and
- healthy children from 2 to 4 years of age.

Pneumococcal Vaccine

Pneumococcal polysaccharide vaccines were developed more than 50 years ago and have progressed from 2-valent vaccines to the current 23-valent vaccines to prevent diseases caused by 23 of the most common serotypes of *S pneumoniae*. Canada-wide estimates suggest that approximately 90% of cases of pneumococcal bacteremia and meningitis are caused by these 23 serotypes. (16) Health Canada has issued licenses for 2 types of 23-valent vaccines to be injected intramuscularly or subcutaneously:

- Pneumovax 23® (Merck & Co Inc. Whitehouse Station, NJ, USA) (17), and
- Pneumo 23® (Sanofi Pasteur SA, Lion, France) for people 2 years of age and older. (16)

Other types of pneumococcal vaccines licensed in Canada are for pediatric use. Pneumococcal polysaccharide vaccine is injected only once. A second dose is applied only in some conditions.

The Centers for Disease Control and Prevention (CDC) provided recommendations for the use of PPSV23 among all adults aged 65 years and older, and those aged 19 to 64 years with underlying medical conditions that put them at a greater risk for serious pneumococcal infection. (18)

The underlying medical conditions for the administration of PPSV23 include the following:

Immunocompetent persons

- chronic heart disease including congestive heart failure and cardiomyopathies (excluding hypertension),
- chronic lung disease including COPD, emphysema, and asthma,
- diabetes mellitus,
- cerebrospinal fluid leaks,
- cochlear implant,
- alcoholism,
- chronic liver disease including cirrhosis, and
- cigarette smoking;

Persons with functional or anatomical asplenia

- sickle cell disease and other hemoglobinopathies, and
- congenital or acquired asplenia, splenic dysfunction, or splenectomy;

Immunocompromised persons

- congenital or acquired immunodeficiency,
- HIV infection,
- chronic renal failure,
- nephrotic syndrome,
- leukemia,
- lymphomas,
- Hodgkin's disease,
- generalized malignancy,
- disease requiring treatment with immunosuppressive drugs including long-term systemic corticosteroids or radiation therapy,

- solid organ transplantation, and
- multiple myeloma.

Evidence-Based Analysis

Research Questions

1. What is the effectiveness of the influenza vaccination and the pneumococcal vaccination compared with no vaccination in COPD patients?
2. What is the safety of these 2 vaccines in COPD patients?
3. What is the budget impact and cost-effectiveness of these 2 vaccines in COPD patients?

Research Methods

Literature Search

Search Strategy

A literature search was performed on July 5, 2010 using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2000 to July 5, 2010. The search was updated monthly through the AutoAlert function of the search up to January 31, 2011.

Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established. Data extraction was carried out by the author.

Inclusion Criteria

- studies comparing clinical efficacy of the influenza vaccine or pneumococcal vaccine with no vaccine or placebo;
- RCTs published between January 1, 2000 and January 31, 2011;
- studies including patients with COPD only ;
- studies investigating the efficacy of the types of vaccines approved by Health Canada;
- English language studies.

Exclusion Criteria

- non-RCTs;
- studies investigating vaccines for other diseases;
- studies comparing different variations of vaccines;
- studies in which patients received 2 or more types of vaccines;
- studies comparing different routes of administering vaccines;
- studies not reporting clinical efficacy of the vaccine or reporting immune response only;
- studies investigating the efficacy of vaccines not approved by Health Canada.

Outcomes of Interest

Primary Outcomes

Influenza vaccination: Episodes of acute respiratory illness due to influenza virus.

Pneumococcal vaccination: Time to the first episode of community-acquired pneumonia due to pneumococcus or of unknown etiology.

Secondary Outcomes

- rate of hospitalization and mechanical ventilation
- mortality rate
- adverse events

Statistical Analysis

Review Manager 5 Version 5.1 software was used for graphical presentation of data. However, only the *P* values reported by the authors were used for this report.

Quality of Evidence

The quality of each included study was assessed taking into consideration the following 7 study design characteristics:

- adequate allocation concealment,
- randomization (study must include a description of the randomization procedure used and this must be a proper method),
- power/sample size (adequate sample size based on a priori calculations; underpowered studies were identified, when possible, using post hoc sample size power calculations),
- blinding (if double blinding is not possible, a single blind study with unbiased assessment of outcome was considered adequate for this criterion),
- < 20% withdrawals/dropouts,
- intention-to-treat analysis conducted and done properly (withdrawals/dropouts considered in analysis), and
- other criteria as appropriate for the particular research question and study design.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (19) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding, and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High Further research is very unlikely to change confidence in the estimate of effect

Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
Very Low	Any estimate of effect is very uncertain

Results of Evidence-Based Analysis

The database search identified 1,286 citations including several existing systematic reviews and health technology assessments. Two systematic reviews performed by the Cochrane Collaboration were identified; one (20) was for the influenza vaccine and the other (21) for the pneumococcal vaccine. The systematic reviews of the influenza vaccine included 11 RCTs published up to May 2009. The systematic reviews of the pneumococcal vaccine included 7 RCTs published up to March 2010.

Tables 2 and 3 list RCTs identified through literature search or published systematic reviews for influenza vaccination and pneumococcal vaccination in patients with respiratory illness conducted since 1961.

Table 2: Randomized Controlled Trials of the Influenza Vaccine in Patients with Respiratory Illness*

Author, Year	Patients	Population	Comparison	Outcomes/Objectives
Howells and Tyler,1961 (22)		Chronic bronchitis with severity grade		• exacerbation • hospitalization • mortality
Cate et al, 1977 (23)		> 50 or high risk (5% lung disease)		• adverse reaction • serology
Fell et al, 1977 (24)		Chronic bronchitis, severity unclear		• adverse reactions • antibody response • hospitalization
Medical Research Council,1980 (25)		Chronic bronchitis and airway obstruction		• respiratory symptoms
Treanor et al, 1992 (26)	523	Nursing home residents	IM trivalent +/- IN	• to compare the rate of lab documented influenza between the 2 groups • respiratory illness
Treanor et al, 1994 (27)	81	High risk (18% COPD)	IM vs. IN	• immunology • influenza-like illness
Govaert et al, 1993 (28)	1,838	People > 60 years old	IM trivalent vs. placebo	• only local and systemic adverse events
Govaert et al, 1994 (29)	1,838	People > 60 years old	IM trivalent vs. placebo	• influenza-like illness within 5 months • antibody titre
Gorse et al, 1995 (30)	50	Nursing home residents	IM trivalent +/- IN	• immune response
Gorse et al, 1997 (31)	29	Veterans Affairs Volunteers with a history of COPD	IM trivalent +/- IN	• antibody response • respiratory symptoms

Author, Year	Patients	Population	Comparison	Outcomes/Objectives
Gorse et al, 2003 (32)	2,215	Veterans Affairs Volunteers with a history of COPD	IM trivalent +/- IN	• to compare the rate of lab documented influenza-caused illness between the 2 immunization groups
Neuzil et al, 2003 (33)	2,215 (n = 585)	Veterans Affairs Volunteers with a history of COPD	IM trivalent +/- IN	• occurrence of respiratory symptoms
Gorse et al, 2004 (34)	2,215	Veterans Affairs Volunteers with a history of COPD	IM trivalent +/- IN	• to compare antibody response between the 2 immunization groups
Wongsurakiat et al, 2004 (35;36)	125	COPD	IM trivalent vs. placebo	• incidence of influenza
Gorse et al, 2006 (37)	2,215	Veterans Affairs Volunteers with a history of COPD	IM trivalent +/- IN	• changes in respiratory functions due to respiratory illness
Chuaychoo et al, 2010 (38)	156	COPD	IM trivalent vs. IN trivalent	• immune response
Clancy, 2010 (39)	64	Smokers	Oral NTHi vaccine vs. placebo	• immune response
Tendon et al, 2010 (40)	38	COPD	Oral NTHi vaccine vs. placebo	• exacerbation

*Abbreviations: COPD, chronic obstructive pulmonary disease; IM, intramuscular; IN, intranasal; NTHi, nontypeable haemophilus influenza.

Table 3: Randomized Controlled Trials of the Pneumococcal Vaccine in Patients with Respiratory Illness*

Author, Year	Patients	Population	Comparison	Outcomes/Objectives
Leech et al, 1987 (41)	189	COPD	IF + PN Vaccine vs. PN+Placebo	• incidence of pneumonia • antibody response • mortality
Davis et al, 1987 (42)	103	COPD	14-valent vaccine vs. placebo	• incidence of pneumonia • mortality
Steentoft et al, 2006 (43)	49 In 4 groups (Steroid+/- vaccine/placebo)	COPD	Effect of steroid on antibody levels Clinical variables	• antibody response • incidence of pneumonia • exacerbation • hospital admission • lung function
Meyer et al, 2006 (44)	30 (3 arms) IM vs. alveolar ventilation vs. bronchial ventilation	COPD	Comparison between 3 arms	• antibody response • adverse events
Alfageme et al, 2006 (45)	596	COPD	23-valent vaccine vs. no vaccine	• CAP diagnosed by chest x-ray (mean of 979 days) • mortality

Author, Year	Patients	Population	Comparison	Outcomes/Objectives
Ya Tseimakh et al, 2006 (46)			Abstract	
Teramoto et al, 2007 (47)			Abstract	
Furumoto et al, 2008 (48)	167	Chronic lung disease	Group 1: IF + PN Group 2: IF	• incidence of pneumonia and acute exacerbation
Dransfield et al, 2009 (49)	120	COPD (Moderate to severe)	7-valent vaccine vs. 23-valent	• immune response

*Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; IF, influenza vaccine; PN, pneumococcal vaccine.

From the above lists, one RCT (35) met the inclusion/exclusion criteria for the influenza vaccination. Adverse effects of the influenza vaccination were reported in a separate citation. (36) One RCT (45) met the criteria for the pneumococcal vaccination (Table 4). The literature search updated to January 31, 2011 did not identify any further RCTs.

For each included study, the study design was identified and is summarized below in Table 4, which is a modified version of a hierarchy of study design by Goodman. (50)

Table 4: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	
Large RCT	Pneumococcal vaccination 1
Small RCT	Influenza vaccination 1
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modeling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	
Total	2

*Abbreviation: RCT, randomized controlled trial.

Clinical Efficacy of the Influenza Vaccination in Immunocompetent Patients with COPD

Study Design and Method

One small RCT (35) investigated the effectiveness of the influenza vaccination on influenza-related acute respiratory illness (ARI) and total ARIs. The study was conducted in Thailand between June 1997 and October 1998 in a single university hospital. The design of the study was double-blinded, placebo controlled with a power of 80%.

Study Population

Patients must have had a clinical diagnosis of COPD, together with a forced expiratory volume in 1 second (FEV_1) less than 70% of the forced vital capacity and a less than 15% increase in FEV_1 predicted, after inhalation of the bronchodilator. Patients under immunosuppressive therapy (except corticosteroids), immunocompromised patients, and those having a malignancy or an expected survival of less than 1 year were excluded. Patients were excluded if they had a history of an allergy to eggs.

The study sample was 125 participants with COPD who were recruited from the COPD clinic. Sixty-two patients were assigned to the vaccine group and 63 patients were assigned to the placebo group. The medical management of all patients was based on the Thai guideline for the management of COPD.

Three patients, 1 in the vaccine group and 2 in the placebo group, dropped out of the study. Eight patients, 5 in the vaccine group and 3 in the placebo group, died from diseases or conditions not related to ARI, but data for these patients were retained in the analysis where possible.

Randomization

All patients were stratified based on the degree of airflow obstruction: mild ($FEV_1 \geq 70\%$ predicted), moderate (FEV_1 50%–69% predicted), and severe ($FEV_1 < 50\%$ predicted). Patients were numbered consecutively within their severity stratum. Numbers were previously randomized to either the vaccine or the placebo groups. Patients' numbers were identified at the vaccination session and the process of checking the assigned numbers and whether vaccine or placebo would be injected was performed by a nurse who did not participate in the care of these patients.

Intervention

Patients in the vaccine group were injected with 0.5 mL of purified, trivalent, split virus vaccine (Pasteur Merieux: Lyon, France). Each dose contained influenza A/Texas/36/91 (H1N1), A/Nanchang/933/95 (H3N2), and B/Harbin/07/94, all with 15 µg of hemagglutinin according to the WHO recommendation. Patients in the placebo group received 0.5 mL of vitamin B1. In both groups, a second dose of the vaccine or placebo was injected 4 weeks after the first dose.

Primary Outcome

The primary outcome of the study was the number of episodes of influenza-related ARI and its relationship to the degree of airflow obstruction.

Classification of Acute Respiratory Illness

Patients were told to notify the study centre immediately if they developed symptoms of ARI. All patients were seen at the COPD clinic at 4-week intervals. At each visit, they were also asked about episodes of

respiratory illness during the past month. The clinical characteristics of each ARI were recorded as one of the following 4 types:

Common cold:

Infection of the upper respiratory tract with predominating rhinitis and pharyngitis;

Influenza-like illness:

At least 2 of the 3 following symptoms with or without upper respiratory symptoms:

- generalized aches,
- fever,
- headache;

Or, 1 of the above 3 symptoms in addition to at least 1 of the following symptoms:

- upper respiratory tract infection (sore throat, nasal discharge) within the past 5 days,
- fever without any other cause,
- increased wheezing,
- increased cough, and
- a 20% or more increase in respiratory rate or heart rate;

Acute exacerbation of COPD:

Increased dyspnea, sputum volume, or sputum purulence;

Pneumonia:

Compatible symptoms plus new infiltrates shown on a chest x-ray.

Laboratory Measurements

Blood samples were taken from each patient for the HI test during the following visits:

- the day of vaccination or placebo injection,
- at 4 weeks,
- at 6 months, and
- at 1 year.

Diagnostic Criteria for Influenza Infection

For each ARI, the HI antibody titre was determined twice: at the first visit (acute serum) and at 4 to 6 weeks afterwards (convalescent serum). If the duration of ARI was less than 6 days, a throat or nasal swab, and a sputum specimen were also collected for viral culture. A fourfold HI titre increase in convalescent serum compared with the acute serum (with a titre ≥ 40) and/or demonstration of influenza antigen with or without a positive culture finding was considered as meeting the criteria for the influenza virus infection.

Classification of the Severity of Acute Respiratory Illness

For each ARI, the severity was classified as one of the 3 following categories:

- treated in an outpatient clinic,
- needed hospitalization, or
- needed mechanical ventilation.

Method of Data Analysis

The incidence of ARI in each group was calculated using an incidence density (number of episodes of ARI over the number and time of follow-up [person-years]), estimated by a Poisson model. The effectiveness of the influenza vaccine was calculated as 1 minus relative risk. The Kaplan-Meier survival analysis was used to demonstrate the probability of not acquiring influenza-related ARI and overall ARI during the study period.

Baseline Characteristics of the Study Population

There were no significant differences between the 2 groups in baseline characteristics of the patients. In each group about 30% of the patients had comorbid diseases such as hypertension, coronary artery disease, and diabetes. Among patients who had an HI titre greater than or equal to 10 at the baseline, about one half had had a previous infection by at least 1 type of influenza virus type A and about one fifth had been infected with influenza virus type B. However, their geometrical means titres were at a low level. There were no significant differences between the 2 groups in baseline HI antibody titre.

Crude Incidence and Incidence Density of Influenza-Related Acute Respiratory Illness

During the study period, a total of 21 patients (4 in the vaccine group and 17 in the placebo group) acquired influenza-related ARI as evidenced by a fourfold rise in the HI antibody titre. Thirteen of these patients had symptoms of acute exacerbation, 6 had symptoms of the common cold, and 2 had symptoms of an influenza-like illness. Two of the 21 cases were caused by influenza type A and only 1 case was caused by influenza type B. There was another patient in the vaccine group who had a fourfold increase in his HI titre against influenza A without ARI symptoms. From a total of 165 specimens collected from the patients' throats, noses, and sputum, only 3 showed positive results on the viral culture.

The incidence density of influenza-related ARI was 6.8 episodes per 100 person-years in the vaccine group and 28.1 episodes per 100 person-years in the placebo group (RR, 0.2; 95% CI, 0.06–0.7; P = 0.005).

Acute exacerbation was the most common presentation of influenza-related ARI (13/21 episodes, 61.9%), as well as the most common presentation of ARI (161/269 episodes, 59.8%). The incidence rate of influenza-like illness was significantly lower in the vaccine group than the placebo group (vaccine group 0.08 episodes per 100 person-years; placebo group 0.2 episodes per 100 person-years; RR, 0.34; 95% CI, 0.1–0.99; P = 0.03).

Vaccine Effectiveness

The crude incidence rate of influenza-related ARIs of the vaccine group over the placebo group was 0.24 (95% CI, 0.09–0.67; P = 0.007) (Figure 1), and the overall effectiveness of vaccination against the influenza virus was 76%. The effectiveness of vaccination against the influenza virus in patients with mild, moderate, and severe COPD was 84%, 45%, and 85% respectively.

The incidence rate ratio of the vaccine group over the placebo group for influenza-related ARIs adjusted for age, sex, smoking status, comorbid diseases, and severity of COPD was 0.24, 0.24, 0.24, 0.22, and 0.24 respectively, and none of the *P* values for the effect modification were statistically significant.

Severity of Influenza-Related Acute Respiratory Illness

Fewer patients in the vaccine group compared with the placebo group required hospitalization; 2 patients in the vaccine group and 5 patients in the placebo group became hospitalized because of influenza-related ARIs ($P = 0.3$). Three of the hospitalized patients, all in the placebo group, underwent mechanical ventilation. None of the patients in the vaccine group underwent mechanical ventilation and the difference did not reach statistical significance due to the low event rate.

All patients in the subgroups of moderate and severe COPD who did not receive the vaccine and were hospitalized because of influenza-related ARIs underwent mechanical ventilation. This included 2 patients in the severe category and 1 patient in the moderate category. One of the patients with severe COPD in the placebo group who required mechanical ventilation died because of ventilation-associated pneumonia.

The crude incidence rate of hospitalization from influenza-related ARIs of the vaccine group over the placebo group was 0.41 (95% CI, 0.08–2.02; $P = 0.27$). The incidence rate of hospitalization due to influenza-related ARIs of the vaccine group over the placebo group adjusted for age, sex, smoking status, comorbid diseases, and severity of COPD was 0.38, 0.42, 0.41, 0.38, and 0.4 respectively, and none of the *P* values for the effect modification were statistically significant.

Figure 1 shows the number of patients who acquired influenza-related ARIs in the 2 groups and the severity of their illness, and relative risk ratios calculated by the Mantel-Haenszel test method using Review Manager 5 Version 5.1 software.

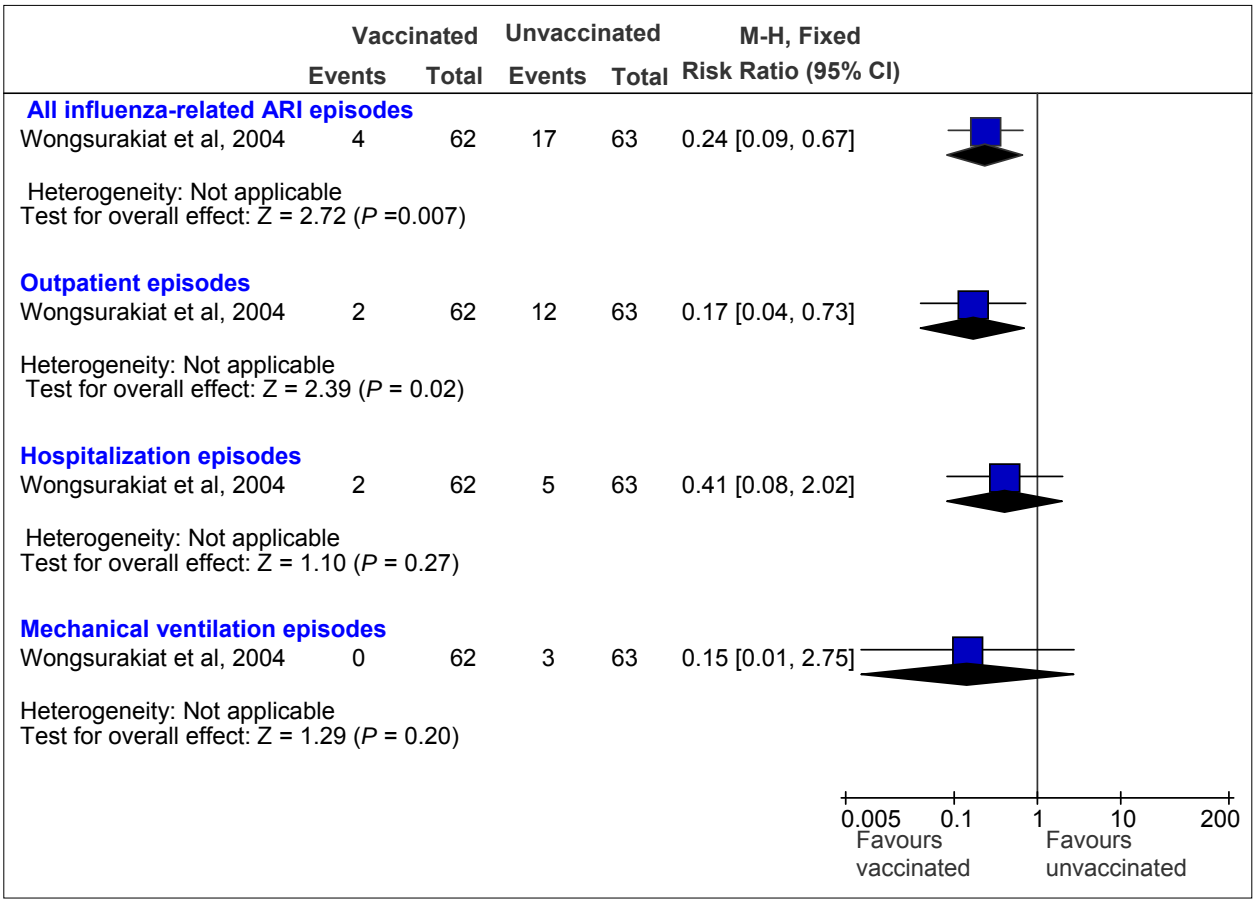


Figure 1: Incidence and Severity of Influenza-Related ARI in Patients with COPD*

*Abbreviations: ARI, acute respiratory illness; CI, confidence interval; COPD, chronic obstructive pulmonary disease; M–H, Mantel–Haenszel.

The incidence density of the vaccine group versus the placebo group for influenza-related ARI and for hospitalization from influenza-related ARI for categories of disease severity is shown in Table 5.

Table 5: Incidence Density for Episodes of Influenza-Related ARI and Episodes Requiring Hospitalization – Vaccine Versus Placebo*

COPD Severity	All Episodes of Influenza-Related ARI/100 Person-Years RR (95% CI)	*P* Value	All Episodes of Influenza-Related ARI That Required Hospitalization/100 Person-Years RR (95% CI)	*P* value
All patients	Vaccine: 6.8 Placebo: 28.1 0.2 (0.06–0.70)	0.005	Vaccine: 3.4 Placebo: 8.3 0.4 (0.04–2.50)	0.3
Mild	Vaccine: 4.5 Placebo: 28.2 0.2 (0.003–1.30)	0.06	Vaccine: 4.5 Placebo: 9.4 0.5 (0.01–9.30)	0.6
Moderate	Vaccine: 13.2 Placebo: 23.8 0.5 (0.05–3.80)	0.5	Vaccine: 0 Placebo: 5.9 0 (0.00–43.10)	0.5
Severe	Vaccine: 4.6 Placebo: 31.2 0.1 (0.003–1.10)	0.04	Vaccine: 3.4 Placebo: 8.3 0.5 (0.01–10.00)	0.6

*Abbreviations: ARI, acute respiratory illness; CI, confidence interval; COPD, chronic obstructive pulmonary disease; RR, relative risk.
Source: Wongsurakiat et al, 2004 (35)

The incidence of influenza-related ARIs requiring mechanical ventilation was 0 per 100 person-years and 5 per 100 person-years in the vaccine group and the placebo group, respectively (RR, 0; 95% CI, 0–2.5; $P = 0.1$).

Survival Analysis

The Kaplan-Meier survival analysis showed a significantly higher probability of not acquiring influenza-related ARIs in favour of the vaccine group ($P = 0.003$ by log-rank test). There was no significant difference in the probability of not acquiring ARIs between the 2 groups.

There was no significant difference between the 2 groups in the probability of not being hospitalized as well as the probability of not receiving mechanical ventilation due to influenza-related ARIs ($P = 0.2$ and $P = 0.4$ respectively by log-rank tests).

Explanatory Factors

The effectiveness of the influenza vaccine was not related to age, sex, severity of COPD, smoking status, or comorbid diseases. The incidence rate ratio of the vaccine group over the placebo group for influenza-related ARIs and hospitalization from influenza-related ARIs adjusted for the above factors are shown in Table 6.

Table 6: Adjusted Incidence Rate Ratios for Vaccine Versus Placebo*

		Influenza-Related ARI		Influenza-Related Hospitalization	
Adjusted	**Categories**	**Risk Ratio**	***P* Value**	**Risk Ratio**	***P* Value**
Age	< 70/ ≥ 70 years	0.24	0.3	0.38	0.3
Sex	Male/Female	0.24	0.8	0.42	0.8
Current smoking status	Yes/No	0.24	0.6	0.41	0.8
Severity of COPD	Mild/Moderate/ Severe	0.22	0.1	0.38	0.9
Comorbid disease	Yes/No	0.24	0.5	0.40	1.0

*Abbreviations: ARI, acute respiratory illness; COPD, chronic obstructive pulmonary disease.
Source: Wongsurakiat et al, 2004 (35)

Adverse Events

Frequency of Acute Exacerbation

There were 269 episodes of ARIs (124 in the vaccine group and 145 in the placebo group). Acute exacerbations accounted for 161 of the total ARIs (76 in the vaccine group and 85 in the placebo group). There was no significant difference between the 2 groups in the incidence of acute exacerbation during the first week and 4 weeks following injection (Table 7). Thirteen (8%) of the acute exacerbations were influenza-related.

Table 7: Development of ARI During the First Week and the First Four Weeks*

First Week, N (%)	*P* Value	First 4 Weeks, N (%)	*P* Value
Vaccine: 4 (6.40) Placebo: 4 (6.30)	1.0	Vaccine:15 (24.20) Placebo: 20 (31.70)	0.5

*Abbreviations: ARI, acute respiratory illness; N, number.
Source: Wongsurakiat et al, 2004 (35)

Local Reaction

Vaccinated patients had significantly more local adverse reactions compared with the placebo group (17 [27%] in the vaccine group vs. 4 [6%] in the placebo group; $P = 0.002$). The most common local reactions among vaccinated patients were swelling, itching, and pain when touched. Significantly more patients in the vaccine group than the placebo group experienced swelling and itching (vaccine 4, placebo 0; $P = 0.04$ for either). The duration of local symptoms was usually less than 48 hours and did not require specific treatment.

Systemic Reaction

Systemic reactions were headache, myalgia, fever, and skin rash. No significant differences in systemic reactions between the 2 groups were observed (47 [76%] in the vaccine group vs. 51 [81%] in the placebo group; $P = 0.5$).

Effects of Vaccination on Lung Function, Dyspneic Symptoms, and Exercise Capacity

Lung function was measured by spirometry, oxygen saturation level in arterial blood was measured by pulse oximetry, dyspneic symptoms were measured by the visual analogue scale, and exercise capacity was measured by the 6 Minute Walking Test. There were no significant differences between the 2 groups for changes in lung function, dyspneic symptoms, and exercise capacity at 1 week and at 4 weeks (Table 8).

Table 8: *P* Value for the Difference in Changes in Lung Function, Dyspneic Symptoms, and Exercise Capacity – Vaccine Versus Placebo*

Measures	*P* Value for Vaccine vs. Placebo	
	1 Week	4 Weeks
FEV_1	1.0	0.7
PImax	0.9	0.5
SpO_2 - pre exercise	0.8	0.2
SpO_2 - post exercise	0.7	0.2
VAS - pre exercise	0.9	0.3
VAS - post exercise	0.7	0.7
6 minute walk	0.2	0.5

*Abbreviations: FEV1 , Forced expiratory volume in 1 second; PImax, maximum inspiratory pressure at residual volume; SpO_2, oxygen saturation level of arterial blood; VAS, visual analogue scale.

Source: Wongsurakiat et al, 2004 (35)

Summary of Efficacy of the Influenza Vaccination in Immunocompetent Patients With COPD

This study was conducted in a year that was not an epidemic influenza period, therefore the incidence of influenza was low.

Clinical Effectiveness

Influenza vaccination was associated with significantly fewer episodes of influenza-related ARIs. The incidence density of influenza-related ARIs was:

- All patients: vaccine group: (total of 4 cases) = 6.8 episodes per 100 person-years; placebo group: (total of 17 cases) = 28.1 episodes per 100 person-years, (RR, 0.2; 95% CI, 0.06–0.70; $P = 0.005$);
- Patients with severe airflow obstruction ($FEV_1 < 50\%$ predicted): vaccine group: (total of 1 case) = 4.6 episodes per 100 person-years; placebo group: (total of 7 cases) = 31.2 episodes per 100 person-years, (RR, 0.1; 95% CI, 0.003–1.1; $P = 0.04$);

- Patients with moderate airflow obstruction (FEV_1 50%–69% predicted): vaccine group: (total of 2 cases) = 13.2 episodes per 100 person-years; placebo group: (total of 4 cases) = 23.8 episodes per 100 person-years, (RR, 0.5; 95% CI, 0.05–3.8; *P* = 0.5);
- Patients with mild airflow obstruction ($FEV_1 \geq 70\%$ predicted): vaccine group: (total of 1 case) = 4.5 episodes per 100 person-years; placebo group: (total of 6 cases) = 28.2 episodes per 100 person-years,(RR, 0.2; 95% CI, 0.003–1.3; *P* = 0.06).

The Kaplan-Meier survival analysis showed a significant difference between the vaccinated group and the placebo group regarding the probability of not acquiring influenza-related ARIs (log-rank test *P* value = 0.003).

Overall, the vaccine effectiveness was 76%. For categories of mild, moderate, or severe COPD the vaccine effectiveness was 84%, 45%, and 85% respectively.

With respect to hospitalization, fewer patients in the vaccine group compared with the placebo group were hospitalized due to influenza-related ARIs, although these differences were not statistically significant. The incidence density of influenza-related ARIs that required hospitalization was 3.4 episodes per 100 person-years in the vaccine group and 8.3 episodes per 100 person-years in the placebo group (RR, 0.4; 95% CI, 0.04–2.5; *P* = 0.3; log-rank test *P* value = 0.2). No statistically significant differences between the 2 groups were observed for the 3 categories of severity of COPD.

Fewer patients in the vaccine group compared with the placebo group required mechanical ventilation due to influenza-related ARI. However, these differences were not statistically significant. The incidence density of influenza-related ARIs that required mechanical ventilation was 0 episodes per 100 person-years in the vaccine group and 5 episodes per 100 person-years in the placebo group (RR, 0.0; 95% CI, 0–2.5; *P* = 0.1; log-rank test *P* value = 0.4). In addition, no statistically significant differences between the 2 groups were observed for the 3 categories of severity of COPD.

The effectiveness of the influenza vaccine in preventing influenza-related ARIs and influenza-related hospitalization was not related to age, sex, severity of COPD, smoking status, or comorbid diseases.

Safety

Overall, significantly more patients in the vaccine group than the placebo group experienced local adverse reactions (vaccine: 17 [27%], placebo: 4 [6%]; *P* = 0.002). Significantly more patients in the vaccine group than the placebo group experienced swelling (vaccine 4, placebo 0; *P* = 0.04) and itching (vaccine 4, placebo 0; *P* = 0.04).

Systemic reactions included headache, myalgia, fever, and skin rash, and there were no significant differences between the 2 groups with regard to these reactions (vaccine: 47 [76%], placebo: 51 [81%]; *P* = 0.5).

With respect to lung function, dyspneic symptoms, and exercise capacity, there were no significant differences between the 2 groups in FEV_1, maximum inspiratory pressure at residual volume, oxygen saturation level of arterial blood, visual analogue scale for dyspneic symptoms, and the 6Minute Walking Test for exercise capacity at 1 week and at 4 weeks.

There was no significant difference between the 2 groups with regard to the probability of not acquiring total ARI (influenza-related and/or non-influenza-related), (log-rank test *P* value = 0.6).

Clinical Efficacy of the Pneumococcal Vaccination in Immunocompetent Patients with COPD

Study Design and Method

A large RCT (45) investigated the clinical efficacy of PPSV23 in patients with COPD. Although the study had a large sample size, the details about the power calculation were not reported. This study was conducted in Spain between October 1999 and July 2004.

Study Population

All patients had a spirometric diagnosis of COPD and were not previously vaccinated. Pregnant patients and those diagnosed with any of the following conditions were excluded from the study:

- immunodeficiency
- neoplasia
- renal insufficiency in dialysis
- HIV infection
- hypogammaglobulinemia
- anatomical or functional asplenia

Initially, 600 patients with a diagnosis of COPD were included in the study (300 in each group). Four patients (2 in each group) were lost to follow-up and were excluded from the final analysis. The analysis was therefore performed for 596 patients. Thirty-four patients were diagnosed with neoplasia during the follow-up period. The mean age of the patients was 65.8 (standard deviation 9.7) years. Baseline characteristics of the patients in the 2 groups were similar.

Randomization

Randomization of patients was performed through computerized generation of random numbers in block lengths of 20 (10 in each group). Patients were randomly assigned to receive the PPSV23 or no vaccine and both groups were checked routinely every 6 months for 3 years. Physicians participating in the study and performing follow-ups were unaware of the patients' assignment. Patients were instructed to contact their physician if they developed symptoms that might suggest pneumonia.

Intervention

Patients who were assigned to the vaccine group received PPSV23 (Pneumo 23; Aventis Pasteur MSD) together with a clinical follow-up examination. Patients in the control arm of the study did not receive the vaccine but had a clinical follow-up examination. The vaccine was given to the patients free of charge at the centre where each patient was recruited.

Diagnosis of Pneumonia

The diagnosis of pneumonia was based on chest x-ray findings, presence of fever, and patients' symptoms suggesting lower respiratory tract infection. The diagnosis of pneumococcal pneumonia was based on the presence of pneumonia and the isolation of streptococcal pneumonia from the patient's sputum, bronchial aspirate, pleural fluid, blood, or cerebrospinal fluid.

Primary Outcome

The main outcome of the study was time to the first episode of developing CAP, either due to pneumococcus or of unknown etiology.

Follow-up

All patients were followed for a period of 3 years except for patients who died before the end of the follow-up period (115 patients). Patients who were diagnosed with pneumonia had a follow-up radiograph 2 to 4 weeks after the first visit.

Method of Data Analysis

The effectiveness of the pneumococcal vaccine was calculated as 1 minus relative risk of acquiring CAP, either due to pneumococcus or of unknown etiology. The Kaplan-Meier survival analysis was used to demonstrate the probability of not acquiring pneumococcal pneumonia or pneumonia of unknown etiology. In this analysis, the effectiveness of the vaccine was investigated in the entire group as well as in subgroups of patients stratified by age and severity of the airflow obstruction (age < 65 vs. ≥ 65; FEV_1 < 40% of expected vs. ≥ 40% of expected). The authors indicated that the threshold for subgroup analysis was based on the previously published data (11;51;52), suggesting that younger patients (< 65 years) and those with severe airflow obstruction (FEV_1 < 40% predicted) would benefit most from the vaccine administration.

The multivariate Cox proportional hazards regression model was used to evaluate the association between vaccine administration and time to the first outcome event. In the general model, age, severity of airflow obstruction (as defined above), and the interaction of the age with vaccine were used as covariates. In another model, the interaction term was not used but the model was run separately for ages less than 65years and greater than or equal to 65 years.

Results

Incidence and Episodes of Pneumonia

Overall, the incidence of global pneumonia (CAP and nosocomial) was 55.1 per 1,000 patients with COPD per year. A total of 75 patients developed pneumonia, from which 38 (12.7%) were in the vaccine group and 37 (12.4%) were in the control group. During the study period, no difference in the incidence of pneumonia was observed between the 2 groups.

A total of 88 episodes of pneumonia occurred during the study period (43 in the vaccine group and 45 in the control group), from which 73 (83%) were treated in hospital and the remaining 15 (17%) were treated as outpatients (Figure 2). Determination of the etiology and method of treatment was based on the decision of the treating physicians. Therefore, an etiological diagnosis was obtained for 23 patients diagnosed with pneumonia and the remaining 65 patients had unknown etiologies. There were no cases of bacteremic pneumococcal infection.

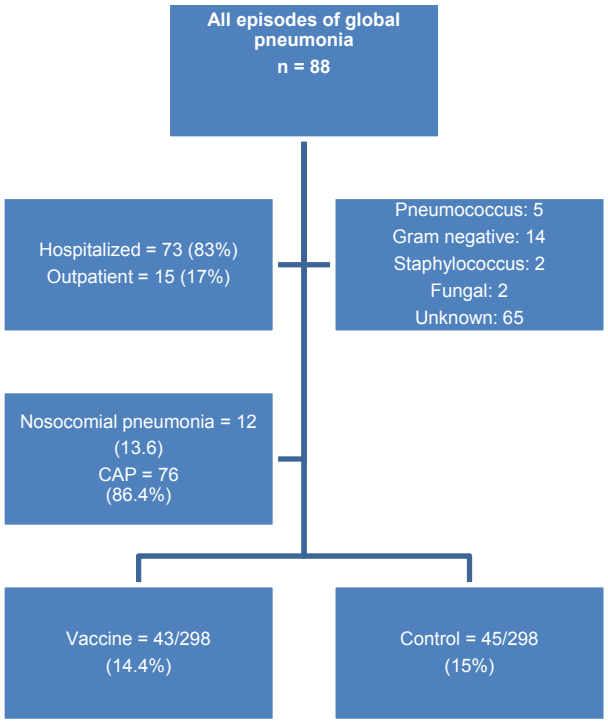


Figure 2: Episodes of Global Pneumonia in Patients with COPD: Vaccinated Versus Unvaccinated*

*Abbreviations: CAP, community-acquired pneumonia; n, number.

Incidence and Episodes of Community-Acquired Pneumonia

Incidence of CAP was 47.6 per 1,000 COPD patients per year (vaccine 46.3, control 49). There was a total of 76 episodes of CAP (vaccine 37, control 39) and 67 first episodes of CAP (vaccine 33, control 34) (Figure 3). Fifty-eight of these were either due to pneumococcus or of unknown etiology (vaccine 25, control 33). Kaplan-Meier survival analysis did not show significant differences between the 2 groups (log-rank test = 1.15; $P = 0.28$). The efficacy of PPSV23 in preventing the first episode of CAP in the whole group of COPD patients was 24% (95% CI, −24 to 54; $P = 0.3$).

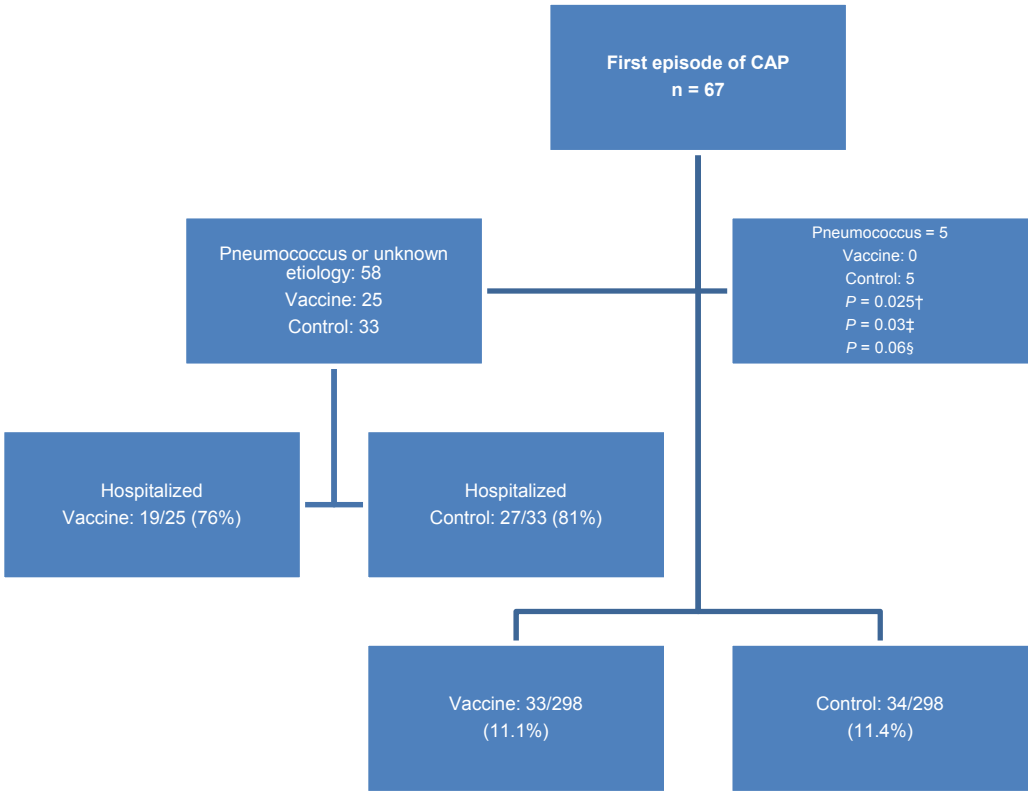


Figure 3: First Episode of Community-Acquired Pneumonia*

*Abbreviation: n, number.
†*P* value by log-rank test
‡*P* value by single-sided Fisher's exact test
§*P* value by two-sided Fisher's exact test

There were 5 cases of pneumococcal pneumonia (all were first episodes) among unvaccinated patients. No cases of pneumococcal pneumonia were observed in the vaccinated group. Analysis by Fisher's exact test showed no significant difference between the 2 groups by the 2-sided test ($P = 0.06$), while a single-sided test provided a significant result ($P = 0.03$). In 2 of these patients, *H influenza* or *P aeroginosa* was detected along with pneumococcus bacteria.

Figure 4 shows the number of patients with first episode of CAP of unknown etiology or pneumococcal pneumonia in the 2 groups of patients, and the relative risk ratios calculated by the Mantel-Haenszel test method using Review Manager 5 Version 5.1 software.

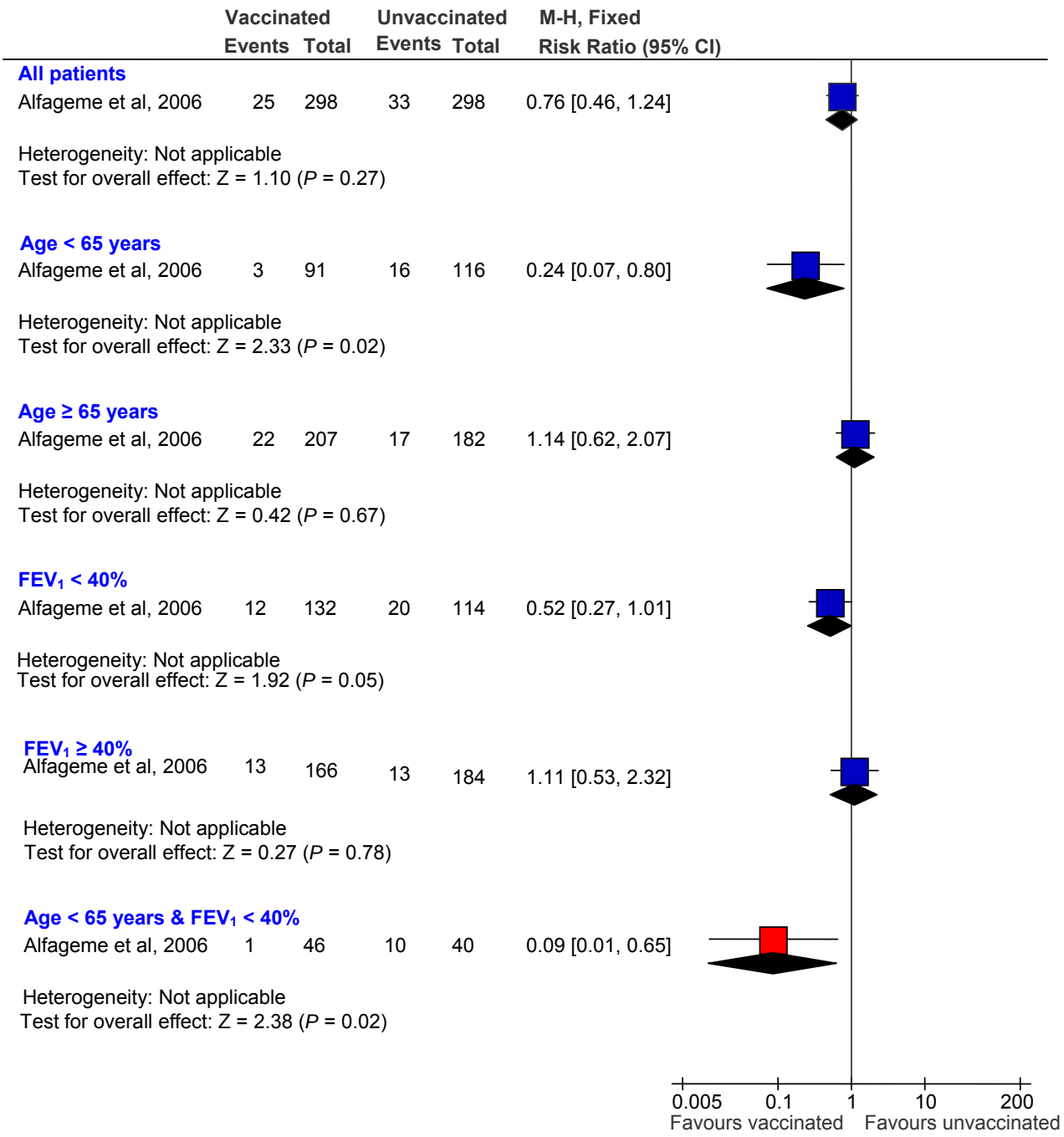


Figure 4: First Episode of Community-Acquired Pneumonia of Unknown Etiology and Pneumococcal Pneumonia in Vaccinated and Unvaccinated Patients*

*Abbreviations: CI, confidence interval; FEV_1, Forced expiratory volume in one second; M-H, Mantel-Haenszel.

Vaccine Efficacy

By univariate analysis there was no significant difference between the vaccinated group and the control group in regard to the vaccine efficacy of 24% (95% CI,−24 to 54; $P = 0.3$). Subgroup analysis showed that while there was no significant difference in the vaccine efficacy between the 2 groups (in the age

group ≥ 65 years), with a vaccine efficacy of −14% (95% CI, −107 to 38; $P = 0.8$), the difference was statistically significant for those who were younger than 65 years of age, with a vaccine efficacy of 76% (95% CI, 20–93; $P = 0.01$).

Vaccine efficacy was not significantly different between the 2 groups when analysis was performed separately for patients with a FEV_1 less than 40% predicted, with a vaccine efficacy of 48% (95% CI, −7 to 80; $P = 0.08$), or those with a FEV_1 greater than or equal to 40% predicted, with a vaccine efficacy of −11% (95% CI, −132 to 47; $P = 0.95$). However, vaccine efficacy was highest among patients who were both under the age of 65 years and had severe airflow obstruction, with a vaccine efficacy of 91% (95% CI, 35–99; $P = 0.002$).

Table 9 summarizes the efficacy of the vaccine in reducing the incidence of a first episode of CAP of unknown etiology and due to pneumococcus in subgroups of patients.

Table 9: Efficacy of the 23-Serotype Pneumococcal Vaccine in Reducing the Incidence of Community-Acquired Pneumonia of Unknown Etiology and due to Pneumococcus*

Subgroups	Vaccine Efficacy (%)	*P* value
All patients	24 (-24 to 54)	0.333
Age < 65 yeas	76 (20 to 93)	0.013
Age ≥ 65 years	-14 (-107 to 38)	0.801
FEV_1 < 40%	48 (-7 to 80)	0.076
FEV_1 ≥ 40%	-11 (-132 to 47)	0.945
Age < 65 years & FEV_1 < 40%	91 (35 to 99)	0.002

*Abbreviation: FEV_1, forced expiratory volume in 1 second.
Source: Alfageme et al, 2006 (45)

Survival Analysis

The Kaplan-Meier survival analysis showed no significant differences between the vaccinated group and the control group for time to the first episode of CAP (log-rank test = 1.15; $P = 0.28$) (Figure 5).

There were significant differences between the 2 groups for pneumonia of unknown etiology and pneumonia due to pneumococcus when data was analyzed according to subgroups of patients for those under age 65 or those who had severe airflow obstruction (Figures 6 and 7).

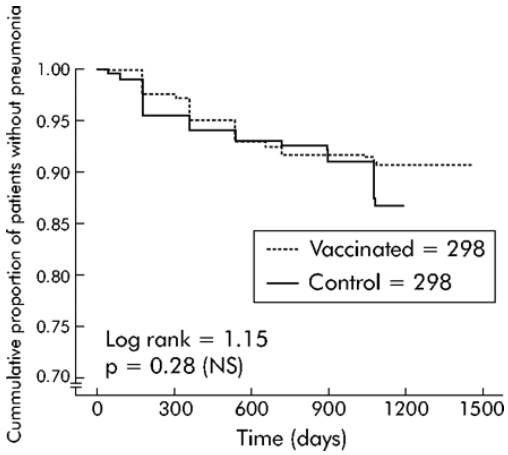


Figure 5: Kaplan-Meier Survival Curve Demonstrating the Cumulative Proportion of Patients Without Pneumonia Over the Follow-up Period

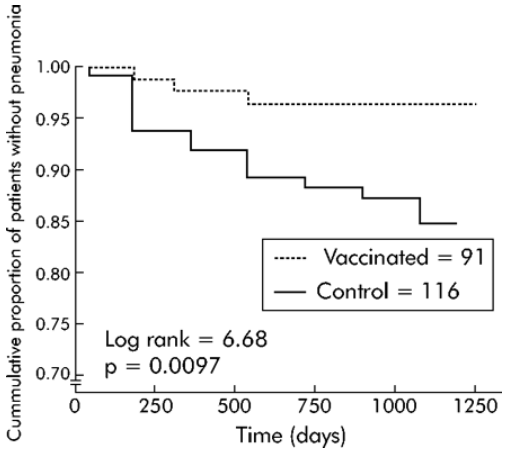


Figure 6: Kaplan-Meier Survival Curve Demonstrating the Cumulative Proportion of Patients Less Than 65 Years of Age Without Pneumonia Over the Follow-up Period

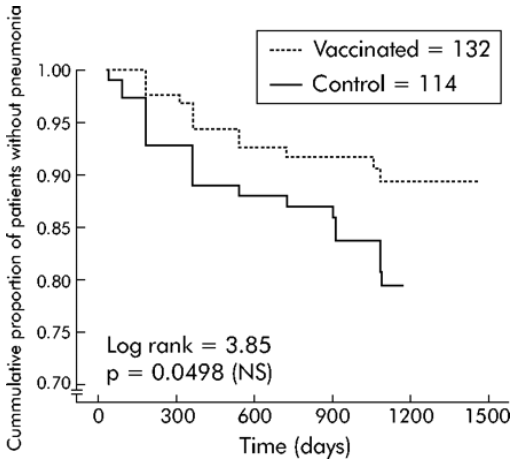


Figure 7: Kaplan-Meier Survival Curve Demonstrating the Cumulative Proportion of Patients with Severe COPD Without Pneumonia Over the Follow-up Period*

*Abbreviation: COPD, chronic obstructive pulmonary disease.

Reproduced from Thorax; Alfageme I, Vazquez R, Reyes N, Munoz J, Fernandez A, Hernandez M et al. 61(3):189-95, 2006, with permission from BMJ Publishing Group Limited. (45)

Influence of Modifying Factors

In the Cox proportional hazards regression model analyses, the hazard ratio (HR) for developing pneumonia was adjusted for the effect of selected factors including age (< 65 years vs. ≥ 65 years), the severity of airflow obstruction (FEV_1 < 40% vs. ≥ 40% predicted), and the interaction of the age with vaccine. The results of this analysis showed that the age of the patients influenced the efficacy of the vaccine. The HR in the global model was 0.2 (95% CI, 0.6–0.68; *P* = 0.01).

Separate models for the 2 age groups showed that the vaccine was not effective in older patients in reducing the incidence of pneumonia, but younger patients in the vaccine group were less likely to develop pneumonia compared with the unvaccinated patients in the same age group. The 2 models also showed that patients with more severe airflow obstruction could benefit from pneumococcal vaccination, and the benefit was statistically significant in the model for younger patients. Results are summarized in Table 10.

Table 10: Cox Proportional Hazards Regression Model*

Model	Factor†	HR (95% CI)	*P* Value
Global model	Vaccine	0.2 (0.06–0.68)	0.01
	Age	0.66 (0.33–1.31)	0.23
	Severe airflow obstruction	2.03 (1.21–3.41)	0.01
	Interaction (Age x vaccine)	5.82 (1.45–23.34)	0.01
Model for age < 65 years	Vaccine	0.19 (0.06–0.66)	0.01
	Severe airflow obstruction	2.62 (1.04–6.55)	0.04
Model for age ≥ 65 years	Vaccine	1.53 (0.61–2.17)	0.66
	Severe airflow obstruction	1.81 (0.96–3.39)	0.07

*Abbreviations: CI, confidence interval; HR, hazard ratio.

†Vaccine (0 = no, 1 = yes); Age (0 equals < 65 years, 1 equals ≥ 65 years); Severe airflow obstruction (0 = no, 1 = yes);

Source: Alfageme et al, 2006 (45)

Hospital Admission Rate

There were 67 first episodes of CAP (33 [11.1%] in the vaccine group, 34 [11.8%] in the control group). Most of the episodes of CAP required hospital admission, but the hospital admission rate did not differ between the 2 groups (vaccine group 19/25 [76%], control group 27/33 [81%]; *P* = 0.59).

The total number of days in the hospital due to CAP was 242 in the vaccine group and 412 in the control group. The median length of hospital stay was lower in the vaccine group than the control group, but the difference did not reach statistical significance (vaccine 9.5 days, control 12 days; *P* = 0.16).

Number Needed to Treat

The number needed to treat to prevent 1 patient from acquiring pneumonia was calculated as 10 (95% CI, 6–31) for vaccinating patients less than 65 years of age and as 3 (95% CI, 2–4) for these patients if they also had severe airflow obstruction.

Mortality

Vaccinated and unvaccinated patients had a similar mortality rate (19%). Mortality rates per 1,000 per year are shown in Table 11. The cause of death was: respiratory failure (n = 34), cardiovascular disease (n = 29), cancer (n = 21), infection (n = 13), gastrointestinal causes (n = 11), other (n = 5), and unknown (n = 2).

Table 11: Mortality Rates Due to Pneumonia*

	CAP and Nosocomial Pneumonia	CAP only
Mortality rates per 1,000 per year	50.80	34.40

*Abbreviation: CAP, community-acquired pneumonia.
Source: Alfageme et al, 2006 (45)

Table 12 shows factors influencing mortality among patients.

Table 12: Factors Influencing Mortality*

Factors	RR (95% CI)	*P* Value
Age	1.05 (1.03–1.08)	< 0.001
FEV_1	0.97 (0.95–0.98)	< 0.001
Current smoker	1.67 (1.08–2.60)	0.022
Presence of neoplasia	6.54 (4.15–10.23)	< 0.001

*Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; RR, relative risk.
Source: Alfageme et al, 2006 (45)

Adverse Events

No patients reported a local or systemic reaction to the vaccine.

Summary of Efficacy of the Pneumococcal Vaccination in Immunocompetent Patients with COPD

Clinical Effectiveness

The Kaplan-Meier survival analysis showed no significant differences between the vaccinated group and the control group for time to the first episode of community-acquired pneumonia due to pneumococcus or of unknown etiology (log-rank test = 1.15; $P = 0.28$). Overall, the vaccine efficacy was 24% (95% CI, −24 to 54; $P = 0.33$).

With respect to the incidence of pneumococcal pneumonia, the Kaplan-Meier survival analysis showed a significant difference between the 2 groups (vaccine: 0/298, control: 5/298; log-rank test 5.03; $P = 0.03$).

Hospital admission rates and median lengths of hospital stay were lower in the vaccine group, but the difference was not statistically significant. The mortality rate was not different between the 2 groups.

Subgroup Analysis

The Kaplan-Meier survival analysis showed significant differences between the vaccine and control groups for pneumonia of unknown etiology and due to pneumococcus when data were analyzed according to the subgroups of patients (age < 65 years, and severe airflow obstruction of FEV_1 < 40% predicted). The accumulated percentage of patients without pneumonia (of unknown etiology and due to pneumococcus) across time was significantly lower in the vaccine group than in the control group in patients younger than 65 years of age (log-rank test 6.68; $P = 0.0097$) and patients with an FEV_1 less than 40% predicted (log-rank test 3.85; $P = 0.0498$).

Vaccine effectiveness was 76% (95% CI, 20–93; $P = 0.01$) for patients who were younger than 65 years of age and −14% (95% CI, -107 to 38; $P = 0.8$) for those who were aged 65 years or older. Vaccine effectiveness for patients with an FEV_1 less than 40% predicted and those who had an FEV_1 greater than

or equal to 40% predicted was 48% (95% CI, −7 to 80; $P = 0.08$) and −11% (95% CI, −132 to 47; $P = 0.95$), respectively. For patients who were less than 65 years of age and had an FEV_1 less than 40% predicted, vaccine effectiveness was 91% (95% CI, 35–99; $P = 0.002$).

Cox modelling showed that the effectiveness of the vaccine was dependent on the age of the patient. The vaccine was not effective in patients greater than or equal to 65 years old (HR, 1.53; 95% CI, 0.61–2.17; $P = 0.66$), but it reduced the risk of acquiring pneumonia by 80% in patients less than 65 years old (HR, 0.19; 95% CI, 0.06–0.66; $P = 0.01$).

Safety

No patients reported any local or systemic adverse reactions to the vaccine.

Economic Analysis

The results of the economic analysis are summarized in issue 12 of the COPD series entitled *Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model*. This report can be accessed at: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Economic_March.pdf.

The results from the systematic review of the clinical evidence for influenza and pneumococcal vaccinations for patients with COPD were not included in the economic model because the appropriate model inputs were not identified in the literature.

Conclusions

Influenza vaccination significantly reduces the risk of acquiring influenza-related ARIs in patients with COPD, especially in patients with severe airflow obstruction. Although it was shown that the rates of hospitalization and subsequent mechanical ventilation due to episodes of influenza-related ARI were lower in patients who received the vaccine compared with those who did not, the study did not have sufficient power to demonstrate the presence of a statistically significant difference.

The study showed that patients' age, sex, severity of COPD, smoking status, or comorbid diseases do not modify the effectiveness of the vaccine. Adverse effects of the influenza vaccination included both systemic reactions (headache, myalgia, fever, and skin rash) and local reactions (swelling and itching) at the site of vaccination. The influenza vaccination was regarded as safe since systemic reactions and measures of lung function, dyspneic symptoms, exercise capacity, and total ARI (influenza-related and non-influenza-related) were not significantly different between the vaccinated group and the control group up to 4 weeks following the vaccination.

The pneumococcal vaccination does not result in a significant reduction in the risk of acquiring CAP due to pneumococcus or of unknown etiology, but it significantly reduces the risk of acquiring pneumococcal pneumonia in patients with COPD. However, for pneumonia due to pneumococcus and of unknown etiology, there were significant findings when data were analyzed according to subgroups of patients (age < 65 years) and severe airflow obstruction (FEV_1 < 40% predicted).

The accumulated percentage of patients without pneumonia due to pneumococcus and of unknown etiology across time was significantly lower in the vaccine group than in the control group in patients younger than 65 years of age and also in patients with severe airflow obstruction (FEV_1 < 40% predicted). The study showed that the efficacy of the vaccine is dependent on the age of the patient. The vaccine was not effective in patients 65 years of age or older, but it reduced the risk of acquiring pneumonia by 80% in patients younger than 65 years.

Hospital admission rates and median lengths of hospital stay were lower in the vaccine group than the control group, but the difference was not statistically significant. No patients reported any local or systemic adverse reactions to the vaccine, and the mortality rate was not different between patients who received the vaccine and patients who did not.

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity (FVC)	The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.
Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.

Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[5]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.
Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.
Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.

[5] The mild-to-moderate classification was created for the purposes of the report.

Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Medical Information Officer

Kellee Kaulback

Editorial Staff

Jan Collins
Irina Alecu

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

Appendices

Appendix 1: Literature Search Strategies

Search date: July 5, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1996 to June Week 4 2010>
Search Strategy:
---
1 exp Pulmonary Disease, Chronic Obstructive/ (13537)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (14459)
3 (copd or coad).ti,ab. (12785)
4 chronic airflow obstruction.ti,ab. (110)
5 exp Emphysema/ (2879)
6 ((chronic adj2 bronchitis) or emphysema).ti,ab. (8342)
7 or/1-6 (29288)
8 exp Vaccines/ (75124)
9 exp Immunotherapy/ (80295)
10 exp Influenza, Human/im [Immunology] (1354)
11 exp Orthomyxoviridae/im [Immunology] (4209)
12 (vaccin* or immuni* or immunotherap* or Flulaval or FluMist or Fluarix or Fluvirin or AgriFlu or Fluzone or Afluria or Prevnar or Pneumovax).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (212365)
13 exp Pneumococcal Infections/im [Immunology] (1064)
14 or/8-13 (233246)
15 7 and 14 (665)
16 limit 15 to (english language and humans and yr="2000 -Current") (430)

Database: EMBASE <1980 to 2010 Week 26>
Search Strategy:
---
1 exp chronic obstructive lung disease/ (35960)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (19439)
3 (copd or coad).ti,ab. (15823)
4 chronic airflow obstruction.ti,ab. (453)
5 exp emphysema/ (14553)
6 exp chronic bronchitis/ (6199)
7 ((chronic adj2 bronchitis) or emphysema).ti,ab. (14573)
8 or/1-7 (58597)
9 exp immunization/ (107323)
10 exp vaccine/ (125618)

11 (vaccin* or immuni* or immunotherap* or Flulaval or FluMist or Fluarix or Fluvirin or AgriFlu or Fluzone or Afluria or Prevnar or Pneumovax).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (353106)
12 or/9-11 (356099)
13 8 and 12 (1811)
14 limit 13 to (human and english language and yr="2000 -Current") (1078)

#	Query	Results
S14	(S7 or S8 or S9 or S10 or S11 or S12) and (S6 and S13)	126
S13	S7 or S8 or S9 or S10 or S11 or S12	31539
S12	vaccin* or immuni* or immunotherap* or Flulaval or FluMist or Fluarix or Fluvirin or AgriFlu or Fluzone or Afluria or Prevnar or Pneumovax	30134
S11	(MH "Pneumococcal Infections/IM")	57
S10	(MH "Influenza, Human+/IM")	46
S9	(MH "Orthomyxoviridae+/IM")	202
S8	(MH "Vaccines+")	16768
S7	(MH "Immunotherapy+")	12124
S6	S1 or S2 or S3 or S4 or S5	7203
S5	chronic bronchitis or emphysema	1550
S4	(MH "Emphysema+")	942
S3	copd or coad	3982
S2	(chronic obstructive and (lung* or pulmonary or airway* or airflow or respiratory) and (disease* or disorder*))	5434
S1	(MH "Pulmonary Disease, Chronic Obstructive+")	4195

Appendix 2: Quality of Studies and GRADE Tables

Quality of Studies for Each Outcome

Table A1: Influenza Vaccination: Episodes of Influenza-Related Acute Respiratory Illness*

Author, Year	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding	Power	Loss to Follow-up	ITT	Overall Quality
Wongsurakiat et al, 2004 (35)	125	✓	✓	✓	✓ Double blinded	80%	3	✓	High

*Abbreviations: ITT, intention-to-treat; N, number of participants.

Table A2: Influenza Vaccination: Hospitalization*

Author, Year	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding	Power	Loss to Follow-up	ITT	Overall Quality
Wongsurakiat et al, 2004 (35)	125	✓	✓	✓	✓ Double blinded	X Inadequate power (Low event rate)	3	✓	Low

*Abbreviations: ITT, intention-to-treat; N, number of participants.

Table A3: Influenza Vaccination: Mechanical Ventilation*

Author, Year	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding	Power	Loss to Follow-up	ITT	Overall Quality
Wongsurakiat et al, 2004 (35)	125	✓	✓	✓	✓ Double blinded	X Inadequate power (Low event rate)	3	✓	Low

*Abbreviations: ITT, intention-to-treat; N, number of participants.

Table A4: Influenza Vaccination: Safety Outcomes*

Author, Year	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding	Power	Loss to Follow-up	ITT	Overall Quality
Wongsurakiat et al, 2004 (35)	125	✓	✓	✓	✓ Double blinded	X Inadequate power (Low event rate)	3	✓	Low

*Abbreviations: ITT, intention-to-treat, N, number of participants.

Table A5: Pneumococcal Vaccination: Time to the First Episode of Community-Acquired Pneumonia Either Due to Pneumococcus or of Unknown Etiology*

Author, Year	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding	Power	Loss to Follow-up	ITT	Overall Quality
Alfageme et al, 2006 (45)	596	✓	✓	Not reported	✓ Treating physicians blinded	Not reported Large RCT	✓ None	✓	High

*Abbreviations: ITT, intention-to-treat; N, number of participants; RCT, randomized controlled trial.

Table A6: Pneumococcal Vaccination: Hospital Admission*

Author, Year	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding	Power	Loss to Follow-up	ITT	Overall Quality
Alfageme et al, 2006 (45)	596	✓	✓	Not reported	✓ Treating physicians blinded	X Inadequate power (Low event rate)	✓ None	✓	Low

*Abbreviations: ITT, intention-to-treat; N, number of participants.

Table A7: Pneumococcal Vaccination: Safety Outcomes*

Author, Year	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding	Power	Loss to Follow-up	ITT	Overall Quality
Alfageme et al, 2006 (45)	596	✓	✓	Not reported	✓ Treating physicians blinded	X Inadequate power (Low event rate)	✓ None	✓	Low

*Abbreviations: ITT, intention-to-treat; N, number of participants.

GRADE Tables

Table A8: GRADE of Evidence for Influenza Vaccination*

No. of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: Episodes of Influenza-Related ARI							
1	RCT	High	No serious limitations	No serious limitations	No serious limitations	n/a	High
Outcome: Hospitalization							
1	RCT	Low	No serious limitations	No serious limitations	No serious limitations	n/a	Low
Outcome: Mechanical Ventilation							
1	RCT	Low	No serious limitations	No serious limitations	No serious limitations	n/a	Low
Outcome: Safety Measures							
1	RCT	Low	No serious limitations	No serious limitations	No serious limitations	n/a	Low

* Abbreviations: ARI, acute respiratory illness; no., number; RCT, randomized controlled trial.

Table A9: GRADE of Evidence for Pneumococcal Vaccination*

No. of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: Time to the First Episode of Community- Acquired Pneumonia							
1	RCT	High	No serious limitations	No serious limitations	No serious limitations	n/a	High
Outcome: Hospital Admission							
1	RCT	Low	No serious limitations	No serious limitations	No serious limitations	n/a	Low
Outcome: Safety Measures							
1	RCT	Low	No serious limitations	No serious limitations	No serious limitations	n/a	Low

*Abbreviations: no., number; RCT, randomized controlled trial.

References

(1) Wesseling G. Occasional review. Influenza in COPD: pathogenesis, prevention, and treatment. Int J Chron Obstruct Pulmon Dis. 2007;2(1):5-10.

(2) Plans-Rubio P. Prevention and control of influenza in persons with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2007;2(1):41-53.

(3) Hovden A-O, Cox RJ, Haaheim LR. Influenza: The virus and prophylaxis with inactivated influenza vaccine in "at risk" groups, including COPD patients. Int J Chron Obstruct Pulmon Dis. 2007;2(3):229-40.

(4) Zuckerman AJ, Banatvala JE, Griffiths P, Schoub B, and Mortimer P. Principles and practice of clinical virology. 6th edition. London, UK: Wiley-Blackwell; 2009. Chapter 16, Influenza; 373-408.

(5) Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza A viruses. Microbiol Rev. 1992;56(1):152-79.

(6) Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. N Engl J Med. 2007 Oct 4;357(14):1373-81.

(7) Gardner EM, Bernstein ED, Dran S, Munk G, Gross P, Abrutyn E, et al. Characterization of antibody responses to annual influenza vaccination over four years in a healthy elderly population. Vaccine. 2001 Sep 14;19(32):4610-7.

(8) World Health Organization. Recommended viruses for influenza vaccines for use in the 2010-2011 northern hemisphere influenza season [Internet]. [updated 2011 Feb 13; cited 201 Feb 13]. Available from: http://www.flutrackers.com/forum/showthread.php?t=141403

(9) Schenkein JG, Nahm MH, Dransfield MT. Pneumococcal vaccination for patients with COPD: current practice and future directions. Chest. 2008 Mar;133(3):767-74.

(10) Fedson DS, Liss C. Precise answers to the wrong question: prospective clinical trials and the meta-analyses of pneumococcal vaccine in elderly and high-risk adults. Vaccine. 2004 Feb 25;22(8):927-46.

(11) Jackson LA, Neuzil KM, Yu O, Benson P, Barlow WE, Adams AL, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. N Engl J Med. 2003 May 1;348(18):1747-55.

(12) Cornu C, Yzebe D, Leophonte P, Gaillat J, Boissel JP, Cucherat M. Efficacy of pneumococcal polysaccharide vaccine in immunocompetent adults: a meta-analysis of randomized trials. Vaccine. 2001;19(32):4780-90.

(13) Ochoa-Gondar O, Vila-Corcoles A, Ansa X, Rodriguez-Blanco T, Salsench E, de Diego C, et al. Effectiveness of pneumococcal vaccination in older adults with chronic respiratory diseases: results of the EVAN-65 study. Vaccine. 2008 Apr 7;26(16):1955-62.

(14) Simberkoff MS, Cross AP, Al-Ibrahim M, Baltch AL, Geiseler PJ, Nadler J, et al. Efficacy of pneumococcal vaccine in high-risk patients. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1986 Nov 20;315(21):1318-27.

(15) Public Health Agency of Canada. Statement on seasonal trivalent inactivated influenza vaccine (TIV) for 2010-2011 [Internet]. [updated 2010; cited 2011 Feb 17]. Available from: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-6/index-eng.php#toc4

(16) Sanofi Pasteur. Product Monograph, Pneumo 23 [Internet]. [updated 2008; cited 2011 Feb 17]. Available from: https://www.vaccineshoppecanada.com/secure/pdfs/ca/Pneumo_23_E.pdf

(17) Merck & Co. Pneumovax 23: Pneumococcal vaccine polyvalent [Internet]. [updated 2011; cited 2011 Feb 13]. Available from: http://www.merck.com/product/usa/pi_circulars/p/pneumovax_23/pneumovax_pi.pdf

(18) Centers for Disease Control and Prevention. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23 valent pneumococcal polysaccharide vaccine (PPSV23) [Internet]. [updated 2010; cited 2011 Feb 17]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5934a3.htm#tab

(19) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490.

(20) Poole P, Chacko EE, Wood-Baker R, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006;Issue 1. Art. No.: CD002733. DOI: 10.1002/14651858.CD002733.pub2.

(21) Walters JA, Smith S, Poole P, Granger RH, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2010;Issue 11. Art. No.: CD001390. DOI: 10.1002/14651858.CD001390.pub3.

(22) Howells C.H., Tyler LE. Prophylactic use of influenza vaccine in patients with chronic bronchitis. A pilot trial. Lancet. 1961 Dec 30;2(7218):1428-32.

(23) Cate TR, Kasel JA, Couch RB, Six HR, Knight V. Clinical trials of bivalent influenza A/New Jersey/76-A/Victoria/75 vaccines in the elderly. J Infect Dis. 1977 Dec;136 Suppl:S518-S525.

(24) Fell PJ, Watson NP, O'Donnell HF, Simmons RL, Hasell SK. Longer term effects of live influenza vaccine in patients with chronic pulmonary disease. Lancet. 1977 Jun 18;1(8025):1282-4.

(25) A study of live influenza virus vaccine in patients with chronic bronchitis. Report to Medical Research Council's Committee on Influenza and Other Respiratory Virus Vaccines. Advisory Group on pulmonary function tests in relation to live influenza virus vaccines. Br J Dis Chest. 1980 Apr;74(2):121-7.

(26) Treanor JJ, Mattison HR, Dumyati G, Yinnon A, Erb S, O'Brien D, et al. Protective efficacy of combined live intranasal and inactivated influenza A virus vaccines in the elderly. Ann Intern Med. 1992 Oct 15;117(8):625-33.

(27) Treanor J, Dumyati G, O'Brien D, Riley MA, Riley G, Erb S, et al. Evaluation of cold-adapted, reassortant influenza B virus vaccines in elderly and chronically ill adults. J Infect Dis. 1994 Feb;169(2):402-7.

(28) Govaert TM, Dinant GJ, Aretz K, Masurel N, Sprenger MJ, Knottnerus JA. Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. BMJ. 1993 Oct 16;307(6910):988-90.

(29) Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. JAMA. 1994 Dec 7;272(21):1661-5.

(30) Gorse GJ, Campbell MJ, Otto EE, Powers DC, Chambers GW, Newman FK. Increased anti-influenza A virus cytotoxic T cell activity following vaccination of the chronically ill elderly with live attenuated or inactivated influenza virus vaccine. J Infect Dis. 1995 Jul;172(1):1-10.

(31) Gorse GJ, Otto EE, Daughaday CC, Newman FK, Eickhoff CS, Powers DC, et al. Influenza virus vaccination of patients with chronic lung disease. Chest. 1997 Nov 5;112(5):1221-33.

(32) Gorse GJ, O'Connor TZ, Young SL, Mendelman PM, Bradley SF, Nichol KL, et al. Efficacy trial of live, cold-adapted and inactivated influenza virus vaccines in older adults with chronic obstructive pulmonary disease: a VA cooperative study. Vaccine. 2003 May 16;21(17-18):2133-44.

(33) Neuzil KM, O'Connor TZ, Gorse GJ, Nichol KL. Recognizing influenza in older patients with chronic obstructive pulmonary disease who have received influenza vaccine. Clin Infect Dis. 2003 Jan 15;36(2):169-74.

(34) Gorse GJ, O'Connor TZ, Newman FK, Mandava MD, Mendelman PM, Wittes J, et al. Immunity to influenza in older adults with chronic obstructive pulmonary disease. J Infect Dis. 2004 Jul 1;190(1):11-9.

(35) Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritrutai W, Charoenratanakul S. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. Chest. 2004 Jun;125(6):2011-20.

(36) Wongsurakiat P, Maranetra KN, Gulprasutdilog P, Aksornint M, Srilum W, Ruengjam C, et al. Adverse effects associated with influenza vaccination in patients with COPD: a randomized controlled study. Respirology. 2004 Nov;9(4):550-6.

(37) Gorse GJ, O'Connor TZ, Young SL, Habib MP, Wittes J, Neuzil KM, et al. Impact of a winter respiratory virus season on patients with COPD and association with influenza vaccination. Chest. 2006 Oct;130(4):1109-16.

(38) Chuaychoo B, Wongsurakiat P, Nana A, Kositanont U, Maranetra KN. The immunogenicity of intradermal influenza vaccination in COPD patients. Vaccine. 2010 May 28;28(24):4045-51.

(39) Clancy RL, Dunkley ML. Oral non-typable Haemophilus influenzae enhances physiological mechanism of airways protection. Clin Exp Immunol. 2010;161(1):127-33.

(40) Tandon MK, Phillips M, Waterer G, Dunkley M, Comans P, Clancy R. Oral immunotherapy with inactivated nontypeable Haemophilus influenzae reduces severity of acute exacerbations in severe COPD. Chest. 2010 Apr;137(4):805-11.

(41) Leech JA, Gervais A, Ruben FL. Efficacy of pneumococcal vaccine in severe chronic obstructive pulmonary disease. CMAJ. 1987 Feb 15;136(4):361-5.

(42) Davis AL, Aranda CP, Schiffman G, Christianson LC. Pneumococcal infection and immunologic response to pneumococcal vaccine in chronic obstructive pulmonary disease. A pilot study. Chest. 1987 Aug;92(2):204-12.

(43) Steentoft J, Konradsen HB, Hilskov J, Gislason G, Andersen JR. Response to pneumococcal vaccine in chronic obstructive lung disease--the effect of ongoing, systemic steroid treatment. Vaccine. 2006 Feb 27;24(9):1408-12.

(44) Meyer P, Menzel M, Muellinger B, Weber N, Haeussinger K, Ziegler-Heitbrock L. Inhalative vaccination with pneumococcal polysaccharide in patients with chronic obstructive pulmonary disease. Vaccine. 2006 Jul 26;24(31-32):5832-8.

(45) Alfageme I, Vazquez R, Reyes N, Munoz J, Fernandez A, Hernandez M, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax. 2006 Mar;61(3):189-95.

(46) Ya Tseimakh I, Martynenko I, Paraeva S. Prophylactic efficacy of pneumococcal vaccination for chronic obstructive pulmonary disease (COPD) [Abstract]. Eur Respir J. 2006 Sep 3;28(suppl 50):178s.

(47) Teramoto S, Yamamoto H, Yamaguchi Y, Hanaoka Y, Ishil M, Ouchi YY. Clinical efficacy of anti-pneumococcal vaccination in elderly patients with COPD [Abstract]. American Thoracic Society International Conference, May 18 - 23, 2007, San Francisco, California, USA.

(48) Furumoto A, Ohkusa Y, Chen M, Kawakami K, Masaki H, Sueyasu Y, et al. Additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbation in patients with chronic lung disease. Vaccine. 2008 Aug 5;26(33):4284-9.

(49) Dransfield MT, Nahm MH, Han MK, Harnden S, Criner GJ, Martinez FJ, et al. Superior immune response to protein-conjugate versus free pneumococcal polysaccharide vaccine in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009 Sep 15;180(6):499-505.

(50) Goodman C. Literature searching and evidence interpretation for assessing health care practices. Stockholm, Sweden: The Swedish Council on Technology Assessment in Health Care; 1993 81 p. SBU-Report No 119E.

(51) Fine MJ, Smith MA, Carson CA, Meffe F, Sankey SS, Weissfeld LA, et al. Efficacy of pneumococcal vaccination in adults. A meta-analysis of randomized controlled trials. Arch Intern Med. 1994 Dec 12;154(23):2666-77.

(52) Melegaro A, Edmunds WJ. The 23-valent pneumococcal polysaccharide vaccine. Part I. Efficacy of PPV in the elderly: a comparison of meta-analyses. Eur J Epidemiol. 2004;19(4):353-63.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-7009-1 (PDF)

Ontario
Health Quality Ontario
Qualité des services
de santé Ontario

Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis

M Thabane and COPD Working Group

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 4, pp. 1–50, March 2012

Suggested Citation

This report should be cited as follows:

Thabane M; COPD Working Group. Smoking cessation for patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2012 March; 12(4) 1–50. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Smoking_Cessation_March.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to: MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit:
http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses:
http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
GOLD	Global Initiative for Chronic Obstructive Lung Disease
MAS	Medical Advisory Secretariat
NRT	Nicotine replacement therapy
OR	Odds ratio
RCT	Randomized controlled trial
RD	Risk difference
RR	Relative risk
SCC	Smoking cessation counselling

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective

The objective of this evidence-based analysis was to determine the effectiveness and cost-effectiveness of smoking cessation interventions in the management of chronic obstructive pulmonary disease (COPD).

Clinical Need: Condition and Target Population

Tobacco smoking is the main risk factor for COPD. It is estimated that 50% of older smokers develop COPD and more than 80% of COPD-associated morbidity is attributed to tobacco smoking. According to the Canadian Community Health Survey, 38.5% of Ontarians who smoke have COPD. In patients with a significant history of smoking, COPD is usually present with symptoms of progressive dyspnea (shortness of breath), cough, and sputum production. Patients with COPD who smoke have a particularly high level of nicotine dependence, and about 30.4% to 43% of patients with moderate to severe COPD continue to smoke. Despite the severe symptoms that COPD patients suffer, the majority of patients with COPD are unable to quit smoking on their own; each year only about 1% of smokers succeed in quitting on their own initiative.

Technology

Smoking cessation is the process of discontinuing the practice of inhaling a smoked substance. Smoking cessation can help to slow or halt the progression of COPD. Smoking cessation programs mainly target tobacco smoking, but may also encompass other substances that can be difficult to stop smoking due to the development of strong physical addictions or psychological dependencies resulting from their habitual use.

Smoking cessation strategies include both pharmacological and nonpharmacological (behavioural or psychosocial) approaches. The basic components of smoking cessation interventions include simple advice, written self-help materials, individual and group behavioural support, telephone quit lines, nicotine replacement therapy (NRT), and antidepressants. As nicotine addiction is a chronic, relapsing condition that usually requires several attempts to overcome, cessation support is often tailored to individual needs, while recognizing that in general, the more intensive the support, the greater the chance of success. Success at quitting smoking decreases in relation to:

- a lack of motivation to quit,
- a history of smoking more than a pack of cigarettes a day for more than 10 years,
- a lack of social support, such as from family and friends, and
- the presence of mental health disorders (such as depression).

Research Question

What are the effectiveness and cost-effectiveness of smoking cessation interventions compared with usual care for patients with COPD?

Research Methods

Literature Search

Search Strategy

A literature search was performed on June 24, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations (1950 to June Week 3 2010), EMBASE (1980 to 2010 Week 24), the

Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Library, and the Centre for Reviews and Dissemination for studies published between 1950 and June 2010. A single reviewer reviewed the abstracts and obtained full-text articles for those studies meeting the eligibility criteria. Reference lists were also examined for any additional relevant studies not identified through the search. Data were extracted using a standardized data abstraction form.

Inclusion Criteria

- English-language, full reports from 1950 to week 3 of June, 2010;
- either randomized controlled trials (RCTs), systematic reviews and meta-analyses, or non-RCTs with controls;
- a proven diagnosis of COPD;
- adult patients (≥18 years);
- a smoking cessation intervention that comprised at least one of the treatment arms;
- ≥ 6 months' abstinence as an outcome; and
- patients followed for ≥ 6 months.

Exclusion Criteria

- case reports
- case series

Outcomes of Interest

- ≥ 6 months' abstinence

Quality of Evidence

The quality of each included study was assessed taking into consideration allocation concealment, randomization, blinding, power/sample size, withdrawals/dropouts, and intention-to-treat analyses.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. The following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Summary of Findings

Nine RCTs were identified from the literature search. The sample sizes ranged from 74 to 5,887 participants. A total of 8,291 participants were included in the nine studies. The mean age of the patients in the studies ranged from 54 to 64 years. The majority of studies used the Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD staging criteria to stage the disease in study subjects. Studies included patients with mild COPD (2 studies), mild–moderate COPD (3 studies), moderate–severe COPD (1 study) and severe–very severe COPD (1 study). One study included persons at risk of COPD in addition to those with mild, moderate, or severe COPD, and 1 study did not define the stages of COPD.

The individual quality of the studies was high. Smoking cessation interventions varied across studies and included counselling or pharmacotherapy or a combination of both. Two studies were delivered in a hospital setting, whereas the remaining 7 studies were delivered in an outpatient setting. All studies reported a usual care group or a placebo-controlled group (for the drug-only trials). The follow-up periods ranged from 6 months to 5 years. Due to excessive clinical heterogeneity in the interventions, studies were first grouped into categories of similar interventions; statistical pooling was subsequently performed, where appropriate. When possible, pooled estimates using relative risks for abstinence rates with 95% confidence intervals were calculated. The remaining studies were reported separately.

Abstinence Rates

Table ES1 provides a summary of the pooled estimates for abstinence, at longest follow-up, from the trials included in this review. It also shows the respective GRADE qualities of evidence.

Table ES1: Summary of Results*

Intervention	Comparison	Number of Studies	Abstinence Rate Pooled Relative Risk (95% CI)	GRADE
Counselling	Usual Care	2	5.85 (3.81–8.97)†	Moderate
Intensive Counselling ≥ 90 minutes	Usual Care	1	7.70 (4.64–12.79)†	
Minimal Counselling < 90 minutes	Usual Care	1	1.56 (0.65–3.72)	
Counselling + NRT	Usual Care	3	4.28 (3.51–5.20)†	Moderate
Intensive Counselling ≥ 90 minutes + NRT	Usual Care	1	4.41 (3.60–5.39)†	
Minimal Counselling < 90 minutes + NRT	Usual Care	2	2.11 (0.90–4.91)	
Minimal Counselling < 90 minutes + Antidepressant	Usual Care	1	1.91 (0.65–5.61)	Low
Minimal Counselling < 90 minutes + NRT + Antidepressant	Usual Care	1	2.25 (0.87–5.85)	Low
NRT	Placebo	1	3.01 (1.02–8.89)†	Moderate
Antidepressant	Placebo‡	2	2.09 (1.35–3.24)†	Moderate
Nortriptyline	Placebo	1	2.54 (0.87–7.44)	Moderate
Bupropion	Placebo	2	2.01 (1.24–3.24)†	

*Abbreviations: CI, confidence interval; NRT, nicotine replacement therapy.
†Statistically significant ($P < 0.05$).
‡One trial used in this comparison had 2 treatment arms each examining a different antidepressant.

Conclusions

- Based on a moderate quality of evidence, compared with usual care, abstinence rates are significantly higher in COPD patients receiving intensive counselling or a combination of intensive counselling and NRT.
- Based on limited and moderate quality of evidence, abstinence rates are significantly higher in COPD patients receiving NRT compared with placebo.
- Based on a moderate quality of evidence, abstinence rates are significantly higher in COPD patients receiving the antidepressant bupropion compared to placebo.

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this evidence-based analysis was to examine the effectiveness and cost-effectiveness of smoking cessation interventions for patients with chronic obstructive pulmonary disease (COPD).

Clinical Need and Target Population

Tobacco smoking is the main risk factor for COPD. It is estimated that 50% of older smokers develop COPD and more than 80% of COPD-associated morbidity is attributed to tobacco smoking. (1) Patients with COPD who smoke have a particularly high level of nicotine dependence, and about 30% to 43% of patients with moderate to severe COPD continue to smoke. (2;3) Despite the severe symptoms that COPD patients suffer, the majority of patients with COPD are unable to quit smoking on their own; each year only about 1% of smokers succeed in quitting on their own initiative. (4)

Technology

Smoking cessation can help to slow or halt the progression of COPD. Smoking cessation programs mainly target tobacco smoking, but may also encompass other substances that can be difficult to stop smoking due to the development of strong physical addictions or psychological dependencies resulting from habitual use. Smoking cessation strategies include both pharmacological and nonpharmacological (behavioural or psychosocial) approaches. The basic components of smoking cessation interventions include simple advice, written self-help materials, individual and group behavioural support, telephone quit lines, nicotine replacement therapy (NRT), and antidepressants.

Since addiction to nicotine is a chronic relapsing condition that usually requires several attempts to overcome, cessation support is usually tailored to individual needs, but with the recognition that, in general, the more intensive the support, the greater the chance of success. Success at quitting smoking decreases in relation to:

- a lack of motivation to quit,
- a history of smoking more than a pack of cigarettes a day for more than 10 years,
- a lack of social support, such as from family and friends, and
- the presence of mental health disorders (such as depression).

Based on self-reported data from the 2003 Canadian Community Health Survey, 38.5% of Ontarians who smoke have been diagnosed with COPD. (5)

Regulatory Status

As shown in Table 1, several drugs to treat nicotine dependence are licensed by Health Canada. The only over-the-counter drug available is the nicotine transdermal patch.

Table 1: Summary of Drugs for Nicotine Dependence Licensed by Health Canada*

Drug Identification Number	Product	Active Ingredient	Strength	Route of Administration
02057743	Prostep TRD patch (30 mg per 7 sq cm)	Nicotine	30 mg	Transdermal
02291177	Champix	Varenicline (Varenicline Titrate)	0.5 mg	Oral
02291185	Champix	Varenicline (Varenicline Titrate)	1.0 mg	Oral
02298309	Champix (kit)	Varenicline (Varenicline Titrate)	0.5 mg and 1.0 mg	Oral
0263399	Ava-Bupropion	Bupropion hydrochloride	100 mg	Oral
02363402	Ava-Bupropion	Bupropion hydrochloride	150 mg	Oral
02325357	Bupropion SR	Bupropion hydrochloride	150 mg	Oral
02331616	Bupropion SR	Bupropion hydrochloride	100 mg	Oral
02260239	Novo-Bupropion	Bupropion hydrochloride	150 mg	Oral
02313421	PMS-Bupropion SR	Bupropion hydrochloride	150 mg	Oral
02325373	PMS-Bupropion	Bupropion hydrochloride	100 mg	Oral
02285657	Ratio-Bupropion	Bupropion hydrochloride	100 mg	Oral
02285665	Ratio-Bupropion SR	Bupropion hydrochloride	150 mg	Oral
02275074	Sandoz Bupropion SR	Bupropion hydrochloride	100 mg	Oral
03375082	Sandoz Bupropion SR	Bupropion hydrochloride	100 mg	Oral
02237825	Wellbutrin SR	Bupropion hydrochloride	150 mg	Oral
02275090	Wellbutrin XL	Bupropion hydrochloride	150 mg	Oral
02275104	Wellbutrin XL	Bupropion hydrochloride	150 mg	Oral
02238441	Zyban	Bupropion hydrochloride	300 mg	Oral

*Abbreviations: SR, sustained release; XL, extended release.

Evidence-Based Analysis

Research Question

What are the effectiveness and cost-effectiveness of smoking cessation interventions compared with usual care for patients with COPD?

Research Methods

Literature Search

Search Strategy

A literature search was performed on June 24, 2010 using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations (1950 to June Week 3 2010), OVID EMBASE (1980 to 2010 Week 24), the EBSCO Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from 1950 to June 2010. The detailed literature search strategy is shown in Appendix 1.

A single reviewer reviewed the abstracts and obtained full-text articles for those studies meeting the eligibility criteria. The reviewer also examined the reference lists for any additional relevant studies not identified through the search. Data were extracted using a standardized data abstraction form.

Inclusion Criteria

- English-language, full reports from 1950 to week 3 of June, 2010;
- either randomized controlled trials (RCTs), systematic reviews and meta-analyses, or non-RCTs with controls;
- a proven diagnosis of COPD;
- adult patients (≥ 18 years);
- a smoking cessation intervention that comprised at least one of the treatment arms;
- ≥ 6 months' abstinence as an outcome; and
- patients followed for ≥ 6 months.

Exclusion Criteria

- case reports
- case series

Outcomes of Interest

- ≥ 6 months' abstinence

Statistical Analysis

Due to substantial clinical heterogeneity across smoking cessation interventions, studies were first grouped into categories of interventions and then pooling was performed where appropriate. Pooled estimates (relative risks [RR] for abstinence with 95% confidence intervals [CI]) were calculated using a fixed-effects model. The remaining studies were reported descriptively. To further address heterogeneity, a priori subgroup analyses were performed based on intensity of smoking cessation counselling (SCC) and type of antidepressant.

Based on previous analyses, (6) the intensity of SCC was defined as

- minimal or brief counselling: < 90 minutes in total; or
- intensive counselling: ≥ 90 minutes in total.

Abstinence was defined as continuous abstinence (synonymous with prolonged or sustained abstinence) that was biochemically validated at all time points. It was anticipated a priori that there would be substantial differences among trials regarding components of smoking cessation strategies and methods of validation for abstinence.

Quality of Evidence

The quality of each included study was assessed taking into consideration the following 7 study design characteristics:

- adequate allocation concealment;
- randomization (study must include a description of the randomization procedure used, which must be a proper method);
- power/sample size (adequate sample size based on a priori calculations; underpowered studies were identified, when possible, using post-hoc sample size power calculations);
- blinding (if double blinding was not possible, a single blind study with unbiased assessment of outcome was considered adequate for this criterion);
- < 20% withdrawals/dropouts;
- intention-to-treat analysis conducted and done properly (i.e., withdrawals/dropouts considered in analysis); and
- other criteria as appropriate for the particular research question and study design.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (7) as presented below.

- Quality refers to criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of the estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

The database search yielded 1,619 citations (with duplicates removed) published between 1950 and week 3 of June 2010. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 summarizes the review of citations at title, abstract, and full text level.

In total, 12 studies met the inclusion criteria: 3 systematic reviews and 9 RCTs. The references lists of the included studies were hand searched to identify any additional potentially relevant studies, and 1 additional citation, a health technology assessment, was added, bringing the total to 13 included citations. Detailed characteristics of the included studies are described in Appendix 2.

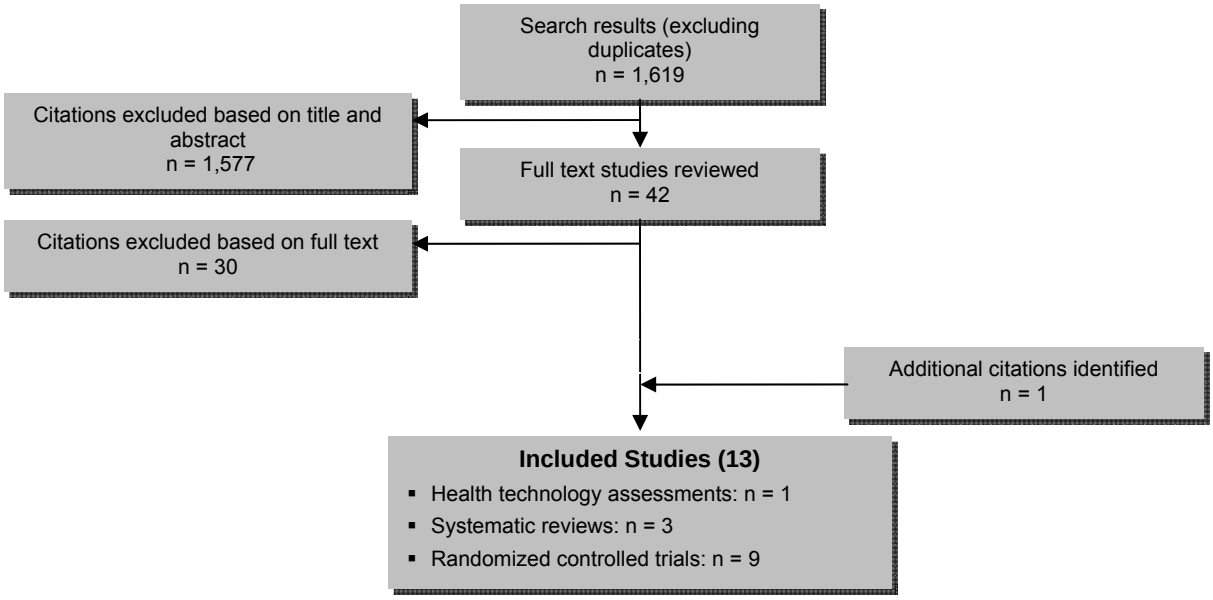


Figure 1: Citation Flow Chart

For each included study, the study design was identified and is summarized below in Table 2, which is a modified version of the hierarchy of study design by Goodman. (8)

Table 2: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	4
Large RCT†	7
Small RCT	2
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	
Total	**13**

*Abbreviation: RCT, randomized controlled trial.

†Large RCT is defined as a sample size of at least 100.

Health Technology Assessments

One health technology assessment by Hoogendoorn et al (6) was identified. The objective was to assess the long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD based on a systematic review of RCTs on smoking cessation interventions in patients with COPD with 12-month biochemically validated abstinence rates.[1]

Interventions were grouped into usual care, minimal or brief counselling (< 90 minutes), intensive counselling (≥ 90 minutes) without pharmacotherapy, and intensive counselling (≥ 90 minutes) with pharmacotherapy. (6) Interventions offering pharmacotherapy on a noncompulsory basis were included in the pharmacotherapy category if it was used by more than 50% of the patients. Patients receiving the placebo drug also often received some form of counselling and were therefore grouped into the categories of minimal counselling or intensive counselling, depending on the duration of counselling. Absolute quit rates for each of the categories were used to populate the model. Two different abstinence rates were calculated:

- continuous abstinence rate at 12 months postintervention
- point-prevalence abstinence rate at 12 months postintervention.

[1] In addition to evaluating the effectiveness of the smoking cessation interventions, a dynamic Dutch COPD population model was developed to estimate the impact of increased implementation of smoking cessation interventions and usual care and the cost-effectiveness of the interventions. These are out of scope of this systematic review, and so the results are not summarized here.

Hoogendoorn et al (6) included 9 RCTs. The average 12-month continuous abstinence rates were: 1.4% for usual care, 2.6% for minimal counselling, 6% for intensive counselling, and 12.3% for intensive counselling with pharmacotherapy (Table 3). (6) Intensive counselling as well as intensive counselling plus pharmacotherapy were significantly more effective than usual care. The authors noted that the analysis did not take into account the duration and intensity of pharmacotherapy; thus, it is likely that longer duration and greater intensity of pharmacotherapy would lead to higher abstinence rates. (6)

Table 3: Abstinence Rates and Associated Intervention Costs for the Four Intervention Groups*

Intervention	12-Month Continuous Abstinence Rates†	
	Average Rate, Percentage	Percent Difference With Usual Care (95% CI)
Usual care	1.4	–
Minimal or brief counselling < 90 minutes	2.6	1.2 (−1.3 to 3.7)
Intensive counselling ≥ 90 minutes	6.0	4.6 (1.8–7.4)
Intensive counselling ≥ 90 minutes with pharmacotherapy	12.3	10.9 (6.9 –15.0)

*Abbreviation: CI, confidence interval.

†Based on random effect meta-analysis performed on the absolute abstinence rates in trial arms.

Reproduced from Thorax, Hoogendoorn M, Feenstra TL, Hoogenveen RT, Rutten-van Molken MP, Vol. 65, p. 711-8, 2010 with permission from BMJ Publishing Group Ltd.

Systematic Reviews

Three systematic reviews were identified. (9;10) All 3 reviews included RCTs only.

In the 2009 systematic review by Strassmann et al (11), a network meta-analysis was performed to assess the effectiveness of smoking cessation interventions for patients with COPD. Behavioural interventions were classified as individual or group, self-help material, and telephone counselling; pharmacological interventions included nicotine replacement therapy (NRT), antidepressants, or other drugs. The primary outcome measure was prolonged biologically confirmed abstinence rates at 6 months or longer follow-up. If prolonged abstinence rates were not available, point-prevalence (defined as smoking cessation 7 days prior to follow-up) rates were considered. (11)

Strassmann et al (11) included 8 RCTs. Smoking cessation counselling (SCC) plus NRT was more effective than SCC alone, no intervention, or usual care (UC). Smoking cessation counselling plus antidepressant was the second most effective intervention. The intensity of SCC had an impact on prolonged abstinence rates. These results are summarized in Table 4.

Table 4: Relative Efficacy of Smoking Cessation Intervention on Prolonged Abstinence*

Intervention	Comparator	OR (95% CI)	*P* Value
Smoking cessation counselling + NRT	Nothing / usual care	5.08 (4.32–5.97)	< 0.001
Smoking cessation counselling + NRT	Smoking cessation counselling	2.80 (1.49–5.26)	0.001
Smoking cessation counselling + NRT	Smoking cessation counselling + antidepressant	1.53 (0.71–3.30)	0.28
Smoking cessation counselling + antidepressant	Nothing / usual care	3.32 (1.53–7.21)	0.002
Smoking cessation counselling + antidepressant	Smoking cessation counselling	1.83 (1.18–2.83)	0.007
Smoking cessation counselling	Nothing / usual care	1.82 (0.96–3.44)	0.07

*Abbreviations: CI, confidence interval; NRT, nicotine replacement therapy; OR, odds ratio.
Source: Strassman et al, 2009 (11)

An in-depth analysis taking into consideration the intensity of SCC showed that the odds of prolonged abstinence were increased with high-intensity SCC versus low-intensity SCC. (11) However, only high-intensity SCC plus NRT was significantly more effective than low-intensity SCC plus NRT (odds ratio [OR], 1.81; 95% CI, 1.04–3.15; $P = 0.04$). When comparing high-intensity SCC alone with low-intensity SCC (OR, 1.46; 95% CI, 0.44–4.90; $P = 0.54$), and high-intensity SCC plus antidepressant with low-intensity SCC plus antidepressant (OR, 1.55; 95% CI, 0.35–6.91; $P = 0.56$), the ORs were not significant.

Point-prevalence was examined in 2 studies. In 1 of these studies, the abstinence rate was not significantly different when comparing rewarding patients for smoking abstinence with lottery tickets and reimbursement for planned visits. (12) In the other study, a statistically significant improvement in abstinence rates was observed (OR, 2.71; 95% CI, 0.62–12.35) when comparing the use of the term "smoker's lung" by nurses instead of chronic bronchitis when speaking to patients with COPD. (13)

Three of the included studies included mortality as an outcome. The mortality results were not pooled; 1 of the 3 studies found a statistically significant reduction in mortality when comparing the 14.5 year mortality in the smoking cessation intervention groups with the usual care group (OR, 0.74; 95% CI, 0.63–0.87). (14;15) No significant differences were observed at 1-year of follow-up in the other 2 studies (Tonnesen et al (16): OR, 0.74, 95% CI 0.22–2.41 comparing NRT with placebo; Brandt et al (13): OR, 1.88; 95% CI, 0.30–12.55 comparing diagnosis of "smoker's lung" with chronic bronchitis).

Overall, the authors concluded that SCC plus NRT appears to be the most effective smoking cessation intervention followed by SCC plus antidepressant. Smoking cessation counselling without additional drug treatment is not much more effective than usual care. (11)

MAS Comments
Although the analysis was stratified by the intensity of counselling, the authors did not define the thresholds for low- and high-intensity counselling, nor how the thresholds were determined.

The authors reported that there was a lack of consistency across studies in reporting patient characteristics such as severity of COPD and the motivation to quit smoking; these are important characteristics which may influence the effectiveness of smoking cessation interventions.

The 2001 van der Meer et al (9) systematic review evaluated the effectiveness of smoking cessation interventions in patients with COPD; however, due to important heterogeneity across the identified RCTs, a meta-analysis was not performed and results were summarized descriptively.

Five RCTs, 2 of high quality, were included in this systematic review. (9) The results of the individual studies are summarized in Table 5.

Table 5: Abstinence Rates of Five Included Individual Studies*

Author, Year	Time of Assessment	Intervention Sample Size (%)	Control Sample Size (%)	Abstinence Rates Risk Difference (95% CI)
Anthonisen et al, 1994 (17)	1 year	680† (34.7)	177 (9.0)	0.26 (0.23–0.28)
		674‡ (34.4)	177 (9.0)	0.25 (0.23–0.28)
	5 years	408† (20.8)	102 (5.2)	0.16 (0.14–0.18)
		427‡ (21.8)	102 (5.2)	0.17 (0.14–0.19)
Brandt et al, 1997 (13)	1 year	8 (40.0)	5 (20.0)	0.20 (−0.07 to 0.47)
Crowley et al, 1995 (12)	6 months	5 (13.9)	5 (13.9)	0
Pederson et al, 1991 (18)	6 months	10 (33.3)	6 (21.4)	0.12 (−0.11 to 0.35)
Tashkin and Murray, 2001 (19)	6 months	32 (15.7)	18 (9.0)	0.07 (0.00–0.13)

*Abbreviation: CI, confidence interval.
†Smoking cessation intervention + bronchodilator.
‡Smoking cessation intervention + placebo.
Source: van der Meer et al, 2001. (9)

Overall, the authors concluded that a combination of psychosocial intervention and pharmacological intervention is superior to no treatment or to psychological intervention alone. Due to the lack of sufficient high quality studies, no absolute or convincing evidence was found to support the effectiveness of psychosocial intervention for patients with COPD. (9) van der Meer et al (9) noted 2 important limitations with their review:

- Heterogeneity existed across studies with regards to patient characteristics, outcome measurements, and the timing of measurements.
- The description of counselling was often unclear, including the intensity of person-to-person clinical contact, types of counselling and behavioural therapies, and formats of psychosocial interventions.

Finally, the 2004 systematic review by Wagena et al (10) evaluated the effectiveness of smoking cessation interventions in patients with COPD. Behavioural interventions included:

- self-help interventions (such as the use of pamphlets, audio tapes, videotapes, mailed information, or computer programs);
- individual or group counselling; and/or
- telephone counselling, with or without the use of pharmacotherapy (NRT, antidepressants, or both).

The primary outcome measure was biochemically confirmed abstinence rates at least 6 months following the intervention. (10)

Wagena et al (10) included 5 RCTs. Due to heterogeneity across studies with regards to the study populations and smoking cessation interventions, the results were not pooled.
Although 3 trials found increased abstinence rates in the smoking cessation group compared with the control group, the differences were not statistically significant (Brandt et al (13): risk difference [RD], 0.16; 95% CI, −0.07 to 0.38 comparing using the term "smoker's lung" instead of chronic bronchitis when speaking with patients; Pederson et al (18): RD, 0.11; 95% CI, −0.08 to 0.29 comparing individual counselling plus self-help smoking cessation manuals with physician's advice to quit; and Crowley et al (12): RD, 0.10; 95% CI, −0.11 to 0.31 comparing contingent reinforcement using lottery tickets with reimbursing patients for their planned visits).

The Lung Health Study (17) evaluated the effect of an intensive smoking cessation intervention combined with either inhaled bronchodilator ipratropium bromide or placebo compared with the usual care group (no definitive smoking intervention) on lung function (forced expiratory volume in 1 second). The smoking cessation intervention consisted of free nicotine gum (NRT) and a 12–group session intervention for 10 weeks, starting with 4 meetings per week and gradually declining over the 10-week period. For those patients who quit smoking, a maintenance program aimed at preventing relapse by teaching coping skills for problems such as stress and weight gain was provided. (17)

After 12 months' follow-up, lung function (defined by the forced expiratory volume in 1 second) was statistically improved in the smoking cessation intervention plus ipratropium bromide group compared with usual care (RD, 0.26; 95% CI, 0.23–0.28). The results remained significantly different at 5-year follow-up (RD, 0.16; 95% CI, 0.14–0.18). The combination of the smoking intervention plus the placebo bronchodilator was also significantly more effective than the usual care group at both 12 months and 5 years (RD, 0.25; 95% CI, 0.23–0.28 and RD, 0.17; 95% CI, 0.15–0.19, respectively). In a follow-up study at 11 years, Murray et al (20) demonstrated that the benefit in lung function remained.

Finally, 1 study reported the efficacy of bupropion sustained release for smoking cessation. (19) The results showed that the combination of bupropion sustained release 300 mg per day for 12 weeks in addition to 10 individual counselling sessions resulted in significantly higher prolonged abstinence rates after 26 weeks compared with placebo combined with the behavioural intervention (RD, 0.07; 95% CI, 0.00–0.13). However, at 12 months, the difference was no longer apparent (RD, 0.02; 95% CI, −0.04 to 0.07). (19)

Overall, the authors concluded that, with the exception of combined use of pharmacotherapy and counselling to reduce craving and withdrawal, the success rates of other smoking cessation interventions in patients with COPD is low. (10)

Randomized Controlled Trials

A total of 9 RCTs that met the inclusion criteria were identified and included in this review. The sample size of the studies ranged from 74 to 5,887 patients. A total of 8,291 participants were included in the 9 studies. The mean age of the patients ranged from 54 to 64 years. The majority of studies compared smoking cessation interventions to usual care; however, 3 studies (16;19;21) examined the use of pharmacotherapy compared to a placebo control group. Smoking cessation interventions included counselling alone and counselling plus pharmacotherapy. In trials where pharmacotherapy was compared to placebo, both the intervention and control arms received identical behavioural counselling.

The duration, intensity, and mode of behavioural counselling and the type of pharmacotherapy varied among studies. Antidepressants were used as pharmacotherapy in 2 of the studies. (19;21) Two studies were conducted in the hospital setting (18;22), while the remainder of studies were conducted in the

outpatient setting. The severity of COPD in patients varied among studies; however, the majority of studies (6 of 9) were conducted in the mild-to-moderate COPD population based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. One study (23) included patients with undiagnosed COPD. However, the patients were only eligible for the study if they had mild or moderate COPD according to the GOLD criteria as determined by spirometry. Studies had varying lengths of follow-up ranging from 6 months to 5 years. The majority of studies followed patients for 1 year. Table 6 provides an assessment of the quality of the individual studies. Appendix 3 provides a detailed summary of characteristics of included studies.

Table 6: Quality of Included Individual Studies*

Author, Year	Number of Patients	Randomization	Allocation Concealment	Blinding	Sample Size Calc.	Withdrawals/ Dropouts	ITT
Pederson et al, 1991 (18)	74	✓		✓	✓	✓	
Sundblad et al, 2008 (22;24)	247	✓	✓	✓		✓	✓
Anthonisen et al, 1994 (17)	5887	✓	✓	✓	✓	✓	✓
Tashkin and Murray, 2001 (19)	404	✓	✓	✓	✓	✓	✓
Hilberink et al, 2010 (25;26)	667	✓	✓		✓	✓	✓
Wilson et al, 2008 (27)	91	✓	✓	✓	✓	✓	✓
Tonnesen et al, 2006 (16;28)	370	✓	✓	✓	✓	✓	✓
Wagena et al, 2005 (21)	255	✓	✓	✓	✓	✓	✓
Kotz et al, 2009 (23;29)	296	✓		✓	✓	✓	✓

*Abbreviations: Calc., calculation; ITT, intention-to-treat.

Abstinence

Validation methods confirming abstinence varied among studies. In 2 studies, smoking cessation was validated by carboxyhemoglobin testing (18;30); in 5 studies by breath carbon monoxide testing; (12;13;16;19;22); in 2 studies by urinary cotinine testing (21;23); in 2 studies by salivary cotinine and carbon monoxide testing (17;27); in 1 study by salivary cotinine alone (31); and in 1 study by self-reported abstinence without a validation test. (26) When prolonged abstinence rates were unavailable, point-prevalence rates (defined as smoking cessation 7 days prior to follow-up) were considered. Time to assessment of abstinence varied among studies, and abstinence at the longest follow-up was used in the meta-analysis.

Results of the pooled estimates for abstinence are summarized in Table 7. Quality of evidence according to GRADE, as shown in Appendix 5, was assessed as moderate for comparisons of counselling with usual care, counselling plus NRT with usual care, NRT with placebo, and antidepressant with placebo.

Table 7: Summary of Results – Abstinence at Longest Follow-Up*

Intervention	Comparison	Number of Studies	Abstinence Rate Pooled Relative Risk (95% CI)	GRADE
Counselling	Usual Care	2	5.85 (3.81–8.97)†	Moderate
Intensive Counselling ≥ 90 minutes	Usual Care	1	7.70 (4.64–12.79)†	
Minimal Counselling < 90 minutes	Usual Care	1	1.56 (0.65–3.72)	
Counselling + NRT	Usual Care	3	4.28 (3.51–5.20)†	Moderate
Intensive Counselling ≥ 90 minutes + NRT	Usual Care	1	4.41 (3.60–5.39)†	
Minimal Counselling < 90 minutes + NRT	Usual Care	2	2.11 (0.90–4.91)	
Minimal Counselling < 90 minutes + Antidepressant	Usual Care	1	1.91 (0.65–5.61)	Low
Minimal Counselling < 90 minutes + NRT + Antidepressant	Usual Care	1	2.25 (0.87–5.85)	Low
NRT	Placebo	1	3.01 (1.02–8.89)†	Moderate
Antidepressant	Placebo‡	2	2.09 (1.35–3.24)†	Moderate
Nortriptyline	Placebo	1	2.54 (0.87–7.44)	Moderate
Bupropion	Placebo	2	2.01 (1.24–3.24)†	

*Abbreviations: CI, confidence interval; NRT, nicotine replacement therapy.

†Statistically significant ($P < 0.05$).

‡One study had 2 treatment arms, each examining a different antidepressant.

Results

Counselling Versus Usual Care

Two studies examined the efficacy of SCC versus usual care in patients with COPD in an inpatient setting (Figure 2). One study (25) included an intervention of intensive counselling (defined as ≥ 90 minutes), while the other study (18) compared minimal counselling (defined as < 90 minutes of counselling) to that of usual care. As expected, high rates of statistical heterogeneity were observed when pooling these studies ($I^2 = 90\%$). Examining the studies separately showed that abstinence rates were statistically higher in those receiving intensive counselling compared to usual care (RR, 7.70; 95% CI, 4.64–12.79; $P < 0.00001$). No significant effect of minimal counselling on abstinence rates was found compared to usual care (RR, 1.56; 95% CI, 0.65–3.72; $P = 0.32$), but this may have been due to a lack of power as a result of a small study sample size.

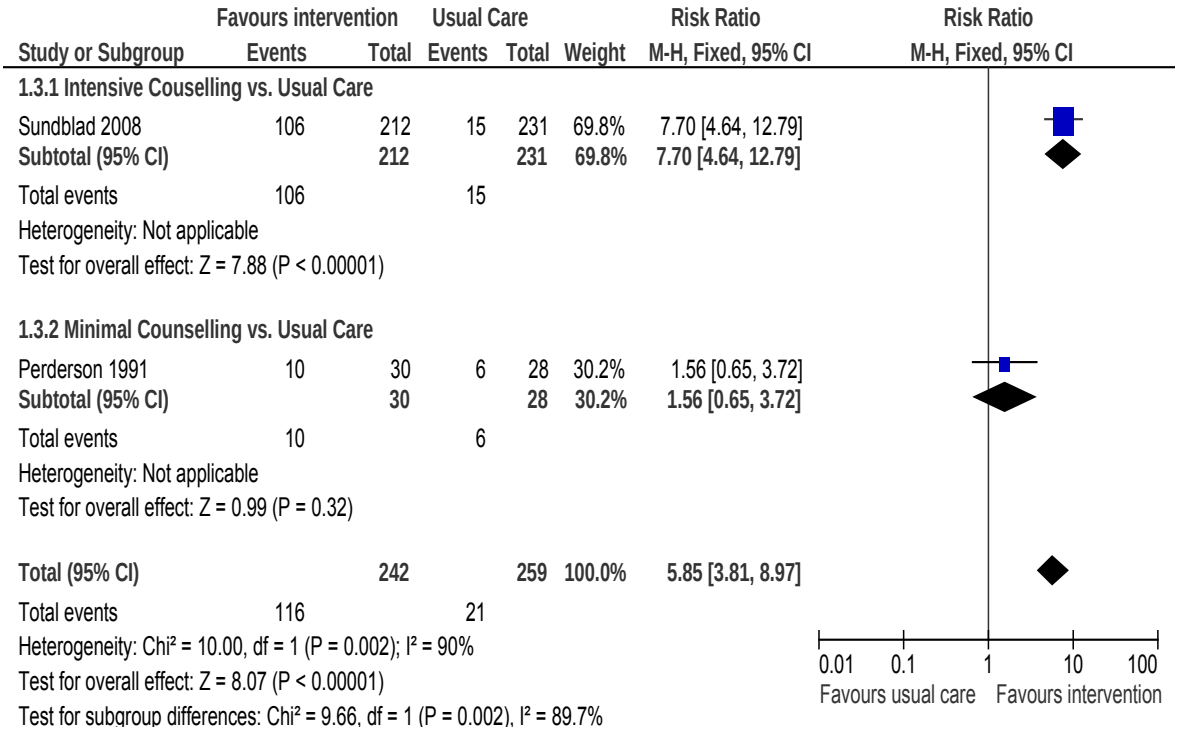


Figure 2: Comparison of Abstinence for Counselling Versus Usual Care Groups at Longest Follow-Up*

*Abbreviations: CI, confidence interval; M-H, Mantel–Haenszel.

Counselling Plus Nicotine Replacement Therapy Versus Usual Care

Three studies reported abstinence rates in patients with COPD receiving SCC plus NRT compared to those receiving usual care (Figure 3). One study (17) examined the effect of intensive counselling plus NRT while the other 2 studies (25;27) used minimal counselling plus NRT. As seen in Figure 3, there is a statistically significant difference in abstinence rates favouring the intervention groups compared with usual care (RR, 4.28; 95% CI, 3.51–5.20; $P < 0.001$). When subgrouped by intensity of counselling, only the study using intensive counselling plus NRT showed a significant difference in abstinence rates compared with usual care ($P < 0.001$).

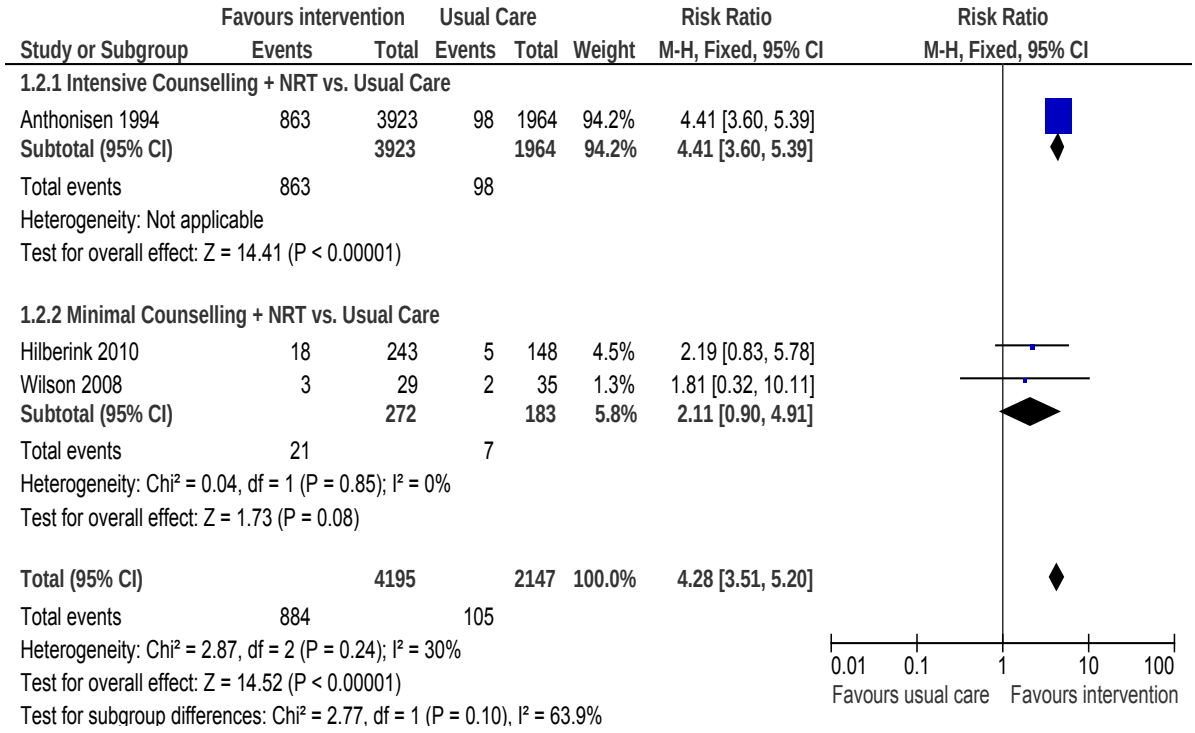


Figure 3: Comparison of Abstinence for Counselling Plus NRT Versus Usual Care Groups at Longest Follow-Up*

*Abbreviations: CI, confidence interval; M–H, Mantel-Haenszel; NRT, nicotine replacement therapy.

Minimal Counselling Plus Antidepressant Versus Usual Care

One study reported (23) abstinence rates in patients with COPD receiving minimal counselling plus an antidepressant (nortriptyline) compared with those receiving usual care (Figure 4). No significant difference in abstinence rates was found between the intervention group and the usual care group (RR, 1.91; 95% CI, 0.65–5.61; $P = 0.24$). Although the study itself was of high quality, patients enrolled into this study had undiagnosed COPD and were only classified by the GOLD criteria upon entering the study. Since patients were unaware of their COPD diagnosis, they may not have been as motivated to quit smoking or to take their illness as seriously as patients who had been previously diagnosed with COPD.

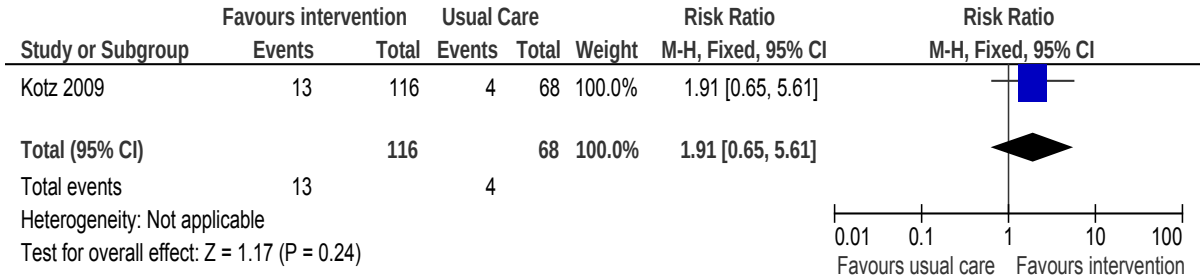


Figure 4: Comparison of Abstinence for Minimal Counselling Plus Antidepressant Versus Usual Care Groups at Longest Follow-Up*

*Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Minimal Counselling Plus NRT Plus Antidepressant Versus Usual Care

The efficacy of receiving minimal counselling, recommended NRT, and a prescribed antidepressant (bupropion) compared to usual care was examined in 1 study. (25) The study was conducted in the outpatient setting. As shown in Figure 5, there was no statistically significant difference in abstinence rates between the intervention and usual care arms (RR, 2.25; 95% CI, 0.87–5.85; $P = 0.10$). Although the study itself was of high quality, several factors may have contributed to the lack of success of the intervention including:

- the inclusion of some unmotivated COPD smokers,
- less intensive counselling (the intervention was integrated into routine care), and
- poor compliance with the use of bupropion and NRT noted at follow-up.

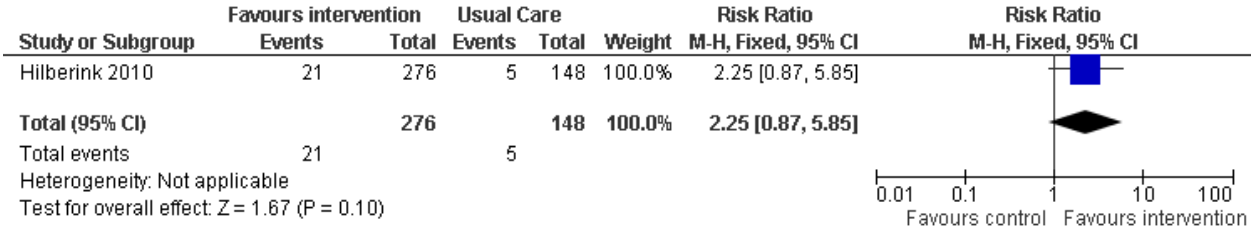


Figure 5: Comparison of Abstinence for Minimal Counselling Plus NRT Plus Antidepressant Versus Usual Care Groups at Longest Follow-Up*

*Abbreviations: CI, confidence interval; M–H, Mantel-Haenszel; NRT, nicotine replacement therapy.

Nicotine Replacement Therapy Versus Placebo

One study (16) reported the efficacy of receiving NRT in a placebo-controlled trial. Both study arms received identical counselling. The study was conducted in an outpatient setting. As shown in Figure 6, there was a statistically significant difference in abstinence rates favouring the intervention group compared with the usual care group (RR, 3.01; 95% CI, 1.02–8.89; $P = 0.05$). The 1-year quit rate of 14% observed in the intervention group receiving the nicotine sublingual tablet is the same range as that reported in previous studies.

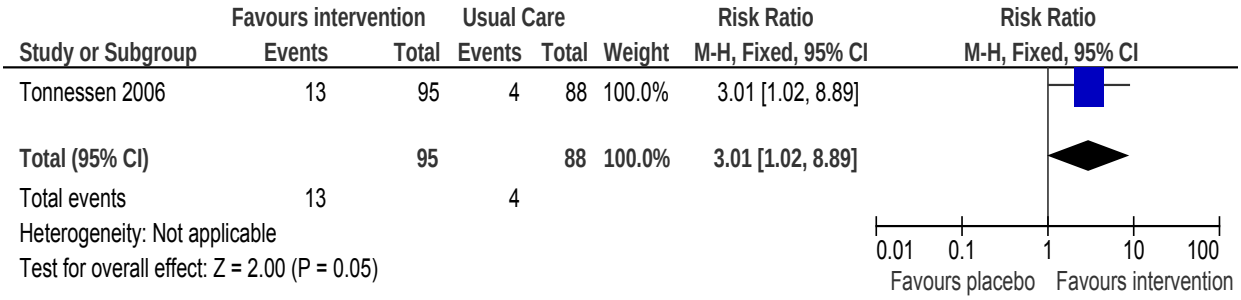


Figure 6: Comparison of Abstinence for NRT Versus Placebo Groups at Longest Follow-Up*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; NRT, nicotine replacement therapy.

Antidepressant Versus Placebo

Two studies (19;21) reported abstinence rates in patients with COPD receiving an antidepressant in a placebo-controlled trial (Figure 7). One study (21) included 2 arms, each examining a different antidepressant. As seen in Figure 7, there is a statistically significant difference in abstinence rates favouring the intervention groups as compared to usual care (RR, 2.09; 95% CI, 1.35–3.24; $P < 0.001$).

When subgrouped by type of antidepressant, only those studies that prescribed bupropion showed a significant difference in abstinence rates as compared to usual care ($P = 0.004$).

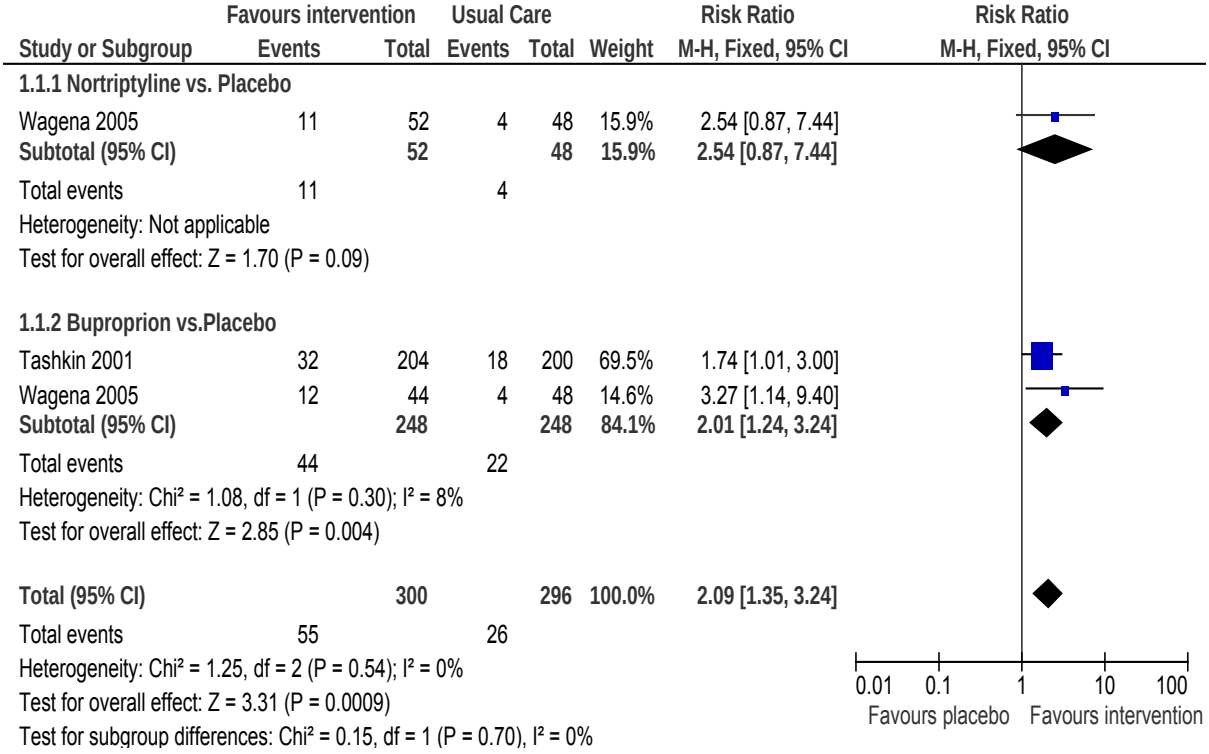


Figure 7: Comparison of Abstinence for Antidepressant Versus Placebo Groups at Longest Follow-Up*

*Abbreviations: CI, confidence interval; M-H, Mantel–Haenszel.

Limitations

Due to the limited amount of studies available for this analysis, it was not possible to examine the characteristics of patients, such as severity of COPD and motivation to quit smoking, which could likely impact the effect of the smoking cessation intervention on abstinence rates.

Economic Analysis

The results of the economic analysis are summarized in issue 12 of the COPD series entitled *Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model*. This report can be accessed at www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Economic_March.pdf.

Conclusions

- Based on a moderate quality of evidence, compared with usual care, abstinence rates are significantly higher in COPD patients receiving intensive counselling or a combination of intensive counselling and NRT.
- Based on limited moderate quality evidence, abstinence rates are significantly higher in COPD patients receiving NRT compared with placebo.
- Based on moderate quality of evidence, abstinence rates are significantly higher in COPD patients receiving the antidepressant bupropion compared to placebo.

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity (FVC)	The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.
Fraction of inspired	The percentage of oxygen participating in gas exchange.

oxygen (FiO_2)	
Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[2]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.
Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.

[2] The mild-to-moderate classification was created for the purposes of the report.

Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.
Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Medical Information Officer

Kellee Kaulback

Editorial Staff

Linda Senzilet
Irina Alecu

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

Appendices

Appendix 1: Literature Search Strategy

Search date: June 24, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, CINAHL, Wiley Cochrane Library, Centre for Reviews and Dissemination

Database: Ovid MEDLINE(R) <1950 to June Week 3 2010>
Search Strategy:

---

1 exp Pulmonary Disease, Chronic Obstructive/ (13760)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (20719)
3 (copd or coad).ti,ab. (15726)
4 chronic airflow obstruction.ti,ab. (484)
5 exp Emphysema/ (6878)
6 ((chronic adj2 bronchitis) or emphysema).ti,ab. (22456)
7 or/1-6 (52513)
8 exp Smoking Cessation/ (14779)
9 (smok* adj2 (cessation or quit* or stop* or ceas*)).ti,ab. (15464)
10 8 or 9 (21492)
11 7 and 10 (1161)
12 limit 11 to (english language and humans) (890)
13 limit 12 to (case reports or comment or editorial or letter) (77)
14 12 not 13 (813)

Database: EMBASE <1980 to 2010 Week 24>
Search Strategy:

---

1 exp chronic obstructive lung disease/ (35741)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (19329)
3 (copd or coad).ti,ab. (15705)
4 chronic airflow obstruction.ti,ab. (453)
5 exp emphysema/ (14502)
6 exp chronic bronchitis/ (6190)
7 ((chronic adj2 bronchitis) or emphysema).ti,ab. (14538)
8 or/1-7 (58318)
9 exp smoking cessation/ (20183)
10 (smok* adj2 (cessation or quit* or stop* or ceas*)).ti,ab. (13485)
11 9 or 10 (23418)
12 8 and 11 (1736)
13 limit 12 to (human and english language) (1392)
14 limit 13 to (editorial or letter or note) (218)
15 case report/ (1108743)
16 14 or 15 (1108959)

17 13 not 16 (1138)

Database: CINAHL
Search Strategy:

S9 (S5 or S6 or S7) and (S4 and S8) (353)
S8 S5 or S6 or S7 (9655)
S7 smok* and (cessation or quit* or stop* or ceas*) (9655)
S6 (MH "Smoking Cessation Programs") (1047)
S5 (MH "Smoking Cessation") (6902)
S4 S1 or S2 or S3 (7064)
S3 chronic bronchitis or Emphysema or chronic obstructive lung (1701)
S2 chronic obstructive pulmonary or copd or chronic airway obstruction (5631)
S1 (MH "Pulmonary Disease, Chronic Obstructive+") (4177)

Appendix 2: Characteristics of Included Studies

The characteristics of the included randomized control trials are described in Table A1.

Table A1: Characteristics of Included Randomized Control Trials*

Author, Year	Patients	Comparison	Outcomes Definitions	Follow-up Period	Authors' Conclusions	Notes
Pederson et al, 1991 (18)	Mean age: 53.4 years (SD 13.7) - Smokers admitted to hospital with exacerbation of COPD. COPD defined according to the American College of Chest Physicians and the American Thoracic Society (ACCP–ATS) Mean FEV_1/FCV = 0.52 (SD = 0.17) **Severity of COPD:** Probably severe or very severe according to GOLD **Motivation to quit:** Advised to quit **Total sample:** N = 74	Self-help manual + counselling session by trained smoking cessation counselor (3 to eight 15–20 minute counselling sessions on alternate days while in hospital (min 45 minutes, max 160 minutes) **[minimal counselling to intensive counselling].** vs. **Usual care**	**Abstinence:** Self-reported and verified by COHB analysis from blood drawn at 6 months. **Mortality:** All-cause, cardiovascular death, lung cancer death.	3 months, 6 months	No significant difference between the 2 groups.	Because of acute exacerbation, it was felt that inpatients were more likely to be amenable to quitting smoking. - Patients in the treatment group received smoking cessation on alternate days for the duration of their hospital stay. - Follow-up visits were used to offer support and encouragement and to answer patient's questions. - Physicians were blinded to group membership.
Sundblad et al, 2008 (22)	Age range: 40–60 years. - Smokers with COPD according to Siafakas et al (32) and according to European Respiratory Society Guidelines. - Smoked at least 8 cigarettes per day) - Average pack-years: 34.9 (SD 12.8) **Severity of COPD:** - 71% had mild COPD, $FEV_1 \geq 70\%$ of predicted.	Comprehensive smoking cessation program Included 11-day hospitalizations, use of NRT and recommended physical exercise, 1 hour daily with trained cessation nurse (660 minutes), structured educational program (physician, physiotherapist, dietician, psychologist, occupational therapist, group discussion with spouse **[intensive**	**Abstinence:** At 3-year follow-up, confirmed by carbon monoxide testing using piCO Smokerlyzer. Abstinence from smoking for at least 6 months. Questionnaires were used to gather information about the smoking habits.	1 year, 3 years	This comprehensive smoking cessation program, including several components, resulted in a high rate of smoke-free patients after 1 year (52%) and long-lasting effect, with 38% of the smokers with COPD remaining free from smoking after 3 years.	Smokers had to be smoking more than 8 cigarettes/day. - Smoking cessation program lasted for 1 year, and included a 2-day stay at the pulmonary rehabilitation clinic. - Patients were hospitalized for 11 days to build up motivation to stop smoking through information and personal support. - Carbon monoxide testing

Author, Year	Patients	Comparison	Outcomes Definitions	Follow-up Period	Authors' Conclusions	Notes
	- 23% had moderate COPD, FEV_1 = 69–50% of predicted. - 6% had severe COPD, $FEV_1 \leq 49\%$ of predicted. **Motivation to quit:** Not stated **Total sample:** N = 247	**counselling+ NRT].** vs. **Usual care**	Nicotine dependence was classified according to Fagerstrom test for nicotine independence.			performed in a random sample of patients. - NRT and distractive activities such as physical exercise were recommended. - Each participant met 1 hour daily with a trained smoking cessation nurse. - Structured educational program including a physician, physiotherapist, dietician, lab technician, psychologist, and occupational therapist, each with a specific role in the education program. - Spouses of smokers were invited to stay in the hospital if they accepted.
Lung Health Study Anthonisen et al, 1994; (17) Anthonisen et al, 2005 (14)	Age range: 35–60 years. - Presence of mild airway obstruction. - Smokers smoking 10 cigarettes/day during 30 days preceding the screening test. **Severity of COPD:** Mild to moderate, $FEV_1/FCV \leq 70\%$ and $55\% < FEV_1 < 90\%$ **Motivation to quit:** Not stated **Total sample:** N = 5887	Smoking intervention: ipratropium bromide **[intensive counselling + bronchodilator**]. vs. Smoking intervention: placebo **[intensive counselling + NRT].** vs. **Usual care** Smoking intervention: physician message, individual session with interventionist for behavioral interview, group orientation meeting, 12 intensive group sessions, clinic visits every 4 months	**Abstinence:** Smoking cessation confirmed by salivary cotinine/carbon monoxide testing. Participants with cotinine levels > 20 ng/mL were considered to be smokers. **Mortality:** All-cause, cardiovascular mortality and lung cancer mortality. **Lung function:** FEV_1	1 year, 5 years, 14.5 years	An aggressive smoking intervention program significantly reduces age-related decline in middle-aged smokers with mild airway obstruction. - Use of anticholinergic bronchodilators results in a relatively small improvement in FEV_1 that appears to be reversed after the drug is discontinued. Use of bronchodilator did not influence the long-term decline of FEV_1. - All-cause mortality was significantly lower in the smoking intervention groups than in the usual	Spouses and significant others of both intervention groups were included in the cessation program if they wished and were treated the same way as participants. - Women tended to have greater improvement in lung function in response to smoking cessation than did men. - In addition to change in smoking status, determinants of the degree of improvement in, or stabilization of, FEV_1 included baseline function, baseline bronchodilator responsiveness, race, methacholine reactivity, intervention group, and age. - Smoking cessation reduced the frequency of lower respiratory illness physician visits.

Author, Year	Patients	Comparison	Outcomes Definitions	Follow-up Period	Authors' Conclusions	Notes
		for 5 years, maintenance program for quitters, extended intervention program for patients still smoking or relapsing, and NRT gum.			care group. Smoking cessation intervention programs have a substantial effect on subsequent mortality even when successful in the minority of participants. - No linear relationship was found between smoking reduction and FEV_1.	- Quitting smoking for an interval followed by relapse to smoking appeared to provide a measurable and lasting benefit in comparison to continuous smoking. Attempts to quit smoking can prevent some loss of lung function. - Changes in AR were primarily related to changes in FEV_1. The greater the decline in FEV_1, the greater the increase in airway reactivity. Smoking cessation had a small additional benefit in AR beyond its favorable effects on FEV_1 changes.
Tashkin et al, 2001 (19)	Aged ≥ 35 years. - Smoked 15 or more cigarettes/day for the previous year and had not stopped smoking for more than 3 months during that year. **Severity of COPD:** Mild–Moderate. Patients with Stage I and II COPD (FEV_1/ FVC ≤ 0.70) according to ATS guidelines and presence of clinically defined COPD (emphysema, chronic bronchitis, and smoking-related small airways disease). **Motivation to quit:** Motivated to quit **Total sample:** N = 404	Counselling: All patients received brief, face-to-face counselling at each of the 9 visits to the clinic + 1 telephone session 3 days after the quit date. Bupropion SR 150mg—days 1–3: once per day; days 4–84: 150 mg twice per day + personalized counselling by trained counsellor. **[intensive counselling + antidepressant**]. vs. Placebo + personalized counselling for 12 weeks **[intensive counselling].**	**Continuous abstinence:** Zero cigarettes per day confirmed by exhaled carbon monoxide values of ≤ 10 ppm. **Point-prevalence abstinence:** Defined as abstinence during the previous 7 days.	6 months	Bupropion SR is a well-tolerated and effective aid to smoking cessation in people with mild to moderate COPD.	12-week treatment phase with follow-up at 6 months. - Block randomization stratified by centre. - Target cessation date was selected. - Predictors of abstinence were tested using multivariable logistic regression, controlling for smoking history, age, sex, centre, and treatment group assignment. - Proportions of patients with either Stage I or Stage II COPD were evenly distributed between treatment groups, as were participants with sub-diagnoses of emphysema, bronchitis, or small airways disease.

Author, Year	Patients	Comparison	Outcomes Definitions	Follow-up Period	Authors' Conclusions	Notes
Hilberink et al, 2010 (25)	Aged > 35 years - Current smokers. - Diagnosis of COPD confirmed by GP. - Recorded medication with ICPC code R95/96. - At least 3 prescriptions for bronchodilators in the past year. - At least 3 prescriptions for inhaled anti-inflammatory medication in the past year. **Severity of COPD:** Not defined, but probably mild to moderate according to GOLD. **Motivation to quit:** Not stated **Total sample:** N = 667	Counselling + NRT **[minimal counselling + NRT].** vs. Counselling + NRT + bupropion **[minimal counselling + NRT + antidepressant**]. vs. **Usual Care** SMOCC intervention: A multi-faceted strategy containing: • 4-hour central training for GPs and practice nurses • 4 support visits at the practice location • detection of patients using an algorithm for electronic medical records • a patient counselling protocol (invitation for control visits, assessment of motivational stage, education materials, 1–3 follow-up visits depending on stage of change, NRT, telephone follow-up by practice nurse)	**Point-prevalence abstinence**: Self-reported abstinence, biochemically verified by urinary cotinine levels of < 50 ng/mL.	6 months, 12 months	The program doubled the cessation rates (statistically nonsignificant). Too few participants used additional bupropion SR to prove its effectiveness.	- Professionally directed intervention consisted of 4-hour group training on COPD, smoking, and smoking cessation. More individual support was provided by an outreach visitor by means of counselling and feedback about performance at the practice location. Support materials included information on smoking and smoking cessation, educational tools for patients, and questionnaires assessing smoking habits. - Data collection included motivation to quit smoking and Fagerstrom test. Severity of COPD was determined according to Medical Research Council Questionnaire and self-efficacy. - Patients were divided into 3 categories: preparers, contemplators, and pre-contemplators.
Wilson et al, 2008 (27)	Mean age: 61 years (SD 84) - Smokers with diagnosis of COPD attending the regional respiratory centre.	Individual support by nurse (5 weekly hour-long sessions) + 12-week course of NRT for those wishing to stop (300 minutes) **[intensive counselling + NRT].**	**Abstinence**: Self-report of complete cessation confirmed by biochemical validation (carbon monoxide ≤ 10 ppm and salivary cotinine ≤ 10 ng/mL).	12 months	Patients with COPD were unable to stop smoking, regardless of the type of support they received.	Study objective was to gain an insight into the nurse's role in changing the smoking behavior of adults with COPD requiring secondary care. - Hypothesis was that intensive

Author, Year	Patients	Comparison	Outcomes Definitions	Follow-up Period	Authors' Conclusions	Notes
	Mean (SD) pack-years: 41.4 (20). **Severity of COPD:** Not defined **Motivation to quit:** Not stated **Total sample:** N = 91	vs. Group support (5 weekly, hour-long sessions) by nurse + 12-week course of NRT for those wishing to stop **[intensive counselling + NRT].** vs. Control (minimal counselling 5–10 min by GP + leaflet about smoking cessation).	**Stages of change—** Nicotine dependence: Measured by heaviness of smoking index. Dyspnea: Assessed by Medical Research Council dyspnea scale.			nursing sessions (individual or group) would increase cessation rates. - Respiratory nurses and a physician providing individual and group support received standardized training. - Stage of Change criteria were used to categorize motivation and assist nurses to stage-match interventions.
Tonnesen et al, 2006 (16)	Aged ≥18 years - Patients with COPD. **Severity of COPD:** *Mild:* 9% had FEV_1 > 80% *Moderate:* 53% had < 50% < FEV_1 < 80% *Severe:* 30% had < 30% < FEV_1 < 50% *Very Severe:* 8% had FEV_1 < 50% **Motivation to quit:** Not stated **Total sample:** N = 370	2 mg nicotine sublingual tablet + low behavioral support **[intensive counselling + NRT].** vs. 2 mg nicotine sublingual tablet + high behavioral support **[intensive counselling + NRT].** vs. Placebo + low behavioral support **[intensive counselling].** vs. Placebo + low behavioral support **[intensive counselling].** Low behavioral support: (individual + telephone sessions (total of 150 minutes by a respiratory nurse) + take-home	**Point-prevalence abstinence at 6 and 12 months:** Self-reported smoking during previous week; cessation verified by exhaled carbon monoxide level < 10 ppm. **Point-prevalence smoking reduction:** Degree of smoking reduction after 12 months. Those still smoking but who reduced their smoking to less than 7 cigarettes daily or who reduced their daily smoking to less than 50%. **Sustained abstinence:** Self-reported smoking cessation at all visits from week 2 to 12 months verified by exhaled carbon monoxide level < 10 ppm.	6 months, 12 months	The results demonstrate that the use of sublingual nicotine tablets in addition to a nurse-run smoking program results in higher rates of smoking cessation compared to placebo.	**Low support:** (4 individual visits + 6 telephone calls: total hours = 2.5). **High support:** (7 individual visits + 5 telephone calls; total hours = 4.5). NRT or placebo tablets were taken for 12 weeks with possibility of continued use for up to 12 months. Recommended study dose of medication was dependent on baseline cigarette consumption (≥16 cigarettes = 1–2 tablets per hour [min 10 and max 40]; 10–15 cigarettes = 1–2 tablets per hour [min 6 and max 30]; 6–9 cigarettes = 1 tablet per hour [min 3 and max 10]). - The term "smoker's lung" was used to explain COPD to patients. - Nurses received standardized training on counselling and counselling guidelines.

Author, Year	Patients	Comparison	Outcomes Definitions	Follow-up Period	Authors' Conclusions	Notes
		material). High behavioral support: (individual + telephone sessions (total of 270 minutes by a respiratory nurse) + take-home material).	**HRQOL:** Changes in QOL measures according to the SGRQ. A reduction in a total SGRQ score of ≥ 4 is considered to represent a clinically significant improvement.			- Nicotine dependence assessed by Fagerstrom test. - Motivation to quit smoking assessed on 10-cm visual analog scale.
Kotz et al, 2009 (23)	Mean age: 53.8 years, SD 7.0. - Patients with smoking history of ≥ 10 pack-years and had airflow limitation defined as FEV_1/FCV < 70%, FEV_1 ≥ 50% according to GOLD guidelines. **Severity of COPD:** Mild–Moderate GOLD I (n): 160 GOLD II (n): 136 **Motivation to quit:** Motivated to quit **Total sample:** N = 296	Confrontation with spirometry results during face-to-face session + 1 telephone session by respiratory nurse (165 minutes) + nortriptyline for 7 weeks **[intensive counselling + antidepressant].** vs. Face-to-face session + 1 telephone session by a respiratory nurse (165 min) + nortriptyline for 7 weeks without confrontation **[intensive counselling + antidepressant].** vs. Usual care (care as usual for smoking cessation provided by patient's own GP **[minimal counselling].**	**Prolonged abstinence:** defined as urine cotinine–validated (< 50 ng/mL) abstinence from smoking at all 3 follow-up visits.	5 weeks, 26 weeks, 52 weeks	Study did not provide evidence that confrontational approach to smoking cessation increases the rate of long-term abstinence from smoking compared with equally intensive treatment without confrontation with spirometry or usual care.	Nortriptyline dose: Days 1–3: 25 mg OD Days 4–7: 50 mg OD Days 8–49: 75 mg OD

Author, Year	Patients	Comparison	Outcomes Definitions	Follow-up Period	Authors' Conclusions	Notes
Wagena et al, 2005 (21)	Age range: 30–70 years. - Patients with COPD or at risk of COPD according to GOLD. - Had a smoking history of at least 5 years, with an average of 10 cigarettes per day in the last year. **Severity of COPD:** Stages 0–III **Motivation to quit:** Had motivation to stop smoking **Total sample:** N = 255	All patients received individual face-to-face (60-minute) and telephone counselling (30-minute) sessions by a respiratory nurse. Bupropion hydrochloride SR **[intensive counselling + antidepressant].** vs. Nortriptyline hydrochloride **[intensive counselling + antidepressant].** vs. Placebo **[intensive counselling].**	**Prolonged abstinence:** Zero cigarettes per day from weeks 4 to week 26—confirmed by urinary cotinine values of 60 ng/mL or less. **Point-prevalence abstinence:** No smoking for previous 7 days assessed at weeks 4, 12, and 26—confirmed by urinary cotinine values of ≤ 60 ng/mL.	4 weeks, 12 weeks, 26 weeks	A small but nonsignificant difference in prolonged abstinence rates was observed between the 2 groups. Smaller differences in prolonged abstinence were observed in patients at risk of COPD (Stage 0). - Authors concluded that bupropion SR treatment is an efficacious aid to smoking cessation in patients with COPD. Nortriptyline treatment seems to be a useful alternative to bupropion.	Includes patients at risk for COPD (Stage 0 according to GOLD). - Patients were stratified based on disease severity according to European Respiratory Society and GOLD.

Abbreviations: AR, airway reactivity; ATS, American Thoracic Society; COHB, carboxyhemoglobin; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GP, general practitioner; ICPC, International Classification for Primary Care; max, maximum; min, minimum; NRT, nicotine replacement therapy; OD, once daily; ppm, parts per million; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; SMOCC, Smoking Cessation in Patients With COPD; SR, sustained release.

Appendix 3: GRADE Quality of Evidence

The GRADE quality of evidence of the randomized controlled trials is shown below in Table A2.

Table A2: GRADE Quality of Evidence (Outcome = Abstinence Rate)*

No. of Studies	Design	Study Quality	Inconsistency	Indirectness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Comparison: Counselling vs. Usual Care							
2	RCT	No serious limitations	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Comparison: Counselling + NRT vs. Usual Care							
3	RCT	No serious limitations	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Comparison: Minimal Counselling (< 90 minutes) + Antidepressant vs. Usual Care							
1	RCT	No serious limitations	n/a	Some serious limitations†	No serious limitations	n/a	Low
Comparison: Minimal Counselling (< 90 minutes) + NRT + Antidepressant vs. Usual Care							
1	RCT	Serious limitations‡	n/a	No serious limitations	No serious limitations	n/a	Low
Comparison: NRT vs. Placebo							
1	RCT	No serious limitations	n/a	No serious limitations	No serious limitations	n/a	Moderate
Comparison: Antidepressant vs. Placebo							
1	RCT	No serious limitations	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate

*Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; n/a, not applicable; No., number; NRT, nicotine replacement therapy; RCT, randomized controlled trial.

†Study quality was downgraded for the outcome of abstinence for the comparison of minimal counselling plus antidepressant versus usual care due to some limitations in the directness. Patients enrolled in the study had undiagnosed COPD; however, they were eligible for enrollment in the study once they had been classified by the GOLD stage criteria. Because patients entering into the study were originally undiagnosed, they may not have been as motivated or may not have taken their illness as seriously as those who had been diagnosed with COPD.

‡ Study quality was downgraded due to limitations in the study design. The study was underpowered to detect a difference; also, at follow-up, there was poor compliance with the prescribed and recommended NRT and bupropion, affecting the overall success of the intervention.

References

(1) Lokke A, Lange P, Scharling H, Fabricius P, Vestbo J. Developing COPD: a 25 year follow up study of the general population. Thorax. 2006 Nov;61(11):935-9.

(2) Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007 Feb 22;356(8):775-89.

(3) Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008 Jan 1;177(1):19-26.

(4) Hughes JR. Motivating and helping smokers to stop smoking. J Gen Intern Med. 2003 Dec;18(12):1053-7.

(5) Vozoris NT, Stanbrook MB. Smoking prevalence, behaviours, and cessation among individuals with COPD or asthma. Respir Med. 2010 Sep 15.

(6) Hoogendoorn M, Feenstra TL, Hoogenveen RT, Rutten-van Molken MP. Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD. Thorax. 2010 Aug;65(8):711-8.

(7) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490.

(8) Goodman, C. Literature searching and evidence interpretation for assessing health care practices. Stockholm, Sweden: Swedish Council on Technology Assessment in Health Care; 1996 81 p. SBU Report No. 119E.

(9) van der Meer RM WEORJAvSOP. Smoking cessation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2001, Issue 1. Art. No.: CD002999. DOI: 10.1002/14651858.CD002999.

(10) Wagena EJ, van der Meer RM, Ostelo RJWG, Jacobs JE, Van Schayck CP. The efficacy of smoking cessation strategies in people with chronic obstructive pulmonary disease: Results from a systematic review. Respir Med. 2004;98(9):805-15.

(11) Strassmann R, Bausch B, Spaar A, Kleijnen J, Braendli O, Puhan MA. Smoking cessation interventions in COPD: a network meta-analysis of randomised trials. Eur Respir J. 2009 Sep;34(3):634-40.

(12) Crowley TJ, Macdonald MJ, Walter MI. Behavioral anti-smoking trial in chronic obstructive pulmonary disease patients. Psychopharmacology (Berl). 1995 May;119(2):193-204.

(13) Brandt CJ, Ellegaard H, Joensen M, Kallan FV, Sorknaes AD, Tougaard L, et al. Effect of diagnosis of 'smoker's lung'. Lancet. 1997;349(9047):253.

(14) Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005;142:233-9.

(15) Tashkin DP, Murray RP. Smoking cessation in chronic obstructive pulmonary disease. Respir Med. 2009 Jul;103(7):963-74.

(16) Tonnesen P, Mikkelsen K, Bremann L. Nurse-conducted smoking cessation in patients with COPD using nicotine sublingual tablets and behavioral support. Chest. 2006 Aug;130(2):334-42.

(17) Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. JAMA. 1994 Nov 16;272(19):1497-505.

(18) Pederson LL, Wanklin JM, Lefcoe NM. The effects of counseling on smoking cessation among patients hospitalized with chronic obstructive pulmonary disease: a randomized clinical trial. Int J Addict. 1991 Jan;26(1):107-19.

(19) Tashkin D, Kanner R, Bailey W, Buist S, Anderson P, Nides M, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. Lancet. 2001 May 19;357(9268):1571-5.

(20) Murray RP, Anthonisen NR, Connett JE, Wise RA, Lindgren PG, Greene PG, et al. Effects of multiple attempts to quit smoking and relapses to smoking on pulmonary function. J Clin Epidemiol. 1998;51(12):1317-26.

(21) Wagena EJ, Knipschild PG, Huibers MJ, Wouters EF, Van Schayck CP. Efficacy of bupropion and nortriptyline for smoking cessation among people at risk for or with chronic obstructive pulmonary disease. Arch Intern Med. 2005 Oct 24;165(19):2286-92.

(22) Sundblad BM, Larsson K, Nathell L. High rate of smoking abstinence in COPD patients: Smoking cessation by hospitalization. Nicotine Tob Res. 2008 May;10(5):883-90.

(23) Kotz D, Wesseling G, Huibers MJ, van Schayck OC. Efficacy of confronting smokers with airflow limitation for smoking cessation. Eur Respir J. 2009 Apr;33(4):754-62.

(24) Sundblad BM, Larsson K, Nathell L. Low awareness of COPD among physicians. Clin Respir J. 2008 Jan;2(1):11-6.

(25) Hilberink SR, Jacobs JE, Breteler M, de Vries H, Grol R. General practice counseling for patients with chronic obstructive pulmonary disease to quit smoking: Impact after 1 year of two complex interventions [Internet]. [updated 2010; cited 2010 Apr 1]. Available from: www.elsevier.com/locate/pateducou

(26) Hilberink SR, Jacobs JE, Bottema BJ, de VH, Grol RP. Smoking cessation in patients with COPD in daily general practice (SMOCC): six months' results. Prev Med. 2005 Nov;41(5-6):822-7.

(27) Wilson JS, Fitzsimons D, Bradbury I, Stuart EJ. Does additional support by nurses enhance the effect of a brief smoking cessation intervention in people with moderate to severe chronic obstructive pulmonary disease? A randomised controlled trial. Int J Nurs Stud. 2008 Apr;45(4):508-17.

(28) Sundblad BM, Larsson K, Nathell L. Lung function testing influences the attitude toward smoking cessation. Nicotine Tob Res. 2010 Jan;12(1):37-42.

(29) Kotz D, van de KK, Jobsis Q, Van Schayck CP. Effects of tobacco exposure on lung health and pulmonary biomarkers in young, healthy smokers aged 12-25 years: a systematic review. Expert Rev Respir Med. 2007 Dec;1(3):403-18.

(30) Borglykke A, Pisinger C, Jorgensen T, Ibsen H. The effectiveness of smoking cessation groups offered to hospitalised patients with symptoms of exacerbations of chronic obstructive pulmonary disease (COPD). Clin Respir J. 2008 Jul;2(3):158-65.

(31) Christenhusz L, Seydel E, Pieterse M, van d, V, van-der PJ. The SMOKE study: 1 year evaluation of an intensive multi-component smoking cessation programme for COPD outpatients [Abstract]. Eur Respir J. 2005;26:Abstract.

(32) Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J. 1995 Aug;8(8):1398-420.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-7010-7 (PDF)

Ontario
Health Quality Ontario
Qualité des services
de santé Ontario

Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis

N Sikich

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 5, pp. 1–51, March 2012

Suggested Citation

This report should be cited as follows:

Sikich N. Community-based multidisciplinary care for patients with stable chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2011 Mar; 12(5) 1–51. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_MDC_March.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to: MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit:
http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses:
http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

CI	Confidence interval(s)
CINAHL	Cumulative Index to Nursing & Allied Health Literature
COPD	Chronic obstructive pulmonary disease
ED	Emergency department
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
MDC	Multidisciplinary care
GOLD	Global Initiative for Chronic Obstructive Lung Disease
I^2	Index of heterogeneity
n	Number
NR	Not reported
NS	Nonsignificant
OHTAC	Ontario Health Technology Advisory Committee
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
UC	Usual care

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective

The objective of this evidence-based analysis was to determine the effectiveness and cost-effectiveness of multidisciplinary care (MDC) compared with usual care (UC, single health care provider) for the treatment of stable chronic obstructive pulmonary disease (COPD).

Clinical Need: Condition and Target Population

Chronic obstructive pulmonary disease is a progressive disorder with episodes of acute exacerbations associated with significant morbidity and mortality. Cigarette smoking is linked causally to COPD in more than 80% of cases. Chronic obstructive pulmonary disease is among the most common chronic diseases worldwide and has an enormous impact on individuals, families, and societies through reduced quality of life and increased health resource utilization and mortality.

The estimated prevalence of COPD in Ontario in 2007 was 708,743 persons.

Technology

Multidisciplinary care involves professionals from a range of disciplines, working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.

Two variables are inherent in the concept of a multidisciplinary team: i) the multidisciplinary components such as an enriched knowledge base and a range of clinical skills and experiences, and ii) the team components, which include but are not limited to, communication and support measures. However, the most effective number of team members and which disciplines should comprise the team for optimal effect is not yet known.

Research Question

What is the effectiveness and cost-effectiveness of MDC compared with UC (single health care provider) for the treatment of stable COPD?

Research Methods

Literature Search

Search Strategy

A literature search was performed on July 19, 2010 using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 1995 until July 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- health technology assessments, systematic reviews, or randomized controlled trials
- studies published between January 1995 and July 2010;
- COPD study population
- studies comparing MDC (2 or more health care disciplines participating in care) compared with UC (single health care provider)

Exclusion Criteria

- grey literature
- duplicate publications
- non-English language publications
- study population less than 18 years of age

Outcomes of Interest

- hospital admissions
- emergency department (ED) visits
- mortality
- health-related quality of life
- lung function

Quality of Evidence

The quality of each included study was assessed, taking into consideration allocation concealment, randomization, blinding, power/sample size, withdrawals/dropouts, and intention-to-treat analyses.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. The following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Summary of Findings

Six randomized controlled trials were obtained from the literature search. Four of the 6 studies were completed in the United States. The sample size of the 6 studies ranged from 40 to 743 participants, with a mean study sample between 66 and 71 years of age. Only 2 studies characterized the study sample in terms of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD stage criteria, and in general the description of the study population in the other 4 studies was limited. The mean percent predicted forced expiratory volume in 1 second (% predicted FEV_1) among study populations was

between 32% and 59%. Using this criterion, 3 studies included persons with severe COPD and 2 with moderate COPD. Information was not available to classify the population in the sixth study.

Four studies had MDC treatment groups which included a physician. All studies except 1 reported a respiratory specialist (i.e., respiratory therapist, specialist nurse, or physician) as part of the multidisciplinary team. The UC group was comprised of a single health care practitioner who may or may not have been a respiratory specialist.

A meta-analysis was completed for 5 of the 7 outcome measures of interest including:

- health-related quality of life,
- lung function,
- all-cause hospitalization,
- COPD-specific hospitalization, and
- mortality.

There was only 1 study contributing to the outcome of all-cause and COPD-specific ED visits which precluded pooling data for these outcomes. Subgroup analyses were not completed either because heterogeneity was not significant or there were a small number of studies that were meta-analysed for the outcome.

Quality of Life

Three studies reported results of quality of life assessment based on the St. George's Respiratory Questionnaire (SGRQ). A mean decrease in the SGRQ indicates an improvement in quality of life while a mean increase indicates deterioration in quality of life. In all studies the mean change score from baseline to the end time point in the MDC treatment group showed either an improvement compared with the control group or less deterioration compared with the control group. The mean difference in change scores between MDC and UC groups was statistically significant in all 3 studies. The pooled weighted mean difference in total SGRQ score was −4.05 (95% confidence interval [CI], −6.47 to 1.63; P = 0.001). The GRADE quality of evidence was assessed as low for this outcome.

Lung Function

Two studies reported results of the FEV_1 % predicted as a measure of lung function. A negative change from baseline infers deterioration in lung function and a positive change from baseline infers an improvement in lung function. The MDC group showed a statistically significant improvement in lung function up to 12 months compared with the UC group (P = 0.01). However this effect is not maintained at 2-year follow-up (P = 0.24). The pooled weighted mean difference in FEV_1 percent predicted was 2.78 (95% CI, −1.82 to −7.37). The GRADE quality of evidence was assessed as very low for this outcome indicating that an estimate of effect is uncertain.

Hospital Admissions

All-Cause

Four studies reported results of all-cause hospital admissions in terms of number of persons with at least 1 admission during the follow-up period. Estimates from these 4 studies were pooled to determine a summary estimate. There is a statistically significant 25% relative risk (RR) reduction in all-cause hospitalizations in the MDC group compared with the UC group (P < 0.001). The index of heterogeneity

(I^2) value is 0%, indicating no statistical heterogeneity between studies. The GRADE quality of evidence was assessed as moderate for this outcome, indicating that further research may change the estimate of effect.

COPD-Specific Hospitalization

Three studies reported results of COPD-specific hospital admissions in terms of number of persons with at least 1 admission during the follow-up period. Estimates from these 3 studies were pooled to determine a summary estimate. There is a statistically significant 33% RR reduction in all-cause hospitalizations in the MDC group compared with the UC group ($P = 0.002$). The I^2 value is 0%, indicating no statistical heterogeneity between studies. The GRADE quality of evidence was assessed as moderate for this outcome, indicating that further research may change the estimate of effect.

Emergency Department Visits

All-Cause

Two studies reported results of all-cause ED visits in terms of number of persons with at least 1 visit during the follow-up period. There is a statistically nonsignificant reduction in all-cause ED visits when data from these 2 studies are pooled (RR, 0.64; 95% CI, 0.31 to −1.33; $P = 0.24$). The GRADE quality of evidence was assessed as very low for this outcome indicating that an estimate of effect is uncertain.

COPD-Specific

One study reported results of COPD-specific ED visits in terms of number of persons with at least 1 visit during the follow-up period. There is a statistically significant 41% reduction in COPD-specific ED visits when the data from these 2 studies are pooled (RR, 0.59; 95% CI, 0.43–0.81; $P < 0.001$). The GRADE quality of evidence was assessed as moderate for this outcome.

Mortality

Three studies reported the mortality during the study follow-up period. Estimates from these 3 studies were pooled to determine a summary estimate. There is a statistically nonsignificant reduction in mortality between treatment groups (RR, 0.81; 95% CI, 0.52–1.27; $P = 0.36$). The I^2 value is 19%, indicating low statistical heterogeneity between studies. All studies had a 12-month follow-up period. The GRADE quality of evidence was assessed as low for this outcome.

Conclusions

Significant effect estimates with moderate quality of evidence were found for all-cause hospitalization, COPD-specific hospitalization, and COPD-specific ED visits (Table ES1). A significant estimate with low quality evidence was found for the outcome of quality of life (Table ES2). All other outcome measures were nonsignificant and supported by low or very low quality of evidence.

Table ES1: Summary of Dichotomous Data

Outcome	Number of Studies (n)	Relative Risk (95% CI)	GRADE
Hospitalizations			
All-cause (number of persons)	4 (1121)	0.75 (0.64–0.87)	Moderate
COPD-specific (number of persons)	3 (916)	0.67 (0.52–0.87)	Moderate
Emergency Department Visits			
All-cause (number of persons)	2 (223)	0.64 (0.31–1.33)	Very Low
COPD-specific (number of persons)	2 (783)	0.59 (0.43–0.81)	Moderate
Mortality			
	3 (1033)	0.81 (0.52–1.27)	Low

*Abbreviations: CI, confidence intervals; COPD, chronic obstructive pulmonary disease; n, number.

Table ES2: Summary of Continuous Data

Outcome	Number of Studies (n)	Weighted Mean Difference (95% CI)	GRADE
Quality of Life (SGRQ)	2 (942)	-4.05 (-6.47 to -1.63)	Low
Lung Function (FEV_1% predicted)	2 (316)	2.78 (-1.82–7.37)	Very Low

*Abbreviations: CI, confidence intervals; FEV_1, forced expiratory volume in 1 second; n, number; SGRQ, St. George's Respiratory Questionnaire.

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this evidence-based analysis was to determine the effectiveness and cost-effectiveness of multidisciplinary care (MDC) compared with usual care (UC, single health care provider) for the treatment of stable chronic obstructive pulmonary disease (COPD).

Clinical Need and Target Population

Description of Problem

Chronic obstructive pulmonary disease is a progressive disorder with episodes of acute exacerbations associated with significant morbidity and mortality. (1) Cigarette smoking is linked causally to COPD in more than 80% of cases. (1;2) Chronic obstructive pulmonary disease is among the most common chronic diseases worldwide and has an enormous impact on individuals, families, and societies through reduced quality of life and increased health resource utilization and mortality. (3)

Ontario Prevalence

The estimated prevalence of COPD in Ontario in 2007 was 708,743 persons. (4)

Technology

Multidisciplinary care involves professionals from a range of disciplines, working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.

Mitchell et al (5) hypothesized that MDC can be delivered by a range of professionals functioning as a team under one organizational umbrella, or from a range of organizations brought together as a unique team.

The concept of MDC for COPD is not a new one. In 1985, The American Thoracic Society Position Paper stated that "the individual with chronic obstructive pulmonary disease (COPD) requires long-term multidisciplinary care because of the physiologic and psychological problems associated with this disease" and that "because of the chronic, progressive nature of COPD, provision of care must be comprehensive and continuous, with particular attention given to outpatient and home care services." (6) The health care of persons with COPD was seen as the responsibility of the health care team, which included at the very least a physician and a pulmonary clinical nurse specialist or respiratory therapist.

Nie et al (7) found that persons in Ontario with COPD who were cared for by both a family physician or general practitioner and a specialist had significantly lower mortality rates than persons cared for by only one physician, suggesting that coordinated care can result in better survival.

Two variables are inherent in the concept of a multidisciplinary team: i) the multidisciplinary components such as an enriched knowledge base and a range of clinical skills and experiences, and ii) the team components, which include but are not limited to, communication and support measures. (5) However, the most effective number of team members and which disciplines should comprise the team for optimal effect is not yet known. (5)

Evidence-Based Analysis

Research Question

What is the effectiveness and cost-effectiveness of MDC compared with UC (single health care provider) for the treatment of stable chronic COPD?

Literature Search

Search Strategy

A literature search was performed on July 19, 2010 using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 1995 until July 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- health technology assessments, systematic reviews, or randomized controlled trials (RCTs)
- studies published between January 1995 and July 2010
- COPD study population
- studies comparing MDC (2 or more health care disciplines participating in care) with UC (single health care provider)

Exclusion Criteria

- grey literature
- duplicate publications
- non-English language publications
- study population less than 18 years of age

Outcomes of Interest

- hospital admissions
- emergency department (ED) visits
- mortality
- health-related quality of life (HRQOL)
- lung function

Statistical Analysis

Where appropriate, a meta-analysis was undertaken to determine the pooled estimate of effect of multidisciplinary care for explicit outcomes using Review Manager 5 version 5.0.25.

Quality of Evidence

The quality of each included study was assessed taking into consideration the following 7 study design characteristics:

- adequate allocation concealment,
- randomization (study must include a description of the randomization procedure used and this must be a proper method),
- power/sample size (adequate sample size based on a priori calculations; underpowered studies were identified, when possible, using post hoc sample size power calculations),
- blinding (if double blinding is not possible, a single blind study with unbiased assessment of outcome was considered adequate for this criterion),
- < 20% withdrawals/dropouts,
- intention-to-treat analysis conducted and done properly (withdrawals/dropouts considered in analysis), and
- other criteria as appropriate for the particular research question and study design.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (8) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

The database search yielded 2,919 citations published between January 1, 1995, and July 2010 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded in the analysis.

Four randomized controlled trials met the inclusion criteria. (9-14) The references lists of the included studies and health technology assessment websites were hand searched to identify any additional potentially relevant studies, and 2 additional citations were included for a total of 6 included citations.

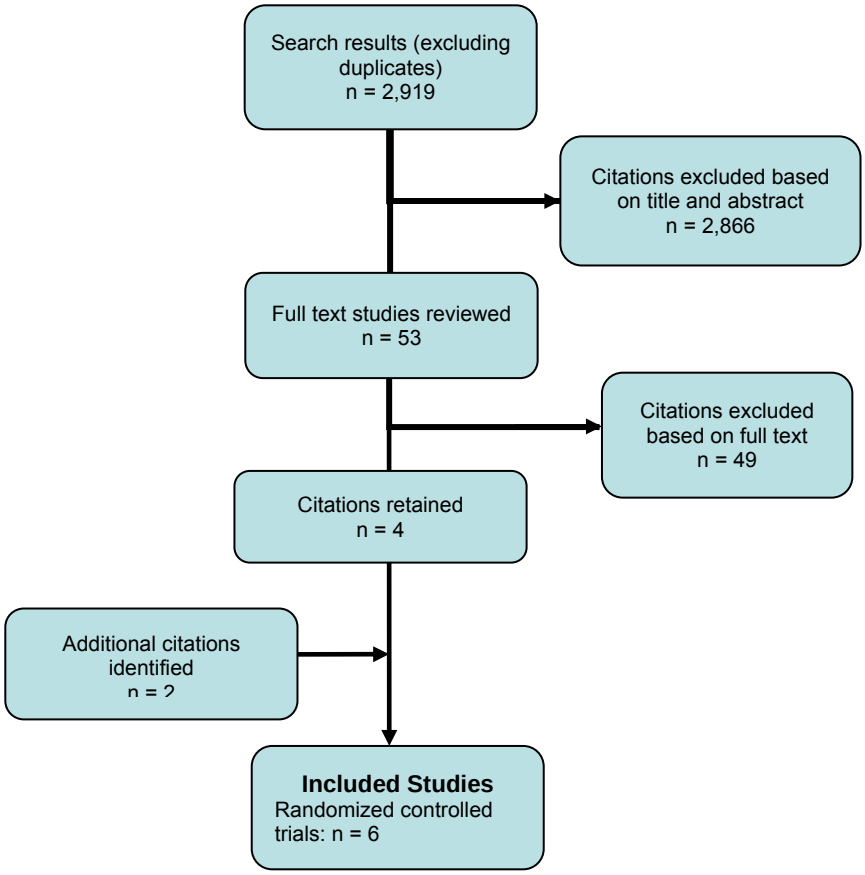


Figure 1: Citation Flow Chart

For each included study, the study design was identified and is summarized below in Table 1, which is a modified version of a hierarchy of study design by Goodman. (15)

Table 1: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	
Large RCT	3
Small RCT	3
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with non-contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference	
Expert opinion	
Total	6

*Abbreviation: RCT, randomized controlled trial.

Characteristics of Included Studies

Table 2 presents an overview of the characteristics of the studies included in this evidence-based analysis and Table 3 reports the methodological characteristics of each study. Complete study details are reported in Appendix 2. Four of the 6 studies were completed in the United States. (10-13) The sample size of the 6 studies ranged from 40 to 743 people, with a mean study sample age between 66 and 71 years. Only the studies by van Wetering et al (14) and Koff et al (10) characterized the study sample in terms of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD stage criteria, and in general the description of the study population in the other 4 studies was limited. The mean percent predicted forced expiratory volume in 1 second (% predicted FEV_1) among study populations was between 32% and 59%.

The GOLD COPD (16) stage criteria are as follows:

Stage I: Mild COPD - Mild airflow limitation (Forced Expiratory Volume in 1 minute/Forced Vital Capacity, $FEV_1/FVC < 70\%$; $FEV_1 \geq 80\%$ predicted) and sometimes, but not always chronic cough and sputum production. At this stage, the individual may not be aware that his or her lung function is abnormal.

Stage II: Moderate COPD - Worsening airflow limitation ($FEV_1/FVC < 70\%$; $50\% > FEV_1 < 80\%$ predicted), with shortness of breath typically developing on exertion. This is the stage at which patients typically seek medical attention for chronic respiratory symptoms or an exacerbation of their disease.

Stage III: Severe COPD - Further worsening of airflow limitation ($FEV_1/FVC < 70\%$; $30\% > FEV_1 < 50\%$ predicted), greater shortness of breath, reduced exercise capacity, and repeated exacerbations, which have an impact on a patient's quality of life.

Stage IV: Very Severe COPD - Severe airflow limitation ($FEV_1/FVC < 70\%$; $FEV_1 < 30\%$ predicted) or ($FEV_1 < 50\%$ predicted plus chronic respiratory failure). Patients may have very severe (Stage IV) COPD (even if the FEV_1 is > 30% predicted) whenever this complication is present. At this stage, quality of life is very appreciably impaired and exacerbations may be life-threatening.

Using the GOLD stage FEV_1 percent predicted criterion, there are 2 studies that have populations with moderate COPD and 3 with populations with severe COPD (Table 2).

Four studies had MDC treatment groups, which included a physician (9-11;13), and 2 did not. (12;14) All studies other than the one by Solomon et al (13) reported a respiratory specialist (i.e., respiratory therapist, specialist nurse, or physician) as part of the multidisciplinary team.

The UC group was comprised of a single health care practitioner that may or may not have been a respiratory specialist. The UC group in the study by Rice et al (12) had access to a 24-hour nursing telephone helpline, which was standard practice for the health care facility where the study was carried out.

Study methodological characteristics are reported in Table 3. Adequate allocation concealment was unclear in 2 studies, those by Rea et al (11) and Solomon et al. (13) The study by Rea et al (11) randomized general practitioner practices and thus randomization was not done at the patient level. However, the data was reported at the patient level. This study has been pooled with the results of the other studies where applicable, with sensitivity analyses undertaken to determine its effect on the overall summary statistic. The studies by van Wetering et al (14) and Casas et al (9) had a loss to follow-up rate of greater than 20%. All methodological assessments have been taken into consideration when determining the GRADE quality of evidence.

Table 2: Characteristics of Studies Included for Analysis*

Study	Country	n	Age (Mean, Yr)	Population	FEV_1% Predicted (Mean) (GOLD Stage)	MDC Group	Usual Care Group	Follow-up (Months)
van Wetering et al, 2010 (14)	Netherlands	199	66	GOLD stage 2 or 3	59 (moderate)	Physiotherapist, dieticians, and respiratory nurses	Respiratory physician	12
Rice et al, 2010 (12)	United States	743	70	Severe, FEV_1 < 70% predicted post bronchodilator 55% used home oxygen	37 (severe)	Respiratory therapist and pharmacist	Usual care which included access to 24 hour nursing helpline	12
Koff et al, 2009 (10)	United States	40	66	GOLD stage 3 or 4	32 (severe)	Respiratory therapist, General practitioner	Healthcare provider	3
Casas 2006 (9)	Spain	155	71	Moderate to severe, persons hospitalized for >48 hours for exacerbation	42 (severe)	Specialized nurse, physician, nurse, social worker	Physician	12
Rea et al, 2004 (11)	New Zealand	135	68	Moderate to severe	51 (moderate)	General practitioner, nurse, respiratory physician, respiratory nurse specialist	General practitioner	12
Solomon et al, 1998 (13)	United States	98	69	Diagnosed with COPD as per the American Thoracic Society Criteria	Not reported (unknown)	Pharmacist and physician	Physician	6

*Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MDC, multidisciplinary care; n, number; yr, years.

Table 3: Methodological Characteristics of Included Studies*

Study	n	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding of Outcome Assessors for Primary Outcome	Sample Size Calculation	Losses to Follow-up	ITT Analysis with Primary Outcome
van Wetering et al, 2010 (14)	199	✓	✓	✓	✓	✓	21% MDC:25% UC:16.5%	✓
Rice et al, 2010 (12)	743	✓	✓	✓	✓	✓	3%	✓
Koff et al, 2009 (10)	40	✓	✓	✓	x	✓	5%	Not reported
Casas et al, 2006 (9)	155	✓	†✓	✓	✓	✓	23% 17% deaths ‡6% other	✓
Rea et al, 2004 (11)	135	✓	✓	unclear	unclear	✓	10% GP practices 13% patients	✓
Solomon et al, 1998 (13)	98	✓	✓	unclear	x	x	11%	Not reported

*Abbreviations: MDC, multidisciplinary care group; n, number; UC, usual care group; GP, general practice; ITT, intention-to-treat.
†Statistically significantly more persons in the control group had influenza vaccinations.
‡ Reasons include palliative care, change of address, neoplasm.

In all studies the MDC group were provided with several COPD interventions, which were often collectively described as a program of care. Table 4 reports the interventions with general descriptions obtained from the 6 studies included in this review.

Table 4: Chronic Obstructive Pulmonary Disease Interventions*

Interventions	Description
Disease specific education	The program provided education about causes, symptoms, and treatment of exacerbations and general knowledge of COPD, including the importance of vaccinations
Medication review	Review and adjustment of COPD medication
Physical activity counselling	Provided exercise training
Smoking cessation counselling	Provided counselling on smoking cessation and smoking cessation interventions
Self-care counselling	Taught awareness for changes in health, worsening symptoms, symptom control, and nutritional management
Evidence-based guidelines	MDC team followed evidence-based guidelines for the management of COPD
Regular follow-up	Regular follow-up visits and/or phone calls were scheduled

*Abbreviations: COPD, chronic obstructive pulmonary disease; MDC, multidisciplinary care.

These interventions were further categorized using Wagner's model of chronic care (Table 5). All studies included a decision support component and a self-management component in their program. Five of the 6 studies used an intervention under the delivery system component. At least 50% of the studies used 2 interventions under each domain (Table 5).

Table 5: Interventions Used in Multidisciplinary Care Treatment Categorized Using Wagner's Chronic Care Model

	Wagner's Chronic Care Model						
	Decision Support		***Self Management (Behaviour Modification)**			**Delivery System**	
Study	**Disease Specific Education**	**Medication Review**	**Physical Activity Counselling**	**Smoking Cessation Counselling**	**Self-Care Counselling**	**Evidence-Based Guidelines**	**Regular Follow-Up**
van Wetering et al, 2010 (14)	✓	x	✓	✓	✓	x	✓
Rice et al, 2010 (12)	✓	✓	✓	✓	✓	✓	✓
Koff et al, 2009 (10)	✓	✓	x	x	✓	✓	✓
Casas et al, 2006 (9)	✓	✓	x	x	✓	✓	✓
Rea et al, 2004 (11)	✓	✓	✓	✓	✓	✓	✓
Solomon et al,1998 (13)	✓	✓	x	x	✓	x	x
Total	**6**	**5**	**3**	**3**	**6**	**4**	**5**

* Domains of Wagner's Chronic Care Model.

Summary of Existing Evidence

A meta-analysis was completed for 5 of the 7 outcome measures of interest including:

- quality of life,
- lung function,
- all-cause hospitalization,
- COPD-specific hospitalization, and
- mortality.

There was only 1 study contributing to the outcome of all-cause and COPD-specific ED visits, which precluded pooling data for these outcomes. Subgroup analyses were also not completed because heterogeneity was not significant or there were a small number of studies that were meta-analysed for the outcome.

Quality of Life

Three studies reported results of the quality of life assessment based on the St. George's Respiratory Questionnaire (SGRQ). (10;12;14) All studies compared the difference in the mean change scores from baseline to the end time point between the MDC and UC groups. The study by van Wetering et al (14) reported the mean difference in change scores between groups at 4 months and at 24 months, while Koff et al (10) reported this change at 3 months, and Rice et al (12) at 12 months. The results from each study are reported in Table 6. A decrease in the SGRQ score indicates an improvement in quality of life, while an increase indicates deterioration of quality of life. In all studies the mean change score from baseline to the end time point in the MDC treatment group showed either an improvement compared with the control group, or in the Rice et al (12) study, less deterioration compared with the control group. The mean difference in change scores between the MDC and UC groups was statistically significant in all 3 studies.

Table 6: Mean Change Scores on the St. George's Respiratory Questionnaire*

Study	n	Follow-Up (Months)	MDC Group Mean Change From Baseline (SD) (95% CI)	UC Group Mean Change From Baseline (SD) (95% CI)	Mean Difference in Mean Change From Baseline (SD)	*P* Value
van Wetering et al (14)	199	4	−3.9 (10.3)	0.3 (9.4)	4.2 (*NR)	0.004
van Wetering et al (14)	199	24	−1.4 (8.6)	1.2 (8.4)	2.6 (NR)	0.045
Koff et al (10)	38	3	−10.3 [−17.4; −2.1]	−0.6 [06.5–5.3]	9.7 (NR)	0.018
Rice et al (12)	743	12	1.3 (13.2)	6.4 (13.6)	5.1 (13.6)	< 0.001

Abbreviations: CI, confidence intervals; MDC, multidisciplinary care; ; NR, not reported; n, number; SD, standard deviation; UC, usual care.

Figure 2 reports the meta-analysis of 2 of the 3 studies. The study by Koff et al (10) could not be included, as it did not report standard deviations for each treatment group. An attempt to contact the authors for this information was unsuccessful. Figure 2 includes the data from van Wetering et al (14) at 24 months and Rice et al (12) at 12 months. There is moderate heterogeneity in the analysis (index of heterogeneity [I^2] = 66%). The overall mean difference in the change from baseline scores is −4.09, which is statistically significant ($P = 0.001$) as well as clinically significant. Limitations in this analysis include the study by van Wetering et al (14) that had a 21% loss to follow-up (25% in the MDC group,

and 16.5% in the control group), which may bias the results of the study. As well, the response rate in the Rice et al (12) study for the SRGQ at 1 year was 55% for the MDC group and 60% for the UC group.

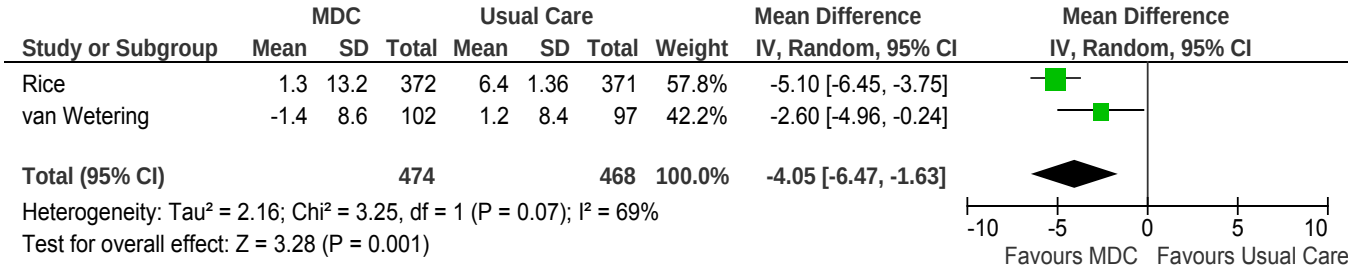


Figure 2: Meta-Analysis of the St. George's Respiratory Questionnaire Mean Change Scores From Baseline*

*Abbreviations: CI, confidence interval; I^2, index of heterogeneity; IV, instrumental variables; MDC, multidisciplinary care; SD, standard deviation.

The GRADE quality of evidence was assessed as low for this outcome, indicating that further research is likely to change the estimate of effect. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Lung Function

Two studies (11;14) reported results of the percent predicted FEV_1 as a measure of lung function (Table 7). van Wetering et al (14) reported this outcome at the 4 and 12-month follow-up, while Rea et al (11) reported it at the 12-month follow-up. A negative change from baseline infers deterioration in lung function and a positive change from baseline infers an improvement in lung function. The MDC group showed a statistically significant improvement in lung function in the van Wetering et al (14) study at 4 months ($P = 0.03$) and in the Rea et al study at 12 months ($P = 0.001$) compared with the UC group. van Wetering et al (14) reported a statistically nonsignificant decrease in lung function in the MDC group compared with the usual care group at the 2-year follow-up.

Table 7: Mean Change From Baseline in FEV_1 (% Predicted)*

Study	n	Follow-up (Months)	MDC Group Mean Change From Baseline (SD)	UC Group Mean Change From Baseline (SD)	Mean Difference in Mean change From Baseline (SD)	*P* Value
van Wetering et al (14)	199	4	0.87 (6.5)	-1.74(7.4)	2.7 (NR)	0.03
van Wetering et al (14)	199	24	-1.6 (7.5)	-2.9 (6.6)	1.3 (NR)	NS
Rea et al (11)	117	12	2.1 (18.7)	-4.40 (18.9)	6.5 (NR)	0.001

*Abbreviations: FEV_1, forced expiratory volume in 1 second; MDC, multidisciplinary care; n, number; NR, not reported; NS, nonsignificant; SD, standard deviation UC, usual care.

These data were pooled and the results are reported in Figures 3 and 4. There is a significant improvement in lung function when the data from Rea et al (11) at 12 months and van Wetering et al (14) at 4 months is pooled ($P = 0.01$) (Figure 3), however this is lost when the data of Rea et al (11) is pooled with the data of van Wetering et al (14) at 2 years ($P = 0.24$) (Figure 4). The study by van Wetering et al (14) indicates that the effect of MDC on lung function is not maintained at the 2-year follow-up.

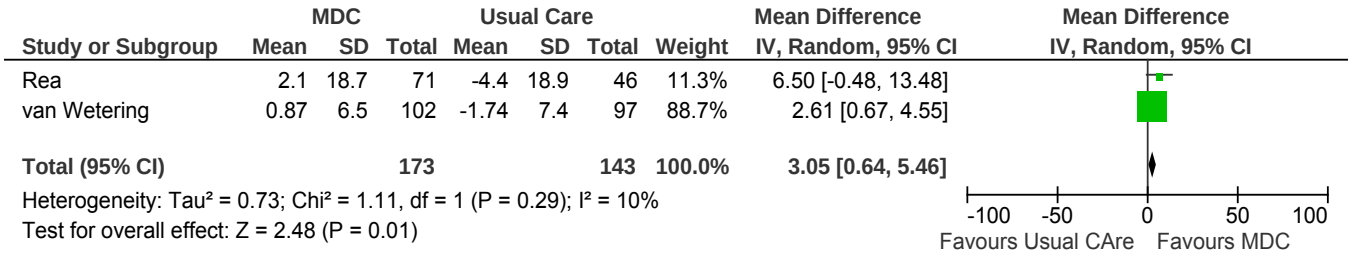


Figure 3: Pooled Results of FEV_1 (% Predicted) Mean Change From Baseline*,†

*Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; I^2, index of heterogeneity; IV, instrumental variables; MDC, multidisciplinary care; SD, standard deviation.
†Data from Rea et al (11) at 12 months pooled with data from van Wetering et al (14) at 4 months.

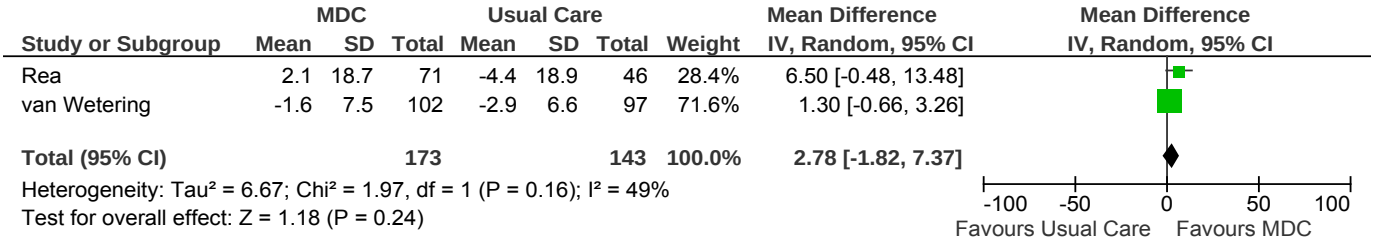


Figure 4: Pooled Results of FEV_1 (% Predicted) Mean Change From Baseline*,†

*Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; I^2, index of heterogeneity; IV, instrumental variables; MDC, multidisciplinary care; SD, standard deviation.
†Data from Rea et al (11) at 12 months pooled with data from van Wetering et al (14) at 2 years.

The GRADE quality of evidence was assessed as very low for this outcome, indicating that an estimate of effect is very uncertain. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Hospital Admissions

All-Cause

Four studies (9;11-13) reported results of all-cause hospital admissions in terms of the number of persons with at least 1 admission during the follow-up period. Estimates from these 4 studies were pooled to determine a summary estimate (Table 8, Figure 5). There is a statistically significant 25% relative risk (RR) reduction ($P < 0.001$) in all-cause hospitalizations in the MDC group compared with the UC group. The I^2 value is 0%, indicating no statistical heterogeneity between the studies.

Table 8: All-Cause Hospital Admissions*

Study	n	Follow-Up (months)	MDC Group	UC Group	RR (95% CI)
Casas et al (9)	155	12	29/65	60/90	0.67 (0.49–0.91)
Rea et al (11)	135	12	29/83	26/52	0.70 (0.47–1.04)
Solomon et al (13)	88	6	4/41	6/47	0.76 (0.23–2.52)
Rice et al (12)	743	12	115/372	144/371	0.80(0.65–0.97)

*Abbreviations: CI, confidence intervals; MDC, multidisciplinary care; n, number; RR, relative risk; UC, usual care.

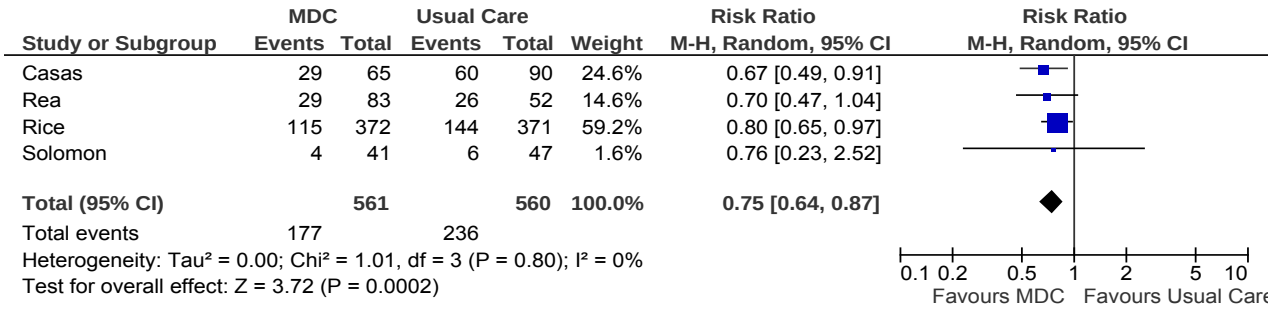


Figure 5: Pooled Results of All-Cause Hospitalizations*

*Abbreviations: CI, confidence interval; I^2, index of heterogeneity; MDC, multidisciplinary care; M–H, Mantel–Haenszel.

Rea et al (11) accounts for 14.6% of the weight in the pooled analysis. As mentioned, this study carried out cluster randomization. If it was removed from the analysis, the RR would be 0.76 (0.64–0.89) and the I^2 value would remain at 0%, with the Rice et al (12) study still contributing the greatest weight in the pooled analysis.

The GRADE quality of evidence was assessed as moderate for this outcome, indicating that further research may change the estimate of effect. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

COPD-Specific

Three studies (10-12) reported results of COPD-specific hospital admissions in terms of the number of persons with at least 1 admission during the follow-up period. Estimates from these 3 studies were pooled to determine a summary estimate (Table 9, Figure 6). There is a statistically significant 33% RR reduction ($P = 0.002$) in COPD-specific hospitalizations in the MDC group compared with the UC group. The I^2 value is 0%, indicating no statistical heterogeneity between studies. Removing the Rea et al (11) study from the analysis due to the cluster randomization resulted in a pooled RR of 0.71 (95% CI, 0.53–0.95). However, the summary estimate remains statistically significant and the I^2 value is 0%. The bulk of the weight (98%) when the Rea et al (11) study is removed is contributed from the Rice et al (12) study.

Table 9: COPD-Specific Hospital Admissions*

Study	n	Follow-Up (Months)	MDC Group	UC Group	RR (95% CI)
Koff et al (10)	38	3	1/19	3/19	0.33 (0.04–2.93)
Rea et al (11)	135	12	18/83	20/52	0.56 (0.33–0.96)
Rice et al (12)	743	12	62/372	86/371	0.72(0.54–0.96)

*Abbreviations: CI, confidence intervals; COPD, chronic obstructive pulmonary disease; MDC, multidisciplinary care; n, number; RR, relative risk; n, number; UC, usual care.

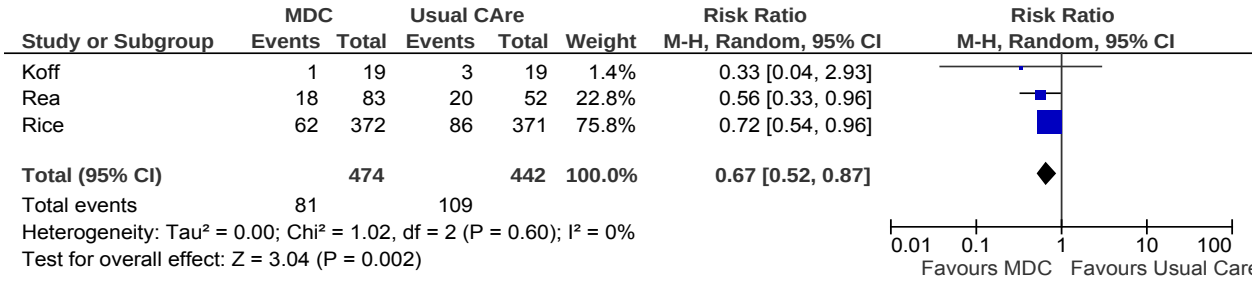


Figure 6: Pooled Results of COPD-Specific Hospital Admissions*

*Abbreviations: CI, confidence interval; I^2, index of heterogeneity; MDC, multidisciplinary care; M–H, Mantel–Haenszel.

The GRADE quality of evidence was assessed as moderate for this outcome, indicating that further research may change the estimate of effect. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Emergency Department Visits

All-Cause

Two studies (11;13) reported results of all-cause ED visits in terms of the number of persons with at least 1 visit during the follow-up period (Table 10). The pooled RR estimate is reported in Figure 7. There is a statistically nonsignificant reduction ($P = 0.24$) in all-cause ED visits when the data from these 2 studies are pooled. There is inconsistency in the RR estimates between the studies and wide confidence estimates denoting imprecision. The relatively low event rates could be contributing to type II error and imprecision. Of note, the study by Rice et al (12) reported a statistically significant reduction in all-cause ED visits ($P < 0.05$). However, data was not provided in the report such that the results could be included in this meta-analysis.

Table 10: All-Cause Emergency Department Visits*

Study	n	End Time Point	MDC Group	UC Group	RR (95% CI)
Solomon et al (13)	88	6 months	6/41	8/47	0.86 (0.33–2.27)
Rea et al (11)	135	12 months	5/83	7/52	0.45(0.15–1.34)

*Abbreviations: CI, confidence intervals; MDC, multidisciplinary care; n, number; RR, relative risk; UC, usual care

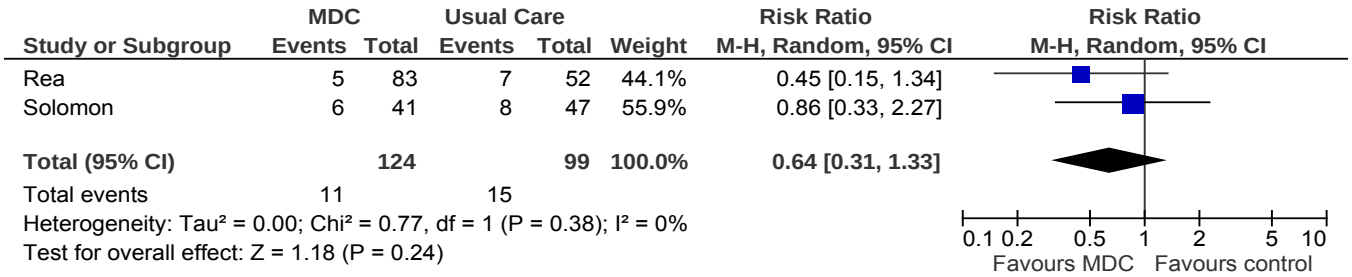


Figure 7: Pooled Results of All-Cause Emergency Department Visits*

*Abbreviations: CI, confidence interval; I^2, index of heterogeneity; MDC, multidisciplinary care; M–H, Mantel–Haenszel.

The GRADE quality of evidence was assessed as very low for this outcome, indicating that an estimate of effect is very uncertain. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

COPD-Specific

Two studies (10; 12) reported results of COPD-specific ED visits in terms of the number of persons with at least 1 visit during the follow-up period (Table 11). The pooled RR estimate is reported in Figure 8. There is a statistically significant reduction ($P < 0.001$) in COPD-specific ED visits when data from the 2 studies are pooled. There is some inconsistency in the RR point estimate from each study, which may be in part due to the low event rates in the study by Koff et al. (10)

Table 11: COPD-Specific Emergency Department Visits*

Study	n	Follow-up (Months)	MDC Group	UC Group	RR (95% CI)
Koff et al (10)	38	3	1/19	3/19	0.33 (0.04–2.93)
Rice et al (12)	743	12	51/372	85/371	0.60(0.44–0.82)

*Abbreviations: CI, confidence intervals; MDC, multidisciplinary care; n, number; RR, relative risk; UC, usual care.

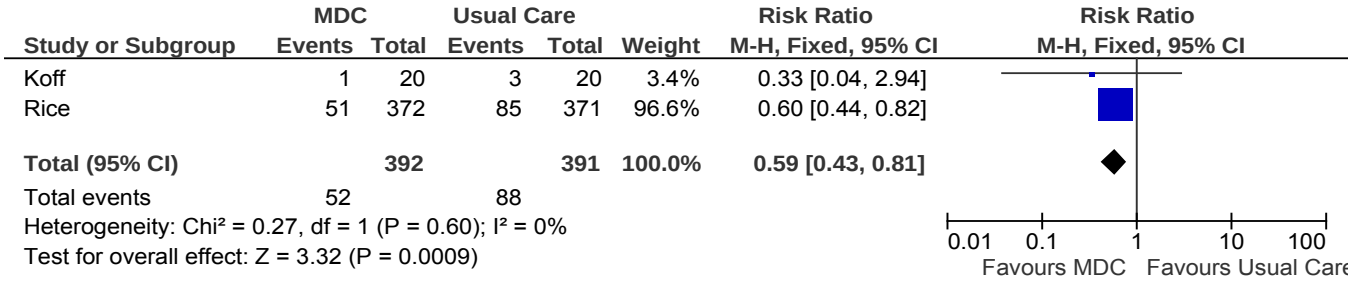


Figure 8: Pooled Results for COPD-Specific Emergency Department Visits*

*Abbreviations: CI, confidence interval; I^2, index of heterogeneity; MDC, multidisciplinary care; M–H, Mantel–Haenszel.

The GRADE quality of evidence was assessed as moderate for this outcome, indicating that further research may change the estimate of effect. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Mortality

Three studies reported mortality during the study follow-up period. (9;11;12) Estimates from these 3 studies were pooled to determine a summary estimate (Table 12, Figure 9). There is a statistically nonsignificant reduction ($P = 0.36$) in mortality between the treatment groups. The I^2 value is 21%, indicating low statistical heterogeneity between studies. All studies had a 12-month follow-up period.

Table 12: All-Cause Mortality*

Study	n	Follow-up (Months)	MDC Group	UC Group	RR (95% CI)
Casas et al (9)	155	12	12/65	14/90	1.19 (0.59–2.39)
Rea et al (11)	135	12	2/71	4/46	0.32 (0.06–1.70)
Rice et al (12)	88	6	36/372	48/371	0.75 (0.50–1.12)

*Abbreviations: CI, confidence intervals; MDC, multidisciplinary care; n, number; RR, relative risk; UC, usual care.

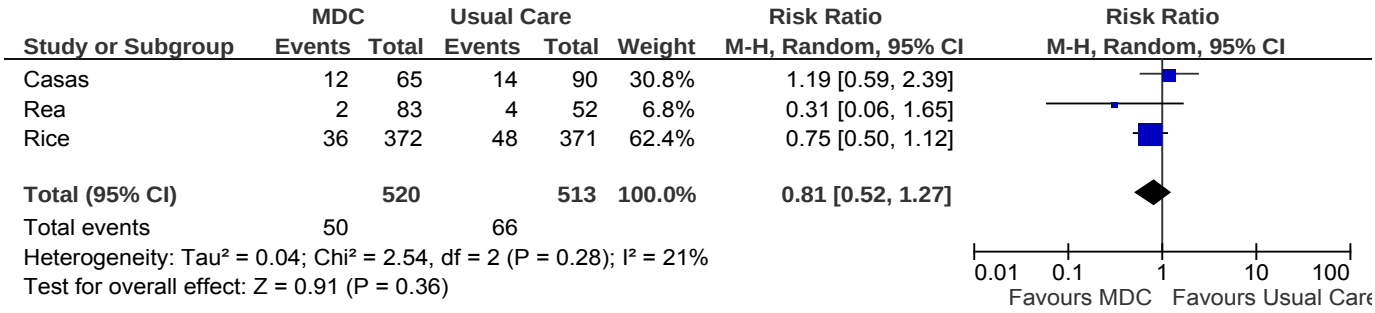


Figure 9: Pooled Results for All-Cause Mortality*

*Abbreviations: CI, confidence interval; I^2, index of heterogeneity; MDC, multidisciplinary care; M–H, Mantel–Haenszel.

The GRADE quality of evidence was assessed as low for this outcome, indicating that further research is likely to change the estimate of effect. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Economic Analysis

The results of the economic analysis are summarized in issue 12 of the COPD series entitled *Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model*. This report can be accessed at: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Economic_March.pdf.

Conclusions

The summary effect of estimates for the outcome measures assessed in this evidence-based analysis are reported in Tables 13 and 14 with the associated GRADE quality of evidence evaluation for each outcome measure. Significant effect estimates with moderate quality of evidence were found for all-cause hospitalization, COPD-specific hospitalization, and COPD-specific ED visits. A significant effect supported by low quality of evidence was found for the quality of life outcome. Effect estimates for all other outcome measures were not significant, and these estimates were supported by either low or very low quality of evidence.

Table 13: Summary of Continuous Data*

Outcome	Number of Studies (n)	Weighted Mean Difference (95% CI)	GRADE
Quality of Life (SGRQ)	2 (942)	-4.05 (-6.47 to -1.63)	Low
Lung Function (FEV_1% predicted)	2 (316)	2.78 (-1.82–7.37)	Very Low

*Abbreviations: CI, Confidence intervals; COPD, chronic obstructive pulmonary disease; FEV_1 , forced expiratory volume in 1 second; n, number; SGRQ, St. George's Respiratory Questionnaire.

Table 14: Summary of Dichotomous Data*

Outcome	Number of Studies (n)	Relative Risk (95% CI)	GRADE
Hospitalizations			
All-cause (no. persons)	4 (1121)	0.75 (0.64–0.87)	Moderate
COPD-specific (no. persons)	3 (916)	0.67 (0.52–0.87)	Moderate
Emergency Department Visits			
All-cause (no. persons)	2 (223)	0.64 (0.31–1.33)	Very Low
COPD-specific (no. persons)	2 (783)	0.59 (0.43–0.81)	Moderate
Mortality			
	3 (1033)	0.81 (0.52–1.27)	Low

*Abbreviations: CI, confidence intervals; COPD; chronic obstructive pulmonary disease; n, number.

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity (FVC)	The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.

Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.
Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[1]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.
Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.

[1] The mild-to-moderate classification was created for the purposes of the report.

Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.
Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Medical Information Officer

Kellee Kaulback

Editorial Staff

Jan Collins
Irina Alecu

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

Appendices

Appendix 1: Literature Search Strategies

July 19, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to July Week 1 2010>
Search Strategy:
---
1 exp Pulmonary Disease, Chronic Obstructive/ (13894)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (20844)
3 (copd or coad).ti,ab. (15846)
4 chronic airflow obstruction.ti,ab. (484)
5 exp Emphysema/ (6903)
6 ((chronic adj2 bronchitis) or emphysema).ti,ab. (22517)
7 or/1-6 (52749)
8 exp Patient Care Team/ (45549)
9 exp "Delivery of Health Care, Integrated"/ (6274)
10 exp Interdisciplinary Communication/ (5170)
11 exp Cooperative Behavior/ (17768)
12 exp Interprofessional Relations/ (43788)
13 exp Program Evaluation/ or disease management program*.mp. or exp Program Development/ (55786)
14 exp "Continuity of Patient Care"/ (11224)
15 (team* or multidisciplin* or multifacet* or multi-disciplin* or multi-facet* or cooperat* or co-operat* or interdisciplin*or inter-disciplin$ or collaborat* or multispecial* or multi-special* or share or sharing or shared or integrat*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (575645)
16 or/8-15 (653664)
17 7 and 16 (1615)
18 limit 17 to (english language and humans and yr="1995 -Current") (1120)
19 limit 18 to (case reports or comment or editorial or letter) (73)
20 18 not 19 (1047)

Database: EMBASE <1980 to 2010 Week 28>
Search Strategy:
---
1 exp chronic obstructive lung disease/ (36092)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (19507)
3 (copd or coad).ti,ab. (15889)
4 chronic airflow obstruction.ti,ab. (453)
5 exp emphysema/ (14600)

6 exp chronic bronchitis/ (6204)
7 ((chronic adj2 bronchitis) or emphysema).ti,ab. (14594)
8 or/1-7 (58780)
9 exp cooperation/ (15758)
10 exp integrative medicine/ (591)
11 exp integrated health care system/ (609)
12 exp health program/ (63761)
13 exp program development/ (1986)
14 (multidisciplin* or multifacet* or multi-disciplin* or multi-facet* or cooperat* or co-operat* or interdisciplin*or inter-disciplin$ or collaborat* or multispecial* or multi-special* or share or sharing or shared or integrat*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (390734)
15 disease management program*.mp. (1036)
16 team*.mp. (49014)
17 or/9-16 (480399)
18 8 and 17 (2206)
19 limit 18 to (human and english language and yr="1995 -Current") (1519)
20 limit 19 to (editorial or letter or note) (112)
21 case report/ (1113858)
22 19 not (20 or 21) (1366)

#	Query	Results
S17	((S1 or S2 or S3 or S4 or S5)) and (S15 and S16)	506
S16	(S1 or S2 or S3 or S4 or S5)	7235
S15	(S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14)	141659
S14	AB (team* or multidisciplin* or multifacet* or multi-disciplin* or multi-facet* or cooperat* or co-operat* or interdisciplin*or inter-disciplin$ or collaborat* or multispecial* or multi-special* or share or sharing or shared or integrat*)	74133
S13	TI (team* or multidisciplin* or multifacet* or multi-disciplin* or multi-facet* or cooperat* or co-operat* or interdisciplin*or inter-disciplin$ or collaborat* or multispecial* or multi-special* or share or sharing or shared or integrat*)	29056
S12	(MH "Program Development+")	29008
S11	(MH "Interprofessional Relations+")	12134
S10	(MH "Teamwork")	4830
S9	(MH "Health Care Delivery, Integrated")	2670
S8	(MH "Cooperative Behavior")	1928
S7	(MH "Continuity of Patient Care+")	6907
S6	(MH "Multidisciplinary Care Team+")	15506
S5	chronic bronchitis or emphysema	1553
S4	(MH "Emphysema+")	945
S3	copd or coad	3996

S2	(chronic obstructive and (lung* or pulmonary or airway* or airflow or respiratory) and (disease* or disorder*))	5471
S1	(MH "Pulmonary Disease, Chronic Obstructive+")	4226

Appendix 2: Description of Studies

Table A1: Description of Included Studies*

Author, Year	Design	N	Country, Sites	Population	Intervention	Control	Outcomes
van Wetering et al, 2010 (14)	RCT computerized randomization with concealed patient allocation.	199	Netherlands, 2 hospitals	GOLD stage 2 or 3 COPD Patients recruited were under the supervision of the department of respiratory medicine of 2 general hospitals in the Netherlands. They were judged to be clinically stable at inclusion by their respiratory physician.	Managed by physiotherapists, dieticians, and respiratory nurses. Phase 1: first 4 months after discharge from hospital the patient visited physiotherapist twice/week, individualized education program was provided, smokers worked with respiratory nurse for standardized smoking cessation counselling, nutritionally depleted patients received 4 visits by a dietician and nutritional supplements. Phase 2: subsequent 20 months following discharge patients visited physiotherapist once a month, nutritionally depleted patients visited dietician at 6, 9, 12, 24 months. Visits to respiratory nurse were scheduled upon request.	Managed by respiratory physician Pharmaco-therapy according to accepted guidelines, smoking cessation advice, and recommendation to eat more if nutritionally depleted.	Primary: Disease specific quality of life by SGRQ, total number of exacerbations Secondary: change in subscores of the SGRQ, dyspnea scale, exercise performance, cycle endurance test, and 6MWT, muscle strength, isometric quadriceps peak torque, maximum inspiratory mouth pressure, body composition, lung function, and global assessment of perceived effectiveness on a 5-point Likert scale Assessed at baseline, 4, 12, and 24 months

Author, Year	Design	N	Country, Sites	Population	Intervention	Control	Outcomes
Koff et al, 2009 (10)	RCT, blinded envelope used for randomization.	40	United States, single centre	GOLD Stage 3 or 4 COPD	Proactive integrated care Patients received disease-specific education, teaching of self-management techniques, enhanced communication with study co-ordinators and remote home monitoring.	Continued usual care with treatment prescribed by their health care provider.	Primary: quality of Life measured by the SGEQ. Secondary: health care costs, identification of unreported exacerbations. Assessed at baseline and 3 months
Rea et al, 2004 (11)	Randomized 51 GP with 116 GPs using computer generated random numbers	51 GPs 135 patients	New Zealand	Persons with moderate to severe COPD	Chronic disease management program. Patients were seen by a respiratory physician and a respiratory nurse specialist. During assessment a patient specific care plan was negotiated with each patient by their GP and practice nurse. Education about smoking cessation, medication and use of inhalers, annual influenza vaccination, and attendance at a pulmonary rehabilitation program were recommended. Visits to practice nurses monthly and to the GP every 3 months unless otherwise needed.	Conventional care Same assessment procedure as intervention group but did not have a care plan, were not seen by a respiratory physician during the assessment and did not have access to the respiratory nurse specialist. GPs had access to the COPD management guidelines and pulmonary rehabilitation program.	Primary: change in hospital bed days. Number of admissions. ITT for primary outcome and number of admissions. Changes in respiratory function, walking distance, and quality of life.

Author, Year	Design	N	Country, Sites	Population	Intervention	Control	Outcomes
Casas et al, 2006 (9)	RCT, computer-generated random numbers	155	Spain, multicentered (2 hospitals)	Persons enrolled after hospital discharge for which they were admitted because of a previous episode or exacerbation requiring hospitalization for > 48 hours.	Integrated care was standardized between the 2 sites and included 4 key features: 1. a comprehensive assessment of the patient at discharge, 2. an educational program on self-management of the disease administered at discharge, 3. agreement on an individually tailored care plan following international guidelines shared via interaction between a specialized nurse case manager and the primary care team, 4. accessibility of the specialized nurse to patients/carers and primary care professionals during follow-up period with an information and communication platform including a web-based call centre.	Usual Care: Patients in this group were visited by their own physician without additional support. Visits were usually scheduled every 6 months. The controls did not receive help from the specialized nurse nor were they included in the educational program or had access to the call centre. They were visited by their own physician without additional support. The attending physician decided on the outpatient control regimen.	1-year follow-up SGRQ and the EuroQll Pulmonary function tests. Use of health care resources by phone or personal interview was carried out at 1,3,6,9 and 12 months in both arms of the study. Hospital admissions and mortality were obtained from hospital records and direct family interviews.

Author, Year	Design	N	Country, Sites	Population	Intervention	Control	Outcomes
Rice et al, 2010 (12)	RCT	743	United States, 5 VA medical centers	COPD patients at high risk for exacerbation of FEV_1 < 70% post bronchodilator spirometry predicted and FEV_1/FVC < 0.70.	Disease management: attended a single 1–1.5 hour group education session conducted by a respiratory therapist case manager. Education session included general information about COPD, including cause, symptoms and treatment of exacerbations, direct observation of inhaler techniques, review and adjustment of medications, smoking cessation counselling if needed, recommendations on influenza and pneumococcal vaccinations, encouragement of regular exercise, instruction on hand hygiene. Each subject received an individualized written action plan. Pharmacist monitored the use of action plan medications Monthly telephone calls to patients by case manager	Usual Care: received a 1-page handout with a summary of the principles of COPD care according to published guidelines, and the telephone number for the 24-hour VA nursing helpline, a service available to all VA patients.	Primary Outcome: combined number of hospitalizations and ED visits for COPD made by each patient during the 12-month follow-up.

Author, Year	Design	N	Country, Sites	Population	Intervention	Control	Outcomes
Solomon et al, 1998 (13)	RCT	98	United States, 11 hospitals	Diagnosed by pulmonary function tests, 40 years of age or older, treated for diagnosis of COPD per American Thoracic Society criteria.	Treatment group received pharmaceutical care in collaboration with physicians 6-month treatment period, scheduled visits at enrolment and then 1-month intervals for a total of 5 visits. Data collection at baseline and at 6-month follow-up (visit 5) Pharmacist involvement with health care team in the management of patient drug therapy, collaboration with physicians to implement a patient specific, optimized, approach to COPD, education of COPD patients about their disease and therapy, counselling for specific concerns, patient assessment and care through clinic visits and telephone follow-up.	Usual care group had no access to the primary pharmacy caregivers and received no supplemental education or assessment of needs beyond what was usually done.	Dyspnea using the Borg Scale Symptom severity scale Compliance by tablet count and self-reported measure Patients questioned on ED visits, office visits, hospital admission, length of stay, and new medication

*Abbreviations: COPD, chronic obstructive pulmonary disease; ED, emergency department; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GP, general practice; GOLD, Global Initiative for Chronic Obstructive Lung Disease ; ITT, intention-to-treat; RCT, randomized controlled trial; SGRQ, St. George's respiratory questionnaire; VA, Veteran's Administration.

Appendix 3: GRADE Profile

Table A2: GRADE Quality of Evidence*

Quality Assessment							Summary of Findings			
							Number of Patients		Effect	Quality
Number of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	MDC	Usual Care	(95% CI)	
Quality of Life (St. George's Respiratory Questionnaire)										
2	RCT	Very serious†	none	none	none	none	474	468	WMD -4.05 (-6.47-1.63)	LOW
FEV_1 (% Predicted)										
2	RCT	Serious‡	Serious§	none	Serious‖	none	173	143	WMD 2.78 (-1.82-7.37)	VERY LOW
All-Cause Hospitalization										
4	RCT	Serious¶	none	none	none	none	561	560	RR 0.75 (0.64-0.87)	MODERATE
COPD-Specific Hospitalization										
3	RCT	Serious#	none	none	none	none	474	442	RR 0.67 (0.52-0.87)	MODERATE
Mortality										
3	RCT	Serious	Serious**	none	Serious‖	none	508	507	RR 0.81 (0.52-1.27)	LOW
All-Cause Emergency Department Visits										
2	RCT	Serious††	none	Serious‡‡	Very serious§§	none	124	99	RR 0.64 (0.31-1.33)	VERY LOW
COPD-Specific Emergency Department Visits										
2	RCT	Serious‖‖	none	none	none	none	392	391	RR 0.59 (0.43- 0.81)	MODERATE

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; MDC, multidisciplinary care; RCT, randomized controlled trial; RR, relative risk; SGRQ, St. George's Respiratory Questionnaire; WMD, weighted mean difference.

†High loss to follow-up or low response rate in both studies.

‡21% loss to follow-up in study by van Wetering et al (14) which may bias the results of the SGRQ mean scores in each group. If the scores of the losses to follow-up were above the group mean for MDC this may reduce the summary effect estimate below clinical significance, which is a score of 4.

§Inconsistency in point estimate.

‖Confidence intervals are sufficiently wide such that the estimate can show an important benefit or no benefit (or important harm).

¶ Two of the 4 studies including Rea et al (11) and Solomon et al (13) (50% of the body of evidence) in the body of evidence did not report if adequate allocation concealment was undertaken. Adequate allocation concealment remains unclear.

#One of the 3 studies, Rea et al, (11) did not report if adequate allocation concealment was carried out. Adequate allocation concealment remains unclear.

**There is inconsistency in the magnitude of the effect estimates across the studies.

††Unclear adequate allocation concealment.

‡‡Population not well described other than having COPD

§§Small event rates; imprecision in estimate.

‖‖ Three-month follow-up.

References

(1) Peytremann-Bridevaux I, Staeger P, Bridevaux PO, Ghali WA, Burnand B. Effectiveness of chronic obstructive pulmonary disease-management programs: systematic review and meta-analysis. Am J Med. 2008 May;121(5):433-43.

(2) Sin DD, McAlister FA, Man SF, Anthonisen NR. Contemporary management of chronic obstructive pulmonary disease: scientific review. JAMA. 2003 Nov 5;290(17):2301-12.

(3) Lemmens KM, Nieboer AP, Huijsman R. A systematic review of integrated use of disease-management interventions in asthma and COPD. Respir Med. 2009;103(5):670-91.

(4) Gershon AS, Wang C, Wilton AS, Raut R, To T. Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in Ontario, Canada, 1996 to 2007: a population-based study. Arch Intern Med. 2010 Mar 22;170(6):560-5.

(5) Mitchell GK, Tieman JJ, Shelby-James TM. Multidisciplinary care planning and teamwork in primary care. Med J Aust. 2008;188(8):S61-S64.

(6) Kirilloff LH, Carpenter V, Kerby GR, Kigin C, Weimer MP. American Thoracic Society. Medical Section of the American Lung Association. Skills of the health team involved in out-of-hospital care for patients with COPD. Am Rev Respir Dis. 1986;133(5):948-9.

(7) Nie JX, Wang L, Upshur RE. Mortality of elderly patients in Ontario after hospital admission for chronic obstructive pulmonary disease. Can Respir J. 2007 Nov;14(8):485-9.

(8) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490-8.

(9) Casas A, Troosters T, Garcia-Aymerich J, Roca J, Hernandez C, Alonso A, et al. Integrated care prevents hospitalisations for exacerbations in COPD patients. Eur Respir J. 2006 Jul;28(1):123-30.

(10) Koff PB, Jones RH, Cashman JM, Voelkel NF, Vandivier RW. Proactive integrated care improves quality of life in patients with COPD. Eur Respir J. 2009 May;33(5):1031-8.

(11) Rea H, McAuley S, Stewart A, Lamont C, Roseman P, Didsbury P. A chronic disease management programme can reduce days in hospital for patients with chronic obstructive pulmonary disease. Intern Med J. 2004 Nov;34(11):608-14.

(12) Rice KL, Dewan N, Bloomfield HE, Grill J, Schult TM, Nelson DB, et al. Disease management program for chronic obstructive pulmonary disease: a randomized controlled trial. Am J Respir Crit Care Med. 2010;182(7):890-6.

(13) Solomon DK, Portner TS, Bass GE, Gourley DR, Gourley GA, Holt JM, et al. Clinical and economic outcomes in the hypertension and COPD arms of a multicenter outcomes study. J Am Pharm Assoc (Wash). 1998;38(5):574-85.

(14) van Wetering CR, Hoogendoorn M, Mol SJ, Rutten-van Molken MP, Schols AM. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. Thorax. 2010 Jan;65(1):7-13.

(15) Goodman, C. Literature searching and evidence interpretation for assessing health care practices. Stockholm, Sweden: Swedish Council on Technology Assessment in Health Care; 1996. 81 p. SBU Report No. 119E.

(16) Global Initiative for Chronic Obstructive Lung Disease. Pocket guide to COPD diagnosis, management, and pervention [Internet]. [updated 2010; cited 2011 Jul 10]. Available from: http://www.goldcopd.org/guidelines-pocket-guide-to-copd-diagnosis.html

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-7011-4 (PDF)

Ontario
Health Quality Ontario
Qualité des services
de santé Ontario

Pulmonary Rehabilitation for Patients With Chronic Pulmonary Disease (COPD): An Evidence-Based Analysis

COPD Working Group

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 6, pp. 1–75, March 2012

Suggested Citation

This report should be cited as follows:

COPD Working Group. Pulmonary rehabilitation for patients with chronic pulmonary disease (COPD): an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2012 Mar; 12(6) 1–75. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_Pulmomary_Rehab_March.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to: MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

6MWT	6 Minute Walking Test
AECOPD	Acute exacerbation of COPD
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval(s)
CRQ	Chronic Respiratory Questionnaire
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQOL	Health-related quality of life
ITT	Intention-to-treat
MCID	Minimal clinically important difference
RCT	Randomized controlled trial
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
UC	Usual care

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective

The objective of this evidence-based review was to determine the effectiveness and cost-effectiveness of pulmonary rehabilitation in the management of chronic obstructive pulmonary disease (COPD).

Technology

Pulmonary rehabilitation refers to a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs, though they may also include components such as patient education and psychological support. Pulmonary rehabilitation is recommended as the standard of care in the treatment and rehabilitation of patients with COPD who remain symptomatic despite treatment with bronchodilators.

For the purpose of this review, the Medical Advisory Secretariat focused on pulmonary rehabilitation programs as defined by the Cochrane Collaboration—that is, any inpatient, outpatient, or home-based rehabilitation program lasting at least 4 weeks that includes exercise therapy with or without any form of education and/or psychological support delivered to patients with exercise limitations attributable to COPD.

Research Questions

1. What is the effectiveness and cost-effectiveness of pulmonary rehabilitation compared with usual care (UC) for patients with stable COPD?

2. Does early pulmonary rehabilitation (within 1 month of hospital discharge) in patients who had an acute exacerbation of COPD improve outcomes compared with UC (or no rehabilitation)?

3. Do maintenance or postrehabilitation programs for patients with COPD who have completed a pulmonary rehabilitation program improve outcomes compared with UC?

Research Methods

Literature Search

Search Strategy

For Research Questions 1and 2, a literature search was performed on August 10, 2010 for studies published from January 1, 2004 to July 31, 2010. For Research Question 3, a literature search was performed on February 3, 2011 for studies published from January 1, 2000 to February 3, 2011. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists and health technology assessment websites were also examined for any additional relevant studies not identified through the systematic search.

Inclusion Criteria

Research questions 1 and 2:

- published between January 1, 2004 and July 31, 2010
- randomized controlled trials, systematic reviews, and meta-analyses
- COPD study population
- studies comparing pulmonary rehabilitation with UC (no pulmonary rehabilitation)
- duration of pulmonary rehabilitation program ≥ 6 weeks
- pulmonary rehabilitation program had to include at minimum exercise training

Research question 3:

- published between January 1, 2000 and February 3, 2011
- randomized controlled trials, systematic reviews, and meta-analyses
- COPD study population
- studies comparing a maintenance or postrehabilitation program with UC (standard follow-up)
- duration of pulmonary rehabilitation program ≥ 6 weeks
- initial pulmonary rehabilitation program had to include at minimum exercise training

Exclusion Criteria

Research questions 1, 2, and 3:

- grey literature
- duplicate publications
- non-English language publications
- study population ≤ 18 years of age
- studies conducted in a palliative population
- studies that did not report primary outcome of interest

Additional exclusion criteria for research question 3:

- studies with ≤ 2 sessions/visits per month

Outcomes of Interest

The primary outcomes of interest for the stable COPD population were exercise capacity and health-related quality of life (HRQOL). For the COPD population following an exacerbation, the primary outcomes of interest were hospital readmissions and HRQOL. The primary outcomes of interest for the COPD population undertaking maintenance programs were functional exercise capacity and HRQOL.

Quality of Evidence

The quality of each included study was assessed taking into consideration allocation concealment, randomization, blinding, power/sample size, withdrawals/dropouts, and intention-to-treat analyses.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. The following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Summary of Findings

Research Question 1: Effect of Pulmonary Rehabilitation on Outcomes in Stable COPD

Seventeen randomized controlled trials met the inclusion criteria and were included in this review.

The following conclusions are based on moderate quality of evidence.

- Pulmonary rehabilitation including at least 4 weeks of exercise training leads to clinically and statistically significant improvements in HRQOL in patients with COPD.[1]
- Pulmonary rehabilitation also leads to a clinically and statistically significant improvement in functional exercise capacity[2] (weighted mean difference, 54.83 m; 95% confidence interval, 35.63–74.03; $P < 0.001$).

Research Question 2: Effect of Pulmonary Rehabilitation on Outcomes Following an Acute Exacerbation of COPD

Five randomized controlled trials met the inclusion criteria and are included in this review. The following conclusion is based on moderate quality of evidence.

- Pulmonary rehabilitation (within 1 month of hospital discharge) after acute exacerbation significantly reduces hospital readmissions (relative risk, 0.50; 95% confidence interval, 0.33–0.77; $P = 0.001$) and leads to a statistically and clinically significant improvement in HRQOL.[3]

Research Question 3: Effect of Pulmonary Rehabilitation Maintenance Programs on COPD Outcomes

Three randomized controlled trials met the inclusion criteria and are included in this review. The conclusions are based on a low quality of evidence and must therefore be considered with caution.

- Maintenance programs have a nonsignificant effect on HRQOL and hospitalizations.
- Maintenance programs have a statistically but not clinically significant effect on exercise capacity ($P = 0.01$). When subgrouped by intensity and quality of study, maintenance programs have a statistically and marginally clinically significant effect on exercise capacity.

[1] As measured by all domains of the Chronic Respiratory Questionnaire
[2] As measured by the 6 Minute Walking Test
[3] As measured by all domains of the Chronic Respiratory Questionnaire and total, impact, and activity scores of the St. George's Respiratory Questionnaire

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this evidence-based review was to determine the effectiveness and cost-effectiveness of pulmonary rehabilitation in the management of chronic obstructive pulmonary disease (COPD).

Technology

Pulmonary rehabilitation refers to a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Pulmonary rehabilitation is recommended as the standard of care in the treatment and rehabilitation of patients with COPD who remain symptomatic despite treatment with bronchodilators.

Exercise training, the cornerstone of pulmonary rehabilitation programs, may include both aerobic and strength training. Other possible components of pulmonary rehabilitation include psychological support, patient education, nutritional counselling, occupational therapy, medication information, and smoking cessation.

While pulmonary rehabilitation can be delivered in multiple settings for varying durations, the optimal delivery site, components, duration, target populations, and timing remain in question.

For the purpose of this review, the Medical Advisory Secretariat focused on pulmonary rehabilitation programs as defined by the Cochrane Collaboration (1)—that is, any inpatient, outpatient, or home-based rehabilitation program lasting at least 4 weeks that includes exercise therapy with or without any form of education and/or psychological support delivered to patients with exercise limitations attributable to COPD.

Evidence-Based Analysis

Research Question(s)

1. What is the effectiveness and cost-effectiveness of pulmonary rehabilitation compared with usual care (UC) for patients with stable COPD?

2. Does early pulmonary rehabilitation (within 1 month of hospital discharge) in patients who had an acute exacerbation of COPD (AECOPD) improve outcomes compared with UC (or no rehabilitation)?

3. Do maintenance or postrehabilitation programs for patients with COPD who have completed a pulmonary rehabilitation program improve outcomes compared with UC?

Research Methods

Literature Search

Search Strategy

Research Questions 1 and 2: A literature search was performed on August 10, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2004 to July 31, 2010 (Appendix 1).

Research Question 3: A literature search was performed on February 3, 2011 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2000 to February 3, 2011 (Appendix 2).

Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles of uncertain eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established. The quality of evidence was assessed as high, moderate, low, or very low according to GRADE methodology.

Definition of a Pulmonary Rehabilitation Program

As noted previously, there is much clinical heterogeneity in the literature with respect to the duration, intensity, components, and delivery of pulmonary rehabilitation programs. In order to reduce the heterogeneity across studies included in this review we adopted the definition of pulmonary rehabilitation used in a Cochrane review (1) of pulmonary rehabilitation: any inpatient, outpatient, or home based-rehabilitation program lasting at least 4 weeks that includes exercise therapy with or without any form of education and/or psychological support delivered to patients with exercise limitations attributable to COPD.

Inclusion Criteria

Research Questions 1 and 2:

- published between January 1, 2004 and July 31, 2010
- randomized controlled trials (RCTs), systematic reviews, and meta-analyses
- COPD study population
- studies comparing pulmonary rehabilitation with UC (no pulmonary rehabilitation)
- duration of pulmonary rehabilitation program ≥ 6 weeks
- pulmonary rehabilitation program had to include at minimum exercise training

Research Question 3:

- published between January 1, 2000 and February 3, 2011
- RCTs, systematic reviews, and meta-analyses
- COPD study population
- studies comparing a maintenance or postrehabilitation program with UC (standard follow-up)
- duration of pulmonary rehabilitation program ≥ 6 weeks
- initial pulmonary rehabilitation program had to include at minimum exercise training

Exclusion Criteria

Research Questions 1, 2, and 3:

- grey literature
- duplicate publications
- non-English language publications
- study population ≤ 18 years of age
- studies conducted in a palliative population
- studies that did not report primary outcome of interest

Additional Exclusion Criteria for Research Question 3:

- studies with ≤ 2 sessions/visits a month

Outcomes of Interest

The primary outcomes of interest for the stable COPD population were exercise capacity and health-related quality of life (HRQOL). For the COPD population following an exacerbation, the primary outcomes of interest were hospital readmissions and HRQOL. Other health outcomes examined in this population were mortality, emergency department visits, and exercise capacity. The primary outcomes of interest for the COPD population undertaking maintenance programs were functional exercise capacity and HRQOL. Other outcomes examined were hospital admissions and length of hospital stay.

Statistical Analysis

Statistical Challenges: Meta-analysis

Meta-analyzing continuous measurements, such as functional exercise capacity using the 6 Minute Walking Test (6MWT), presents statistical challenges, as studies quite often report only baseline (pre) and final values (post) for intervention and control groups without reporting change-from-baseline values. While the absolute difference between pre and post values is easy to obtain (final value minus baseline value), the standard deviation (SD) necessary for meta-analysis is often lacking.

To clarify the statistical challenges relevant to this report, it is important to define some terms:

The *intra-group change from baseline to final* refers to the mean difference between baseline and final values **within** intervention or **within** control groups (i.e., the difference in pre and post measurements within groups).

The *inter-group difference* refers to the mean difference in intra-group change from baseline to final values (as defined above) **between** intervention and control (i.e., the difference in change from baseline values between groups).

Solutions to Challenges

To solve the problem of missing SDs, the Cochrane Handbook for Systematic Reviews has identified 2 solutions (http://www.cochrane-handbook.org/), both of which are usually explored in any one meta-analysis:

Meta-analyze only the inter-group difference in mean final values between intervention and control. This approach assumes that, if baseline values do not significantly differ between intervention and control, the inter-group difference in mean final values will be similar to the inter-group difference of the intra-group change from baseline to final. One can test for significant differences at baseline; if they do not differ, this approach is valid.

Use statistical calculations to derive the standard deviations for the intra-group change from baseline to final, then meta-analyze these data. Repeated (pre and post) measurements made on the same participants tend to be correlated, thus lowering standard errors and creating tighter confidence intervals in comparison to single measurements. A correlation coefficient quantifies the correlation between measurements. This explains why meta-analyzing the change from baseline to final is preferable to meta-analyzing final values only, particularly if there are significant differences between intervention and control at baseline.

There are 2 ways to derive the standard deviations for the intra-group change from baseline to final when information is lacking:

Derive the standard deviation of the intra-group change from baseline to final using P values, confidence intervals, or standard errors reported from a t-test for the intra-group change from baseline to final. It should be noted, however, that if a study does not report standard deviations for the intra-group change from baseline to final, it is unlikely (though not impossible) that the study will report relevant t-test values. This approach is thus rare.

Calculate the standard deviation of the intra-group change from baseline to final by imputing a correlation coefficient. Correlation coefficients can be calculated from studies that report all relevant data (baseline ± SD, final ± SD, difference ± SD). These correlation coefficients can then be applied to studies lacking relevant information to derive appropriate SDs. Alternatively, one can impute varying correlation coefficients and run multiple sensitivity meta-analyses to observe any changes in effect. It should be noted, however, that imputation has been historically shown to have little effect on the summary estimates and conclusions of a meta-analysis. (2;3)

For this particular analysis, changes from baseline values were meta-analyzed. Standard deviations for these changes were generated by imputing a correlation coefficient of 0.5.

Quality of Evidence

The quality of each included study was assessed taking into consideration the following 7 study design characteristics:

- adequate allocation concealment,
- randomization (study must include a description of the randomization procedure used and this must be a proper method),
- power/sample size (adequate sample size based on a priori calculations; underpowered studies were identified, when possible, using post-hoc sample size power calculations),
- blinding (if double blinding was not possible, a single-blind study with unbiased assessment of outcome was considered adequate for this criterion),
- Fewer than 20% withdrawals/dropouts,
- intention-to-treat (ITT) analysis conducted and done properly (withdrawals/dropouts considered in analysis), and
- other criteria as appropriate for the particular research question and study design.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (4) as presented below.

- Quality refers to criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

Research Question 1: Effect of Pulmonary Rehabilitation on Outcomes in Stable COPD

The database search yielded 2,069 citations published between January 2004 and July 2010. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when citations were excluded in the analysis.

Twenty studies met the inclusion criteria described above; of these, 1 paper was a health technology assessment, 2 studies were systematic reviews, and the remaining 17 studies were RCTs (Table 1).

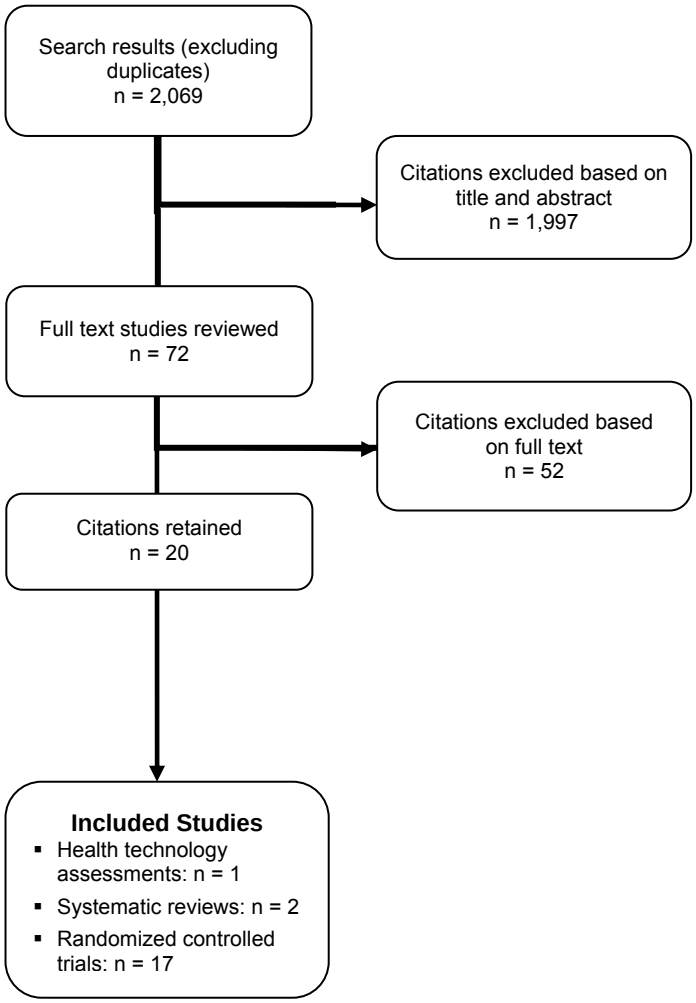


Figure 1: Citation Flow Chart

For each included study, the study design was identified and is summarized below in Table 1, which is a modified version of a hierarchy of study design by Goodman. (5) The additional designation "g" was added for preliminary reports of studies that had been presented to international scientific meetings. Table 1 lists the body of evidence examined according to study design and the number of studies identified.

Table 1: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	3
Large RCT†	3
Small RCT	14
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	
Total	20

*Abbreviation: RCT, randomized controlled trial.
†Large RCT is defined as having a sample size of at least 100.

The literature search identified 3 reviews focusing on pulmonary rehabilitation for COPD. A summary of the reviews can be found below (Table 2). Two of them were narrative reviews, (6;7) of which 1 focused solely on home-based pulmonary rehabilitation. The remaining review, conducted in 2006 by Lacasse et al, (8) included a meta-analysis of the effects of pulmonary rehabilitation on exercise capacity and HRQOL based on 31 studies from the years 1966 to 2004. The authors concluded that pulmonary rehabilitation featuring at least 4 weeks of exercise training leads to clinically and statistically significant improvements in important domains of quality of life including dyspnea, fatigue, emotional function, and mastery. For exercise capacity, the results favoured the pulmonary rehabilitation group over the UC group, with a weighted mean 6MWT difference of 48 m (95% confidence interval [CI], 32–65 m). (Sixteen studies were included in this pooled estimate.) Subgroup analyses based on a priori reasons for clinical heterogeneity did not have an effect on study results.

Table 2: Summary of Existing Evidence on Pulmonary Rehabilitation Interventions for Stable COPD*

Study (Type)	Number of Trials Search Years	Conclusions
CADTH, 2010 (HTA) (6)	102 1998 onwards	Pulmonary rehabilitation improves short-term exercise capacity, HRQOL, and mental health outcomes for patients with COPD.
Lacasse et al, 2006 (MA) (8)	31 1966–2004	Pulmonary rehabilitation including at least 4 weeks of exercise training leads to clinically and statistically significant improvements in important domains of quality of life including dyspnea, fatigue, emotional function, and mastery.
Viera et al, 2010 (SR) (7)	8	Self-monitored, home-based pulmonary rehabilitation is useful and, if properly done, may be an equivalent alternative to outpatient pulmonary rehabilitation. Many programs with endurance training have been found beneficial in improving HRQOL and exercise capacity.

*Abbreviations: CADTH, Canadian Agency for Technologies and Health; COPD, chronic obstructive pulmonary disease; HRQOL, health-related quality of life; HTA, health technology assessment; MA, meta-analysis; SR, systematic review.

Randomized Controlled Trials

A total of 17 RCTs that met the inclusion criteria were identified and included in this review. (9-24) The sample size of the studies ranged from 28 to 200, with a total of 1,155 participants in the 17 studies. The mean reported age of the participants was 66 years. All studies reported gender, and the mean percentage of females was 67 percent. The percent predicted forced expiratory volume in 1 second (% predicted FEV_1) in the study populations ranged from 27 to 72. Few studies characterised the study sample in terms of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD stage criteria (see below) based on FEV_1 and forced vital capacity (FVC). Using these criteria, the population of the remaining studies was assessed. In total, 77% of studies were conducted in a severe COPD population, 18% in a moderate COPD population, and 5% in a very severe COPD population.

The GOLD COPD stage criteria are as follows:

Stage I (Mild COPD): Mild airflow limitation ($FEV_1/FVC < 70\%$; $FEV_1 \geq 80\%$ predicted) and sometimes, but not always, chronic cough and sputum production. (At this stage, the individual may not be aware that his or her lung function is abnormal.)

Stage II (Moderate COPD): Worsening airflow limitation ($FEV_1/FVC < 70\%$; $50\% > FEV_1 < 80\%$ predicted), with shortness of breath typically developing on exertion. (This is the stage at which patients typically seek medical attention because of chronic respiratory symptoms or exacerbations.)

Stage III (Severe COPD): Further worsening of airflow limitation ($FEV_1/FVC < 70\%$; $30\% > FEV_1 < 50\%$ predicted), greater shortness of breath, reduced exercise capacity, and repeated exacerbations that have an impact on patients' quality of life.

Stage IV (Very Severe COPD): Severe airflow limitation ($FEV_1/FVC < 70\%$; $FEV_1 < 30\%$ predicted) or $FEV_1 < 50\%$ predicted plus chronic respiratory failure. When this complication is present, patients may have very severe (Stage IV) COPD even if the FEV_1 is greater than 30% predicted. (At this stage, quality of life is very appreciably impaired and exacerbations may be life-threatening.)

Nine studies excluded patients with comorbidities that precluded participation in a rehabilitation program or that could limit exercise training. Some of these trials specifically excluded patients with neurological or musculoskeletal disease, cancer and/or diabetes. Eight trials specifically excluded patients with heart failure, ischemic heart disease, or a history of heart disease.

Study Characteristics

Studies were conducted between 1990 and 2009. Two studies were conducted in Canada, with the remainder from the United Kingdom, Europe, India, and Australia. Sample sizes ranged from 28 to 200 participants. A detailed description of the studies can be found in Appendix 2. The individual quality of the studies varied, with differences in quality mainly due to methodological issues such as inadequate description of randomization, sample size calculation, allocation concealment, blinding, and uncertainty around the use of ITT analysis (Appendix 3). Pulmonary rehabilitation programs were delivered through a variety of settings, although the majority of studies (71%) were conducted in an outpatient setting of a hospital. All 17 studies reported a UC control group and 3 reported a wait-list control group.

Intervention Characteristics

All the interventions examined in the studies included a minimum of exercise training. Exercise programs consisted of aerobic training and in many cases included a strength-training component. Some interventions also featured disease education, dietary education/advice, self-care, smoking cessation advice, endurance training, self-management skills, breathing and relaxation exercises, referrals to social services, and/or psychological support. Many of the programs also included an individualized home training program that participants were encouraged to follow. All the studies examined the outcomes of HRQOL and exercise capacity. Despite homogeneity in outcome assessment, clinical heterogeneity was evident in intervention characteristics such as duration, intensity, setting, and interventionist.

Duration and Intensity

Intervention durations ranged from 4 weeks to 1 year. The majority of interventions lasted 6 to12 weeks (13 studies), while the rest fell into categories of 4 weeks (1 study), 6 months (2 studies), or 1 year (1 study). The intensity of the interventions varied between trials, although the majority of studies had pulmonary rehabilitation programs that were 3 to 6 hours per week.

Interventions and Setting

The majority of interventions were carried out by a multidisciplinary team of physiotherapists, occupational therapists, dieticians, and nurses. However, a physiotherapist and/or physical therapist alone carried out the intervention in 5 studies, and a sole nurse in 1 other study. In 3 studies, a primary care physician was involved in supervision of the rehabilitation group during outpatient care. Three studies had an unclear description of who delivered the intervention. The majority of interventions occurred in an outpatient setting (71%).

Outcomes

Duration of follow-up ranged from 8 weeks to 2 years, with the most common reported length being 12 weeks. In addition, 41% of studies followed patients at a minimum of 2 time points.

All studies reported 6MWT results as a measure of exercise capacity. (Two studies reporting functional exercise capacity in terms of the shuttle walk test were not included in the meta-analysis.) Eighty-two percent of trials measured HRQOL using the Chronic Respiratory Questionnaire (CRQ) or St. George's Respiratory Questionnaire (SGRQ). Additional outcomes examined in the trials included patient satisfaction, fatigue, lung function, anxiety and depression, functional dyspnea, psychological general well-being, health status, exacerbations, and hospitalizations.

The results of the meta-analyses identified in the literature search are summarized below in Table 3. Forest plots are found in Appendix 4.

Table 3: Summary of Findings of Meta-Analyses of Studies Investigating the Effectiveness of Pulmonary Rehabilitation on HRQOL and Functional Exercise Capacity in Patients With COPD*

Outcome	Number of Studies	Number of Participants	Effect Size Mean Difference (95% CI)	GRADE
Quality of Life – Change in SGRQ				
Total Score	8	514	-8.40 (-13.30, -3.50)	Moderate
Symptoms	8	514	-3.40 (-7.85, 1.04)	
Impacts	8	514	-3.41 (11.03, 4.21)	
Activity	8	514	-7.73 (-14.24, -1.22)	
Quality of Life – Change in CRQ				
Fatigue	8	507	0.83 (0.62, 1.04)	Moderate
Emotional Function	8	507	0.70 (0.45, 0.95)	
Mastery	8	507	0.85 (0.63, 1.06)	
Dyspnea	8	507	0.97 (0.77, 1.17)	
Functional Exercise Capacity (6MWT)	15	659	54.83 (35.63, 74.03)	Moderate

*Abbreviations: 6MWT, 6 Minute Walking Test; CI, confidence interval; CRQ, Chronic Respiratory Questionnaire; SGRQ, St. George's Respiratory Questionnaire.

Health-Related Quality of Life

Eight studies reported results of an HRQOL assessment based on the SGRQ. (12-15;17;20;22;23) All studies compared the difference in the mean change scores from baseline to follow-up between the pulmonary rehabilitation and UC groups. A mean decrease in the SGRQ indicates an improvement in quality of life, while a mean increase indicates a deterioration in quality of life. The minimal clinically important difference (MCID)—that is, the smallest difference in score corresponding to the smallest difference perceived by the average patient that would mandate, in the absence of troublesome side effects and excessive costs, a change in patient management—for the SGRQ is 4 units. As seen above (Table 3), there was a statistically and clinically significant improvement in quality of life for the pulmonary rehabilitation group compared with the UC group as reflected in the total score ($P < 0.001$) and activity scores ($P = 0.02$) of the SGRQ.

The GRADE quality of evidence was assessed as moderate for this outcome. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Eight studies reported results of the quality-of-life assessment based on the CRQ. (16-19;24-27) All studies compared the difference in the mean change scores from baseline to follow-up between the pulmonary rehabilitation and UC groups. A mean increase in CRQ indicates an improvement in quality of life, while a mean decrease indicates a deterioration in quality of life. The MCID for the CRQ has been established as 0.5 units. Taking this figure into consideration, pulmonary rehabilitation (including all CRQ domains) was associated with a statistically and clinically significant improvement in quality of life ($P < 0.001$) (Table 3).

Exercise Capacity

Eighty-eight percent of studies reported results of functional exercise capacity assessments based on the 6MWT. All studies compared the difference in the mean change in scores from baseline to follow-up between the pulmonary rehabilitation and UC groups. The MCID for the 6MWT has been reported to be

from 25 to 35 meters. (28;29) As seen above (Table 3), there was a statistically and clinically significant improvement in functional exercise capacity for the pulmonary rehabilitation group compared with the UC group, with an estimated pooled difference of 54.83 meters ($P < 0.001$). The GRADE quality of evidence was assessed as moderate for this outcome.

Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Conclusion

Based on moderate-quality evidence, pulmonary rehabilitation including at least 4 weeks of exercise training leads to clinically and statistically significant improvements in HRQOL in patients with COPD.[1]

Pulmonary rehabilitation also leads to a clinically and statistically significant improvement in functional exercise capacity[2] (weighted mean difference, 54.83 m; 95% CI, 35.63–74.03; P < 0.001).

Research Question 2: Effect of Pulmonary Rehabilitation on Outcomes Following an Acute Exacerbation of COPD

The database search yielded 2,069 citations published between January 2004 and July 2010. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 2 shows the breakdown of when citations were excluded in the analysis.

Six studies met the inclusion criteria for this research question; of these, 1 paper was a meta-analysis and the remainder were RCTs (Table 4).

[1] As measured by all domains of the CRQ
[2] As measured by the 6MWT

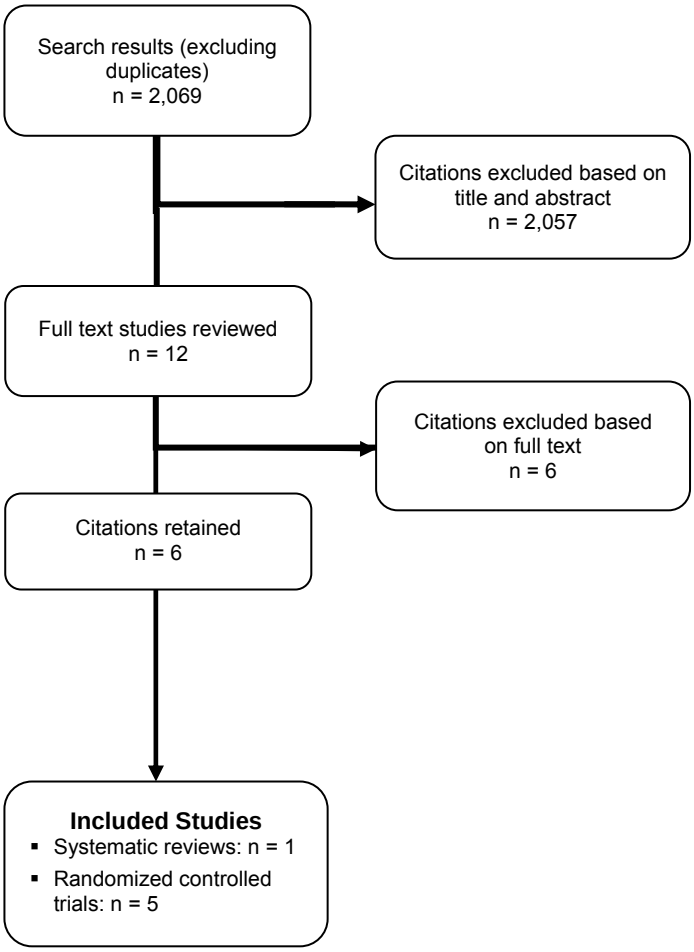


Figure 2: Citation Flow Chart

For each included study, the study design was identified and is summarized below in Table 4, which is modified version of a hierarchy of study design by Goodman. (5)

Table 4: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	1
Large RCT†	
Small RCT	5
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	
Total	6

*Abbreviation: RCT, randomized controlled trial
†Large RCT is defined as having a sample size of at least 100.

One systematic review, conducted in 2010 by Puhan et al,(30) focused on pulmonary rehabilitation following an AECOPD and included a meta-analysis. The review aimed to evaluate the effects of pulmonary rehabilitation on future hospital admissions (primary outcome) and other important outcomes (mortality, health-related quality of life, and exercise capacity) after COPD exacerbations. Six studies from 1966 to 2008 were included in the review.

The authors concluded that these studies suggest that pulmonary rehabilitation is highly effective and safe in reducing hospital admissions and mortality and improving HRQOL in COPD patients following an exacerbation. There were highly clinically and statistically significant differences between the rehabilitation group and the UC group for all domains of the CRQ and for the total, impact, and activity scores of the SGRQ. Pulmonary rehabilitation also improved exercise capacity measured by the 6MWT or shuttle test.

In assessing the Puhan et al review, (31) the Medical Advisory Secretariat excluded 3 of the 6 RCTs because:

- 2 studies had pulmonary rehabilitation programs lasting no longer than 10 days.
- 1 study excluded patients with an exacerbation in the previous month.

Randomized Controlled Trials

The database search identified citations published between 2004 and August 2010, but the literature was searched from 2008 forward. Five RCTs met the inclusion criteria and were thus included in this review. (9;32-35) The sample size of the studies ranged from 31 to 97, with a total of 276 participants in the 5 studies. The mean age of the participants was about 68 years. All studies reported gender, and the mean percentage of females was about 46 percent. The percent predicted FEV_1 in the study populations ranged from 35 to 59. None of the studies characterised the study sample in terms of the GOLD COPD stage criteria. Using these criteria, 60% of studies included patients with severe COPD while the remaining studies included patients with moderate COPD.

Study Characteristics

Studies were conducted between 2000 and 2010. A detailed description of the studies can be found in Appendix 2. Two studies were conducted in the United Kingdom and the remainder in Germany, Ireland, and New Zealand. Sample sizes ranged from 31 to 97 participants. The individual quality of the studies varied, with differences in quality mainly due to methodological issues such as inadequate description of randomization, sample size calculation, allocation concealment, blinding, and uncertainty around the use of ITT analysis (Appendix 3). Pulmonary rehabilitation programs were delivered through a variety of settings. Two studies had outpatient pulmonary rehabilitation programs (35;36), 2 studies began with an inpatient program followed by an outpatient program (home-based in 1 case) (9;32), and the remaining study had a home-based program for patients discharged from hospital (34). All studies reported a UC control group.

Intervention Characteristics

All the interventions examined in the studies included a minimum of aerobic exercise training, with a strength-training component also included in many cases. Some interventions also featured disease education, dietary education/advice, self-care, smoking cessation advice, endurance training, self-management skills, breathing and relaxation exercises, referrals to social services, and psychological support. All the studies examined the outcomes of hospital readmissions, HRQOL, and exercise capacity. Despite homogeneity in outcome assessment, there was some clinical heterogeneity in intervention characteristics such as duration, intensity, setting, and individuals delivering the intervention.

Duration and Intensity

Intervention durations ranged from 6 weeks to 6 months. Eighty percent of studies had interventions lasting from 6 to 8 weeks. The intensities of the interventions were comparable in the studies, typically involving 2 to 3 two-hour sessions per week for the duration of the rehabilitation program.

Interventions and Setting

Two interventions were carried out by a multidisciplinary team that included 2 or more of the following health care professionals: COPD nurse, physiotherapist, occupational therapist, and dietician. The remaining studies either used a single physiotherapist to carry out the intervention or did not clearly describe who carried out the intervention.

Outcomes

Duration of follow-up ranged from 1 month to 6 months from baseline. Two of the 5 studies followed patients at a minimum of 2 time points. (9;34)

All studies reported hospital readmissions (9;32-35) and 3 reported COPD-specific readmissions. (9;32;35) All 5 trials measured quality of life using the CRQ or the SGRQ. Exercise capacity, (9;32) mortality, (9;33) and emergency department visits, (33;35) were each reported in 2 of the 5 studies. Other outcomes reported in some of the trials included dyspnea, lung function, body mass index (BMI), and

fatigue. The results of the meta-analyses identified in the literature search are summarized below in Tables 5 and 6. Forest plots are found in Appendix 4.

Table 5: Summary of Findings of a Meta-Analysis of Studies Investigating the Effectiveness of Pulmonary Rehabilitation on Hospital Readmission in Patients with COPD Following an Acute Exacerbation*

Outcome	Number of Studies	Number of Participants	Pooled Rate Ratio (95% CI)	GRADE
All hospital readmissions	5	251	0.50 (0.33–0.77)	
COPD-related readmission	3	183	0.41 (0.18–0.93)	Moderate
General readmission	2	68	0.54 (0.29–1.03)	

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Table 6: Summary of Findings of Meta-Analyses of Studies Investigating the Effectiveness of Pulmonary Rehabilitation on HRQOL in Patients with COPD Following an Acute Exacerbation*

Outcome	Number of Studies	Number of Participants	Effect Size Mean Difference (95% CI)	GRADE
Quality of Life – Change in SGRQ				
Total Score	3	109	−11.44 (−16.71 to −6.17)	
Symptoms	3	109	−1.59 (−5.16 to 8.35)	Moderate
Impact	3	109	−14.51 (−21.52 to −7.51)	
Activity	3	109	−11.44 (−18..3 to −4.52)	
Quality of Life – Change in CRQ				
Fatigue	4	196	2.54 (2.11, 2.97)	
Emotional Function	4	196	2.11 (1.63, 2.60)	Moderate
Mastery	4	196	3.17 (2.70, 3.64)	
Dyspnea	4	196	3.42 (2.99, 3.85)	

*Abbreviations: CI, confidence interval; CRQ, Chronic Respiratory Questionnaire; HRQOL, health-related quality of life; SGRQ, St. George's Respiratory Questionnaire.

Hospital Readmissions

All studies reported hospital readmissions as an outcome. (9;32-35) Three of the studies reported COPD-related readmissions (9;32;35), while 2 of the studies reported general admissions. (33;34) There was a decrease in all hospital readmissions as seen by the pooled relative risk of 0.50 (95% CI, 0.33–0.77; P = 0.001) favouring pulmonary rehabilitation versus UC. When admissions were subgrouped by type, the effect observed was greater for COPD-related readmissions than for general readmissions.

Health-Related Quality of Life

Three studies reported results of HRQOL assessments based on the SGRQ. (33-35) All studies compared the difference in the mean change scores from baseline to follow-up between the pulmonary rehabilitation and UC groups. (9;32-35) Based on the MCID, there was a statistically and clinically significant improvement in quality of life for the pulmonary rehabilitation group as compared to the UC group reflected in the total ($P < 0.001$), impact ($P < 0.001$), and activity scores ($P = 0.001$) of the SGRQ (Table 6).

The GRADE quality of evidence was assessed as moderate for this outcome. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Four studies reported results of the quality-of-life assessment based on the CRQ. (9;32;33;35) Based on the MCID, there was a statistically and clinically significant improvement in quality of life for the pulmonary rehabilitation group compared with the UC group reflected in all domains of the CRQ ($P < 0.001$) (Table 6).

The GRADE quality of evidence was assessed as moderate for this outcome. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Additional Outcomes

Additional relevant outcomes were reported in several of the studies. Functional exercise capacity as measured by the 6MWT was reported in 2 studies. (9;32) There was a statistically and clinically significant improvement in exercise capacity as measured by the 6MWT favouring the pulmonary rehabilitation group as compared to the UC group (weighted mean difference, 203.14 m; 95% CI, 185.17–221.11; $P < 0.001$). Two studies reported emergency department visits (33;35) and 2 studies reported mortality, (9;33) but no statistically significant differences were found for any of these outcomes between the pulmonary rehabilitation and UC groups.

Conclusion

Based on moderate-quality evidence, pulmonary rehabilitation (within 1 month of hospital discharge) after an AECOPD significantly reduces hospital readmissions (relative risk, 0.34; 95% CI, 0.25– 0.46; $P < 0.001$) and leads to a statistically and clinically significant improvement in HRQOL.[3]

Research Question 3: Effect of Maintenance Programs on COPD Outcomes

The database search yielded 1,000 citations published between January 2000 and February 2011. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 3 shows the breakdown of when citations were excluded in the analysis.

Three studies met the inclusion criteria for this research question. All studies included were RCTs (Table 7).

[3] As measured by all domains of the CRQ and total, impact, and activity scores of the SGRQ

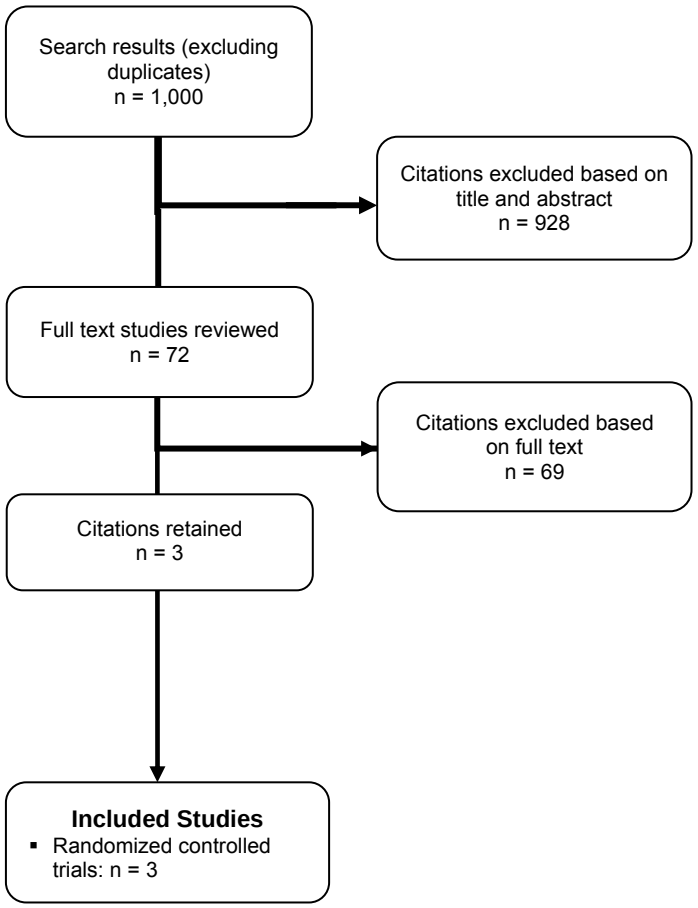


Figure 3: Citation Flow Chart

For each included study, the study design was identified and is summarized below in Table 7, which is a modified version of a hierarchy of study design by Goodman. (5)

Table 7: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	
Large RCT†	1
Small RCT	2
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	
Total	3

*Abbreviation: RCT, randomized controlled trial
†Large RCT is defined as a sample size of at least 100.

The search did not identify any systematic reviews or meta-analyses focused on maintenance programs following pulmonary rehabilitation for COPD patients.

Randomized Controlled Trials

The database search identified 1,000 citations published between January 2000 and February 2011. Of the 72 full-text articles reviewed, only 3 studies met the inclusion criteria described earlier, of which one was a large RTC and 2 were small RTCs (Table 7). (37-39) Sample sizes in the studies ranged from 48 to 140, with a total of 284 participants in the 3 studies. The mean reported age of the participants was 67 years. All studies reported gender, and the mean percentage of females ranged from 44 to 64 percent. The percent predicted FEV_1 in the study populations ranged from 35 to 59. None of the studies characterised the study sample in terms of the GOLD COPD stage criteria. Using these criteria, 2 studies included patients with moderate COPD (37;39) and 1 included patients with severe COPD. (38)

The majority of studies mentioned exclusion criteria. Criteria included subjects who had experienced an AECOPD in the previous month, required supplemental oxygen, or had comorbidities precluding participation in exercise training, and subjects who had a medical condition limiting their ability to participate in exercise training.

Study Characteristics

Studies were conducted between 2000 and 2010. A detailed description of the studies can be found in Appendix 2. One study was carried out in Australia and the other 2 in Denmark and the United States. Sample sizes ranged from 48 to 140 participants. The individual quality of the studies was generally poor due to methodological issues such as inadequate description of randomization, sample size calculation,

allocation concealment, blinding, and uncertainty around the use of ITT analysis (Appendix 3). All the maintenance programs were delivered in an outpatient setting. All studies reported a UC control group.

Intervention Characteristics

All the interventions examined in the studies included a minimum of aerobic exercise training, while some also included a strength-training component. Two studies included unsupervised home exercise as part of the interventions (38;39), and one of them also supplemented the exercise training with weekly educational sessions. (38) Some clinical heterogeneity was evident in the intervention characteristics, such as duration of the initial program, duration of the maintenance program, and intensity of the maintenance program.

Duration of Initial Pulmonary Rehabilitation Program

The duration of the initial pulmonary rehabilitation programs ranged from 7 to 12 weeks.

Duration and Intensity of Maintenance Programs

The duration of the maintenance programs ranged from 12 to18 months. In 2 of the studies these maintenance programs had comparable intensities, typically involving one 1-to-2-hour session per week plus unsupervised home exercise training. (38;39) The remaining study was more intense, with maintenance sessions carried out 3 times per week. (37)

Outcomes

Outcomes were measured at various time points. One study assessed outcomes at 3, 6, and 12 months post-randomization, (38) another followed patients 3, 6, and 12 months following the intervention, (39) and the remaining study evaluated outcomes 3 months after the intervention as well as at 9, 15, and 18 months from baseline. (37)

Two of the 3 studies reported on exercise capacity as measured by the 6MWT (37;39) and 2 studies also reported on HRQOL. (38;39) The latter 2 studies also included hospitalizations and length of stay as outcomes.

The results of the findings for the maintenance programs identified in the literature search are summarized below in Tables 8 through 10. For studies in which results were meta-analyzed, forest plots can be found in Appendix 4.

Table 8: Summary of Findings of Meta-Analyses of Studies Investigating the Effectiveness of Maintenance Programs on Functional Exercise Capacity*

Outcome	Number of Studies	Number of Participants	Mean Difference (95% CI)	*P* Value	GRADE
Functional Exercise Capacity (6MWT)	2	166	22.93 (5.16–40.71)†	0.01	LOW

*Abbreviations: 6MWT, Six Minute Walking Test; CI, confidence interval.
†Minimally clinically important difference ~25-35 m.

Table 9: Summary of Findings of Studies Investigating the Effectiveness of Maintenance Programs on Health-Related Quality of Life*

Outcome	N	Effect Size Mean Difference (95% CI)	*P* Value	GRADE
HRQOL - Change in SGRQ				
Spencer et al, 2010 (39)	48	5 (−2, 11)	NR	LOW
Ringbaek et al, 2010 (38)	96	NR†	NR	

*Abbreviations; CI, confidence interval; HRQOL, health-related quality of life; N, sample size; NR, not reported; SGRQ, St. George's Respiratory Questionnaire.
†Data not reported; authors concluded there was no significant difference between groups.

Table 10: Summary of Findings of Studies Investigating the Effectiveness of Maintenance Programs on Hospitalizations and Length of Stay*

Outcome	N	Maintenance	Usual Care	*P* Value
Mean Number of Hospital Admissions per Patient Over 12 Months (Mean)				
Ringbaek et al, 2010 (38)	96	0.8	0.8	0.83
Spencer et al, 2010 (39)	48	0.3	0.5	NR†
Mean Number of Days Spent in Hospital per Patient Over 12 Months (Mean)				
Ringbaek et al, 2010 (38)	96	2.8	3.0	0.78
Spencer et al, 2010 (39)	48	Reported no difference in the length of hospital stay between the 2 groups over the 12 months (*P* value not reported)		

*Abbreviations: N, sample size; NR, not reported.
†Data not reported.

Exercise Capacity

Two studies reported results of a functional exercise capacity assessment based on the 6MWT.(37;39) Both studies compared the difference in the mean change in scores from baseline to follow-up between the maintenance and UC groups. Based on the MCID, there was a statistically but not clinically significant improvement in functional exercise capacity for the maintenance group compared with the UC group, with an estimated pooled difference of 22.93 m (95% CI, 5.16–40.71; $P = 0.01$) (Table 8). When higher-intensity maintenance programs were considered individually, the pooled difference reached marginal clinical significance at 25.88 m (95% CI, 25.27–26.49). The GRADE quality of evidence was assessed as low for this outcome. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Health-Related Quality of Life

Two studies reported results of HRQOL assessments based on the SGRQ. (38;39) Both studies compared the difference in the mean change scores from baseline to follow-up between the maintenance program and UC groups. Based on the MCID, one study failed to show a statistically or clinically significant improvement in quality of life for patients receiving the maintenance program compared with those receiving UC. (39) The other study failed to report data for this outcome, although the authors noted that there was no significant difference between the groups. (38) The GRADE quality of evidence was assessed as low for this outcome.

Hospitalizations and Length of Stay

Two studies reported hospitalizations and length of stay as an outcome. (38;39) There was no difference in the mean number of hospital admissions per patient over a 12-month period between patients receiving a maintenance program and those receiving UC (Table 10). There was also no difference in the mean number of days spent in hospital per patient over the 12 months between these 2 groups (Table 10). The GRADE quality of evidence was assessed as low for this outcome.

Conclusion

Based on low-quality evidence, pulmonary rehabilitation maintenance programs have a nonsignificant effect on HRQOL and hospitalizations.

Based on low-quality evidence, pulmonary rehabilitation maintenance programs for COPD patients have a statistically but not clinically significant effect on exercise capacity ($P = 0.01$). When studies are subgrouped by intensity and quality, the difference becomes marginally clinically significant.

Economic Analysis

The results of the economic analysis are summarized in issue 12 of the COPD series entitled *Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model*. This report can be accessed at: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Economic_March.pdf.

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity (FVC)	The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.
Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.

Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[4]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.
Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.
Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.

[4] The mild-to-moderate classification was created for the purposes of the report.

Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Medical Information Officer

Kellee Kaulback

Editorial Staff

Gabrielle Bauer
Irina Alecu

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

Appendices

Appendix 1: Literature Search Strategies

Initial Literature Search on Pulmonary Rehabilitation for COPD

Search date: August 10, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to July Week 4 2010>
Search Strategy:
---
1 exp Pulmonary Disease, Chronic Obstructive/ (14057)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (20996)
3 (copd or coad).ti,ab. (15985)
4 chronic airflow obstruction.ti,ab. (486)
5 exp Emphysema/ (6925)
6 ((chronic adj2 bronchitis) or emphysema).ti,ab. (22569)
7 or/1-6 (53015)
8 exp Rehabilitation/ (120272)
9 exp Physical Therapy Modalities/ (98967)
10 ((pulmonary or lung* or respirat*) adj2 (physiotherap* or therap* or rehabilitat*)).ti,ab. (8251)
11 rh.fs. (135769)
12 or/8-11 (297725)
13 7 and 12 (3342)
14 limit 13 to (english language and humans and yr="2004 - 2010") (1206)
15 limit 14 to (case reports or comment or editorial or letter) (124)
16 14 not 15 (1082)

Database: EMBASE <1980 to 2010 Week 31>
Search Strategy:
---
1 exp chronic obstructive lung disease/ (47119)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (25414)
3 (copd or coad).ti,ab. (20656)
4 chronic airflow obstruction.ti,ab. (548)
5 exp emphysema/ (25316)
6 exp chronic bronchitis/ (6517)
7 ((chronic adj2 bronchitis) or emphysema).ti,ab. (25290)
8 or/1-7 (86799)
9 exp pulmonary rehabilitation/ (993)
10 exp physical medicine/ (288069)
11 ((pulmonary or lung* or respirat*) adj2 (physiotherap* or therap* or rehabilitat*)).ti,ab. (9992)
12 rh.fs. (108684)
13 or/9-12 (387063)

14 8 and 13 (5140)
15 limit 14 to (human and english language and yr="2004 -Current") (1758)
16 limit 15 to (editorial or letter or note) (195)
17 15 not 16 (1563)
18 case report/ (1665922)
19 17 not 18 (1459)

#	Query	Results
S13	S12 Limiters - Published Date from: 20040101-20101231	546
S12	S6 and S11	942
S11	(S7 or S8 or S9 or S10)	54560
S10	pulmonary rehabilitat* or pulmonary therap* or lung rehabilitat* or respiratory therap*	2776
S9	(MH "Home Rehabilitation+")	945
S8	(MH "Physical Therapy+")	50558
S7	(MH "Rehabilitation, Pulmonary+")	1644
S6	S1 or S2 or S3 or S4 or S5	7306
S5	chronic bronchitis or emphysema	1562
S4	(MH "Emphysema+")	954
S3	copd or coad	4032
S2	(chronic obstructive and (lung* or pulmonary or airway* or airflow or respiratory) and (disease* or disorder*))	5524
S1	(MH "Pulmonary Disease, Chronic Obstructive+")	4266

Final Revised Search for COPD-Rehabilitation Revised to Include 2000-2011

Search date: February 3, 2011
Databases Searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1948 to January Week 3 2011>
Search Strategy:
---
1 exp Pulmonary Disease, Chronic Obstructive/ (14676)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (21256)
3 (copd or coad).ti,ab. (16373)
4 chronic airflow obstruction.ti,ab. (478)
5 exp Emphysema/ (9400)
6 ((chronic adj2 bronchitis) or emphysema).ti,ab. (22372)
7 or/1-6 (54975)
8 exp Rehabilitation/ (120569)
9 exp Physical Therapy Modalities/ (99270)

10 ((pulmonary or lung* or respirat*) adj2 (physiotherap* or therap* or rehabilitat*)).ti,ab. (8341)
11 rh.fs. (135921)
12 or/8-11 (298194)
13 7 and 12 (3404)
14 limit 13 to (english language and humans and yr="2000 -Current") (1730)
15 limit 14 to (case reports or comment or editorial or letter) (164)
16 14 not 15 (1566)

Database: EMBASE <1980 to 2011 Week 04>
Search Strategy:
---
1 exp chronic obstructive lung disease/ (49584)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (26878)
3 (copd or coad).ti,ab. (22292)
4 chronic airflow obstruction.ti,ab. (553)
5 exp emphysema/ (25972)
6 exp chronic bronchitis/ (6645)
7 ((chronic adj2 bronchitis) or emphysema).ti,ab. (25749)
8 or/1-7 (90366)
9 exp pulmonary rehabilitation/ (1194)
10 exp physical medicine/ (300551)
11 ((pulmonary or lung* or respirat*) adj2 (physiotherap* or therap* or rehabilitat*)).ti,ab. (10482)
12 rh.fs. (110909)
13 or/9-12 (401639)
14 8 and 13 (5385)
15 limit 14 to (human and english language and yr="2000 -Current") (2478)

CINAHL

#	**Query**	**Results**
S12	S6 AND S11 Limiters - Published Date from: 20000101-20111231 English Language	787
S11	S7 or S8 or S9 or S10	60613
S10	pulmonary rehabilitat* or pulmonary therap* or lung rehabilitat* or respiratory therap*	7241
S9	(MH "Home Rehabilitation+")	976
S8	(MH "Physical Therapy+")	52603
S7	(MH "Rehabilitation, Pulmonary+")	1682
S6	S1 or S2 or S3 or S4 or S5	7702
S5	chronic bronchitis or emphysema	1623
S4	(MH "Emphysema+")	994
S3	copd or coad	4205
S2	(chronic obstructive and (lung* or pulmonary or airway* or airflow or respiratory) and (disease* or disorder*))	5860
S1	(MH "Pulmonary Disease, Chronic Obstructive+")	4568

Appendix 2: Study Characteristics of Included Studies

Table A1: Description of Studies Examining Pulmonary Rehabilitation in the Stable COPD Population* (n = 18)

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
Theander et al (23) 2009 Sweden	N = 30 Rehab: 15 Control: 15 Subject characteristics: ~65 years FEV_1 % predicted ~33 BMI ~25 Optimized on pharmacological treatment prior to study initiation	Pulmonary outpatient department Optimized on pharmacological treatment prior to study initiation	Control group Rehab group Control group did not receive any of the rehab program or care from professionals who performed the program	Physiotherapist, dietician, occupational therapist, nurse	12 weeks physiotherapy 1 hr, 2–5 days/week dietician/ occupational therapist 1 hr, 3x during program	Multi-disciplinary Aerobic training, strength training; after 1 month, pts received an individualized home training program Dietary education/ advice, self-care, smoking cessation advice	12 weeks from baseline	QOL (SGRQ) Functional exercise capacity (6MWT)	Fatigue; fatigue- related functional limitations; functional performance and satisfaction; lung function; grip strength	Not adequately powered; significant difference in gender distribution between groups; no blinding in outcome assessment; calculated sample size based on CRQ but used SGRQ; Dropout: 3/15 in rehab group, 1/15 in control group
Elci et al (13) 2008 Turkey	N = 78 Rehab: 39 Control: 39 Subject characteristics: ~59 years ~85% male FEV_1 % predicted ~47 ~51% GOLD stage III	Outpatient department of community hospital Lacked specialist pulmonary rehab services	Control group Rehab group Control group received standard medical care including instructions on the use of respiratory medicines	Nurses Received training in the pulmonary rehab program 2 weeks prior 1 session supervised by nurse (the remaining sessions supervised by a family member) Standard telephone questionnaire once weekly	12 weeks	Educational activities aimed at improving self-management skills Individualized rehab plan Exercises at home: 24 sessions of up to 90 min 2x/week Endurance training: abdominal, upper and lower limb muscle strengthening	4, 8, 12 weeks from baseline	QOL (SGRQ) Functional exercise capacity (6MWT)	Lung function; anxiety and depression; functional dyspnea No difference in lung function between control and rehab groups	Outcome assessors not blinded; unclear allocation concealment; no sample size calculation; no mention of droupouts Emailed author for individual data from SGRQ, 4-week data assumed to be baseline (according to author); potential underestimation of effect

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
Karapolat et al (20) 2007 Turkey	N = 49 Rehab: 27 Control: 22 Subject characteristics: ~65 years ~87% male FEV_1 % predicted ~72, ~57% GOLD stage II	Outpatient program	Control group Rehab group	Physiotherapist	8 weeks	Educational component (1-hour session weekly for 16 weeks): respiratory physiology, disease education, dietary advice, relaxation, etc. Exercise training component (3x/week): aerobic, strength training, breathing and relaxation, etc.	8 and 12 weeks from baseline	QOL (SGRQ) Functional exercise capacity (6MWT)	Lung function; arterial blood gas analysis; dyspnea	Outcome assessors not blinded; unclear allocation concealment; no sample size calculation; no mention of dropouts Emailed author for individual data from SGRQ, 4-week data assumed to be baseline (according to author); potential underestimation of effect
Guell et al (18) 2000 Spain	N = 60 Rehab: 30 Control: 30 Subject characteristics: ~65 years ~100% male FEV_1 % predicted ~35	Outpatient clinic of hospital	Control group Rehab group	Unclear	6 months	Breathing retraining: chest wall exercises, abdominal exercises, etc. Exercise training: aerobic, home exercise Maintenance group sessions: breathing exercises, no formal exercise program	3, 6, 9, 12, 18, and 24 months from baseline	QOL (CRQ) Functional exercise capacity (6MWT) Maximal exercise capacity	Lung function; dyspnea; breathlessness; exacerbations; hospitalizations	Generalizable to men only; no allocation concealment; formal exercise component began after 3 months

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
Engstrom et al (14) 1999 Sweden	N = 55 Rehab: 28 Control: 27 Subject characteristics: ~ 66 years ~52% male FEV_1 % predicted: Rehab, 35.8 (11.9) Control, 34.1 (10.2)	Outpatient	Usual outpatient care Rehabilitation program	Physiotherapist, occupational therapist, dietician Information program (self-care, smoking cessation): COPD outpatient team (respiratory nurse, physician)	12 months 45-min sessions 2x/week for 6 weeks; 1x every 2nd week for 6 weeks; 1x/month thereafter	Physiotherapy program: breathing techniques, aerobic exercise, arm training, muscle strength training, instruction to walk daily, individual 30-min home training program, education	12 months from baseline	QOL (SGRQ) Functional exercise capacity (6MWT) Days in hospital	Sickness impact profile; Mood Adjective Check List; maximum symptoms; limited incremental exercise test	Unclear randomization and allocation concealment; blinded outcome assessors with the exception of the 6MWT; no sample size calculation
Ringbaek et al (22) 2000 Denmark	N = 45 Rehab: 24 Control: 21 Subject characteristics: ~ 63 years ~15% male FEV_1 % predicted: Rehab: 49.5 (17.4) Control: 44.3 (13.7)	Outpatient	Control group Rehabilitation program	Physiotherapist, nutritional therapist, occupational therapist Patient education: physician and nurse	8 weeks 2-hour sessions 2x/week	Aerobic and strength training; dietary counselling; relaxation; breathing techniques; patient education; nutritional counselling	8 weeks from baseline	QOL (SGRQ) Functional exercise capacity (6MWT)	Psychological general well-being index; Borg Dyspnea Score	Unclear randomization and allocation concealment; no sample size calculation; high dropout rate
Borghi-Silva et al (11) 2009	N = 40 Rehab: 20 Control: 20 Subject characteristics: ~ 67 years ~74% male FEV_1 % predicted: Treatment: 64 (16.0) Control: 64 (18) Moderate to severe COPD	Outpatient	Usual care Supervised aerobic training program *All pts received regular treatment consisting of inhaled bronchodilators and steroids. Patients in UC received no physical training	Physiotherapist, physical therapist	6 weeks 3x/week for 6 weeks	Supervised program with: stretching of lower and upper limbs and treadmill ambulation (30 min); stretching exercises (back, hamstrings, shoulders, neck, etc.); breathing exercises	6 weeks from baseline	Functional exercise capacity (6MWT)	Borg Dyspnea Score; lung function; cardio-pulmonary exercise testing	Unclear randomization and allocation concealment; no sample size calculation; high dropout in control group

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
Singh (26) 2002 India	N = 40 Rehab: 20 Control: 20 Subject Characteristics: ~ 59 years ~80% male FEV_1 % predicted: Treatment: 28 (7.5) Control: 26 (7.1) Severe airway obstruction	Outpatient	Pulmonary rehab Usual care Usual care patients were asked to continue their activities as usual	Not reported Supervised weekly	4 weeks 30 min 2x /day	Removal of secretions; lower extremity exercises (walking 2x/day); breathing strategies; energy conservation and work simplification	4 weeks from baseline	Functional exercise capacity (6MWT) QOL (CRQ)	FEV_1	Unclear randomization and allocation concealment; no sample size calculation; no mention of blinding
Lake et al (21) 1990 Australia	N = 28 Treatment: 20 Control: 8 Subject characteristics: ~ 66 years ~85% male FEV_1: Treatment 1: 0.97 (±0.29) Treatment 2: 0.73 (±0.24) Treatment 3: 0.83 (±0.25) Control: 0.97 (±0.29) FEV1 % predicted < 55	Outpatient	Training group 1 (upper limb) Training group 2 (lower limb) Training group 3 (combined) Control group Control group offered active program at end of study	Supervised by physiotherapist	8 weeks 1 hour 3x/week	Upper limb group: 10-min warm-up, 20-min circuit training, 10-min cool-off Lower-limb group: 10-min warm-up, 20-min walking, and 10-min cool-off Combined group: 10-min warm-up, 15-min circuit training, 12-min walking, and 10-min cool-off	8 weeks from baseline	Functional exercise capacity (6MWT) QOL (Self-Efficacy Scale)	FEV_1; FVC; maximal exercise tolerance	Unclear randomization and allocation concealment; no sample size calculation; no mention of blinding; population may not be representative of COPD
Goldstein et al (16) 1994 Canada	N = 89 Rehab: 45 Control: 44 Subject characteristics: ~ 66 years ~49 % male FEV_1 % predicted:	Inpatient rehab followed by outpatient care	Conventional community care Rehabilitation Conventional care group received care from their family doctors and respiratory specialists	Multidisciplinary, medically supervised team	24 weeks Inpatient: 8 weeks, ~3x/week Outpatient care: 16 weeks; home training routine; graduated discharge	Stretching; breathing techniques; interval training (40 min 3x/week); treadmill (2–3 x/week); upper-extremity training; leisure walking (30 min 1x/week)	12, 18, and 24 weeks from baseline	Functional exercise capacity (6MWT) QOL (CRQ) Incremental exercise capacity	Pulmonary function	Unclear randomization and allocation concealment; no sample size calculation; no mention of blinding; high dropout rate

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
	Treatment: 34.8 (14.5); Control: 34.6 (11.8) Severe stable COPD FEV_1 < 40%				program supervised by a member of rehab staff; periodic visits by a home care physiotherapist)					
Simpson and Rocker (25) 1992 Canada	N = 34 Rehab: 17 Control: 17 Subject characteristics: ~ 72 years ~54% male FEV_1 % predicted: Treatment: 39.5 (18.96); Control: 39.2 (21.39)	Community-based, local physiotherapy practices	Control Rehabilitation	Physiotherapist	8 weeks 3x/week	Weightlifting program: arm curls, leg extensions, leg press exercises, resistance training	8 weeks from baseline	QOL (CRQ) Functional exercise capacity (6MWT)	Borg Dyspnea Scale	Unclear allocation concealment; no sample size calculation; no ITT
Wijkstra et al (27) 1994 Netherlands	N = 45 Rehab: 30 Control: 15 Subject characteristics: FEV_1 % pred: Treatment: 34.8 (14.5) Control: 34.6 (11.8) Severe airflow limitation: FEV_1 % pred < 60%	Community-based (home-based program)	Control Rehabilitation	Supervised by multidisciplinary team: physiotherapist, nurse, pulmonologist, family doctor	12 weeks 2x/week visit to physiotherapist	Conventional physiotherapy: relaxation exercises, breathing retraining, upper limb training, exercise training (1 hr/day) Exercise training: 30 min 2x/day according to an individual protocol Patient education: supervised monthly by nurse Supervised clinical status: monthly GP visits	12 weeks after rehab	QOL (CRQ) Cycle ergometer test	FEV_1, IVC	Unclear randomization and allocation concealment; no sample size calculation; no mention of blinding

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
Boxall et al (12) 2005 Australia	N = 60 Rehab: 30 Control: 30 Subject Characteristics ~ 76 years ~56% male FEV_1 % predicted: Treatment: 40.5 (15.9) Control: 37.7 (15.0) House-bound elderly COPD patients > 60 years	Community-based (home-based program)	Control Rehabilitation Control group offered program after initial 12 weeks	Nurse, occupational therapist, physiotherapist	12 weeks 11 total home visits	Graduated walking and arm exercises (1x daily): resistance; strengthening upper limb muscles used for respiration; exercise diaries; weekly physiotherapy visits for the first 6 weeks, then every 2 weeks until end of program; education sessions (~6 total)	12 weeks from baseline	QOL (SGRQ) Exercise tolerance (6MWT)	Dyspnea; hospital admission rates with exacerbation of COPD; average length of stay at readmission	No blinding of outcome assessors; sample size was calculated but study was underpowered due to dropouts
Hernandez et al (19) 2000 Spain	N = 60 Rehab: 30 Control: 30 Subject Characteristics: ~ 64.3 years FEV_1 % predicted: Treatment: 41.7 (15.6) Control: 40 (16.4) All patients were medically optimized	Community-based (home-based program)	Control Rehabilitation Control : standard medical treatment alone, but visited hospital every 2 weeks for a clinical check-up and supervision of treatment	Unclear	12 weeks 1 hour sessions, 6 days/week	Lower extremity training, walking Patients also went to hospital every 2 weeks for supervision of clinical status, treatment, and exercise-training compliance	12 weeks from baseline	QOL (CRQ) Exercise capacity (SWT)	Pulmonary function Resistance Test Dyspnea	Unclear randomization and allocation concealment; no sample size calculation; no/unclear ITT; high dropout rate; unclear description of who delivered rehabilitation
Griffiths et al (17) 2000 United Kingdom	N = 200 Rehab: 99 Control: 101 Subject characteristics: ~ 68 years 60 % male FEV1 % predicted: Treatment: 39.7 (16.2) Control: 39.4 (16.4)	Outpatient	Control Rehabilitation Control: outpatients or primary care patients followed for 1 year and then offered pulmonary rehab	Multidisciplinary: occupational therapists, physiotherapists, dieticians, respiratory nurse, smoking cessation counsellor	6 weeks 3 half-days/week, 2-hour sessions	1/3 time: educational activities: understanding of disease, nutrition, medicines, exercise Individualized sessions; aerobic training, circuit	6 weeks and 1 year from baseline	QOL (SGRQ and CRQ) Exercise capacity (SWT)	Health status (SF-36); hospital anxiety and depression score; number of admissions and days spent in hospital	Well-described randomization and allocation concealment; ITT analysis completed; sample size calculated

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
						training Patients encouraged to follow a home exercise routine Psychological support and education At end of rehab program, patients were invited to join a patient-run group that met weekly at a local recreation centre for social activities and exercise				
Troosters et al (24) 2000 Belgium	N = 100 Rehab: 50 Control: 50 Subject characteristics: ~ 62 years ~85 % male FEV1 % predicted: Treatment: 41 (16) Control: 43 (12) Severe COPD	Outpatient	Control Rehabilitation	Supervised by physiotherapists	6 weeks Outpatient sessions: 1.5 hours 3x/week in first 3 months, 2x/week in subsequent 3 months	Training: aerobic (cycling, treadmill, etc.) and muscle strength training	6 and 18 months from baseline	QOL (CRQ) Functional exercise capacity (6MWT)	Maximal exercise capacity	Unclear randomization and allocation concealment; no sample size calculation; no/unclear ITT
Finnerty et al (15) 2001	N = 100 Rehab: 50 Control: 50 Subject characteristics: ~ 69 years ~68% male FEV_1 % predicted: Rehab: 41.2 (19.2) Control: 41.2 (16.2)	Outpatient	Routine outpatient attendance Rehabilitation program	Physiotherapist, occupational therapist, respiratory specialist nurse, dietician	6 weeks	2 visits/week: 2-hour education visit and 1-hour exercise (aerobic) visit Patients asked to exercise 1 to 2x daily 5x/week	12 and 24 weeks from baseline	QOL (SGRQ) Functional exercise capacity (6MWT)	None	Blinded outcome assessors; no sample size calculation; outcome assessed 6 weeks after program completed

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
						Dietary advice, referrals to social services, coping strategies, psychological input				
Behnke et al, 2000 (9) Behnke et al, 2003 (10)	N = 46 Rehab: 15 Control: 15 Baseline characteristics given for 30 patients who completed the study Subject characteristics: ~66 years 77% male FEV_1 % predicted: Treatment: 34.1 ±7.4 Control: 37.5 ±6.6 N = 30 26 analyzed	Inpatient pulmonary rehab and home-based program	Control group Training group Control group: standard in-patient care with no exercise and standard community care with respirologist	Unclear Investigators visited pts every 2 weeks for the first 3 months, then monthly telephone contact	10 day hospital-based program and 6-month home-based program after discharge Started 4–7 days after admission	10-day hospital-based walking program (5 walking sessions/day for 10 days) + supervised home-based training program (3 walking sessions/day for 6 months) Monthly patient diaries	1, 2, 3, and 6 months after discharge 12 month follow-up	Lung function QOL (CRQ) Functional Exercise capacity (6MWT) Dyspnea scores Hospital readmission		Unclear randomization; allocation concealment; no ITT; high dropout rate; primary outcome not identified; no sample size calculation Follow-up at 12 months on only 26/46 original patients

*Abbreviations: 6MWT, Six Minute Walking Test; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Questionnaire; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GP, general practitioner; hr, hour; min, minutes; ITT, intention-to-treat analysis; IVC, inspiratory vital capacity; N, sample size; QOL, quality of life; pts, patients; rehab, rehabilitation; SGRQ, St. George's Respiratory Questionnaire; SF-36, Short form 36; SWT, Shuttle Walking Test; UC, usual care.

Table A2: Description of Studies Examining Pulmonary Rehabilitation Within One Month of an Acute Exacerbation of COPD (n = 4 Plus Behnke et al, 2000)

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes
Man et al (36) 2004 United Kingdom	N = 42 Rehab: 21 Control: 21 Subject characteristics: ~70 years ~41% male FEV_1 % predicted ~39% after inpatient treatment for acute exacerbation	Outpatient	Control group Rehab group Control: standard community care with respirologist	Multidisciplinary team: physiotherapists, respiratory nurses, occupational therapist, dietician, respiratory doctor, smoking cessation adviser, social worker, pharmacist, lay member of a patients' group	8 weeks	Outpatient PR (within 10 days of discharge) Aerobic and strength exercise and patient education for 12 weeks (two 2-hour sessions/week)	12 weeks	Incremental shuttle walk distance (SGRQ, CRQ, and SF-36)	Hospital readmission; hospital days; emergency admissions; mortality
Murphy et al (34) 2005 Ireland	N = 31 Rehab: 16 Control: 15 Subject characteristics: ~66 years ~65% male Moderate COPD FEV_1 % predicted < 60% Long history of smoking	Supervised home exercise program Admitted to a COPD home-from-hospital treatment program	Control group Rehab group Control group: Standard medical treatment without any form of rehabilitation exercises or lifestyle change advice	Physiotherapist	6 weeks	2x/week for 6 weeks 12 supervised exercise sessions (30–40 min each) Patients were instructed to exercise for at least 15 min on other days Use of diaries Aerobic exercise, upper limb exercises	6 weeks from baseline 3-month follow-up for exacerbations	Functional exercise capacity (shuttle walk test, 3-min step test)	Dyspnea QOL: SGRQ admissions exacerbations
Eaton et al (32) 2009	N = 97 Rehab: 47 Control: 50 Subject characteristics: ~70 years ~44% male FEV_1 % predicted ~35 Elderly	Inpatient followed by outpatient Mean of 2.6 days after admission	Usual Care Rehabilitation program Usual care: received standardized advice on benefits of exercise; COPD nurse administered standardized care	Inpatient program: COPD nurse Outpatient education: multidisciplinary	~8 weeks + inpatient program	Inpatient program: structured, supervised exercise regimen (at least 30 min/day) with aerobic and upper/lower limb strengthening Outpatient program: 1-hour sessions of supervised	3 months from baseline	No. COPD-related readmissions; time to first COPD-related readmission; no. inpatient days; unscheduled ED visits	BMI, airflow obstruction, dyspnea, exercise capacity, functional capacity (6MWT), and HRQOL (CRQ)

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes
	Severe impairment of pulmonary function, poor HRQOL, and high COPD-related morbidity					exercise training 2x/week for 8 weeks Educational sessions At end of program, prescribed 30 min daily activity with government-funded opportunity to attend local gym			
Seymour et al (35) 2010	N = 60 Rehab: 30 Control: 30 Subject characteristics: ~ 66 years ~45% male FEV_1 % predicted ~52	Outpatient Initiated within 1 week after discharge	Usual Care Rehabilitation program UC and rehab arms offered general information about COPD prior to randomization and outpatient appointments with patients' family doctor or respiratory team	2 physiotherapists	8 weeks	2x /week exercise and education sessions (each lasting 2 hours) for 8 weeks Individually tailored aerobic and limb strengthening	3 months after admission	Primary outcome: hospital admission for exacerbation Hospital or emergency department attendance for exacerbation	Quadriceps strength; exercise capacity (paced incremental and endurance shuttle walking tests); fatigue; HRQOL(SGRQ, CRQ)

*Abbreviations: 6MWT, 6 Minute Walking Test; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Questionnaire; Ctrl, control; ED, emergency department; FEV_1, forced expiratory volume in 1 second; HRQOL, health-related quality of life; min, minutes; N, sample size; no., number; PR, pulmonary rehabilitation; rehab, rehabilitation; SF-36, Short form 36, SGRQ, St. George's Respiratory Questionnaire; UC, usual care.

Table A3: Description of Studies Examining Pulmonary Rehabilitation Maintenance Programs (n = 3)*

Study	Population	Setting	Groups	Delivered By	Length/ Description of Initial PR	Length of Maintenance Program	Description	Follow-up	Outcomes of Interest
Ringbaek et al (38) 2010	N = 96 MT: 55 Control: 41 Subject characteristics: ~ 68 years ~33% male FEV_1 % predicted: Treatment: 35.6 (14.0) Control: 36.9 (16.0) Stable COPD Excluded: patients with significant cardiac, musculoskeletal, or cognitive problems	Outpatient	Maintenance training Control group Both groups requested to continue	No mention	7-week outpatient program Supervised walking and cycling 2x/week combined with unsupervised daily training at home Educational sessions 1x/week Patients instructed to continue the unsupervised training at home after program end	1 year supervised training (every week in first 6 months and every second week in next 6 months) + 6 months unsupervised	Supervised training sessions (assumed to be similar to initial rehab)	Prior to rehab, at randomization, 3, 6, 12, 18 months after randomization	Functional exercise capacity (SWT) QOL (SGRQ) Other outcomes: adherence to supervised training, dropout rates, hospitalization
Spencer et al (39) 2010	N = 48 MT: 24 Control: 24 Subject characteristics: ~ 67 years ~46% male FEV_1 % predicted: Treatment: 51 ±11 Control: 54 ±11 Moderate COPD Excluded: cardiovascular, neurological, musculoskeletal comorbidities; exacerbation in previous month	Outpatient	Intervention group Control group Control group performed unsupervised home exercise 5 days/ week and received home exercise booklet and diary	No mention	8-week program 20 min walking, 20 min cycling, 10 min arm cycling and upper and lower limb strength training exercises using weight equipment and free weights	1 year	Supervised exercise 1 day/week plus unsupervised home exercise on 4 other days Supervised exercise same as initial rehab program Unsupervised home exercise: 30 min walking + 30 min upper and lower limb strengthening exercises using free weights and body weight; included exercise booklet and diary	3, 6, and 12 months following pulmonary rehab	Functional exercise capacity (6MWT) QOL (SGRQ) Other outcomes: lung function; incremental shuttle walk test; hospital anxiety and depression scale; hospital admission; length of stay; exacerbations

Study	Population	Setting	Groups	Delivered By	Length/ Description of Initial PR	Length of Maintenance Program	Description	Follow-up	Outcomes of Interest
Berry et al (37) 2003	N = 140 MT: 70 Control: 70 Subject characteristics: ~ 67 years ~56% male FEV_1 % predicted: Treatment: 57.6 (53.2–62.0) Control: 59.1 (55.0–63.2) Excluded: cardiac and peripheral vascular disease, concurrent cancer treatment, uncontrolled diabetes or hypertension	Community and university centre	Long-term intervention Short-term intervention (control group) Control group: All participants completed a 3-month pulmonary rehabilitation program prior to randomization Patients in control group were encouraged to continue exercising on their own	Not reported	3-month supervised centre-based program Exercise sessions with both aerobic and upper-extremity resistance training: included walking, biceps curls, triceps extension, shoulder exercises Sessions were 3x weekly for 1 hour	15 months		After initial 3-month rehab, and 9, 15, and 18 months from this point	Functional exercise capacity (6MWT) Other outcomes: physical disability; physical function (stairs climbed); peak oxygen uptake; pulmonary function; physical activity scale; compliance; training intensity

*Abbreviations: 6MWT, 6 Minute Walking Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; min, minutes; MT, maintenance training; N, sample size; PR, pulmonary rehabilitation; QOL, quality of life; rehab, rehabilitation; SGRQ, St. George's Respiratory Questionnaire; SWT, Shuttle Walking Test.

Appendix 3: Methodological Quality and GRADE Profile of Studies

Table A4: Methodological Quality of Studies Examining Stable COPD* (n = 18)

Study	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding of Outcome Assessors for Primary Outcome	Sample Size Calculation	Losses to Follow-up	ITT
Theander et al, 2009 (23)	30	?	✓	✓	No	✓†	21% T: 25%; C: 16.5%	No
Elci et al, 2008 (13)		✓	✓	Unclear	No	X	NR	NR
Karapolat et al, 2007 (20)	49	?	✓	✓	NR	X	6% patients	No
Borghi-Silva et al, 2009 (11)	40	Unclear	✓	Unclear	NR	✓‖	15% T:0%; C: 30%	No
Guell et al, 2000 (18)	60	Unclear	✓	no	Yes	X	None at end of program	No
Finnerty et al, 2001 (15)	100	✓	✓	Unclear	Yes	X	27% T: 20%; C: 34%	No
Engstrom et al, 1999 (14)	55	Unclear	✓	Unclear	Yes‡	X	9% T: 7%; C: 11%	No
Ringbaek et al, 2000 (22)	45	Unclear	X§	Unclear	NR	X	16% T: 29%; C: 0%	No
Wijkstra et al, 1994 (27)	45	Unclear	✓	Unclear	NR	X	4.4% T: 6.7%; C: 0%	No
Troosters et al, 2000 (24)	100	Unclear	✓	Unclear	NR	X	38% T: 32%; C: 44%*	No
Behnke et al, 2000 (9)	46	Unclear	✓	✓	X	X	35% T: 35%; C: 35%	No
Boxall et al, 2005 (12)	60	✓	✓	✓	X	✓#	23% T: 23%; C: 23%	X
Simpson and Rocker, 1992 (25)	34	✓	✓	NR	✓	X	17.6% T: 17.6%; C:17.6 %	X

Study	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding of Outcome Assessors for Primary Outcome	Sample Size Calculation	Losses to Follow-up	ITT
Lake et al, 1990 (21)	28	Unclear	✓	NR	NR	X	7.1% T: 5%; C: 12.5%	X
Griffiths et al, 2000 (17)	200	✓	✓	✓	✓	✓	10% T: 7%; C: 12.9%	✓
Singh, 2003 (26)	40	Unclear	✓	NR	NR	X	NR	?
Hernandez et al, 2000 (19)	60	Unclear	✓	NR	NR	X	38.3% T: 33.3%; C: 43.3%	?
Goldstein et al, 1994 (16)	89	Unclear	✓	NR	NR	✓¶	20.2% T: 15.5%; C: 9%	?

*Abbreviations: 6 MWT, 6 Minute Walking Test; C, control; COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Questionnaire; ITT, intention-to-treat analysis; n, number of studies; N: sample size; NR, not reported; SGRQ, St. Georger's Respiratory Questionnaire; T, treatment.
†Theander et al, 2009 (12) was underpowered. The sample size was calculated based on the CRQ, but the SGRQ was used in the study. Also, the baseline gender distribution between the 2 groups was not comparable.
‡Engstrom et al, 1999 (13) had all outcomes blinded with the exception of the 6MWT.
§Ringbaek et al, 2000 (16) had more females in the control group at baseline and more smokers in the treatment group at baseline.
‖Borghi-Silva et al, 2009 (11) was underpowered.
¶Goldstein et al, 1994 (17) was not well-described in terms of power.
#Boxall et al, 2005 (9) was underpowered.

Table A5: Methodological Quality of Studies Following an Acute Exacerbation of COPD* (n = 5)

Study	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding of Outcome Assessors for Primary Outcome	Sample Size Calculation	Losses to Follow-up	ITT
Behnke et al, 2000 (9)	46	Unclear	✓	Unclear	Yes	X	35%	No
Man et al, 2004 (36)	42	✓	✓	Unclear	No	✓	19% T: 14%; C: 24%	✓
Murphy et al, 2005 (34)	31	Unclear	✓	Yes	Yes	X	16% T:19%; C: 13%	No
Eaton et al, 2009 (32)	97	✓	✓	Unclear	No	✓†	13% T:17%; C: 10%	✓
Seymour et al, 2010 (35)	60	Unclear	✓	Unclear	No	✓	18% T:23%; C: 13%	✓

*Abbreviations: C, control; COPD, chronic obstructive pulmonary disease; ITT, intention-to-treat analysis; n, number of studies; N, sample size; T, treatment.
†Eaton et al, 2009 (28) was underpowered to show a difference in primary outcome.

Table A6: Methodological Quality of Studies Examining Maintenance Programs* (n = 3)

Study	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding of Outcome Assessors for Primary Outcome	Sample Size Calculation	Losses to Follow-up	ITT
Spencer et al, 2010 (39)	48	Unclear	✓	Unclear	No	✓	19% T: 23%; C: 14%	Yes
Ringbaek et al, 2010 (38)	96	Unclear	✓†	Unclear	Unclear	X	At 12 months: 13% T: 15%: C: 24% At 18 months: 29% T: 24%; C: 34%	Unclear
Berry et al, 2003 (37)	140	Unclear	✓	Yes	Yes	X	16% T:19%; C: 13%	No

*Abbreviations: C, control; ITT, intention-to-treat analysis; n, number of studies; N, sample size; T, treatment.
†Ringbaek et al, 2010 (34): Baseline characteristics comparable with the exception of % of heart diseases: treatment group 41.8% versus 9.8% in the Control arm, $P < 0.01$.

Table A7: GRADE Quality of Evidence for Studies Examining Stable COPD*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: Exercise Capacity – 6MWT							
15	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: HRQL – CRQ							
8	RCT	Serious limitations‡	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: HRQL – SGRQ							
8	RCT	Serious limitations§	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate

*Abbreviations: 6MWT, Six Minute Walking Test; CRQ, chronic respiratory questionnaire; HRQOL, health-related quality of life; n/a, not applicable; RCT, randomized controlled trial; SGRQ, St. George's Respiratory Questionnaire

†Study quality was downgraded for the exercise capacity because of serious limitations in many of the studies including: unknown or inadequate allocation concealment (12 of 15 studies); unclear randomization process based on published trials (12 of 15 studies); unclear whether assessor was blinded (single blind) (11 of15 studies); lack of a priori power calculations (11 of 15 studies); inadequately powered studies based on post hoc sample size calculations (3 of 15 studies), withdrawals/dropouts > 20% (5 of 15 studies); and intention-to-treat (ITT) analysis not used or unknown (15 of 15 studies).

‡ Study quality was downgraded for health-related quality of life (CRQ) because of serious limitations in many of the studies including: unknown or inadequate allocation concealment (12 of 15 studies); unclear randomization process based on published trials (7 of 8 studies); unclear whether assessor was blinded (single blind) (5 of 8 studies); lack of a priori power calculations (6 of 8 studies); withdrawals/dropouts > 20% (3 of 8 studies); and intention-to-treat (ITT) analysis not used or unknown (8 of 8 studies).

§Study quality was downgraded for health-related quality of Life (SGRQ) because of serious limitations in many of the studies including: unknown or inadequate allocation concealment (3 of 8 studies); unclear randomization process based on published trials (4 of 8 studies); unclear whether assessor was blinded (single blind) (4 of 8 studies); lack of a priori power calculations (4 of 8 studies); inadequately powered studies based on post hoc sample size calculations (2 of 8 studies); withdrawals/dropouts > 20% (2 of 8 studies); and intention-to-treat (ITT) analysis not used or unknown (8 of 8 studies).

Table A8: GRADE Quality of Evidence for Studies Examining Pulmonary Rehabilitation Following an Acute Exacerbation of COPD*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: Hospital Readmissions							
5	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: HRQL – CRQ							
4	RCT	Serious limitations‡	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: HRQL – SGRQ							
3	RCT	Serious limitations‡	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate

* Abbreviations: 6MWT, Six Minute Walking Test; CRQ, Chronic Respiratory Questionnaire; HRQOL, health-related quality of life; n/a, not applicable; RCT, randomized controlled trial; SGRQ, St. George's Respiratory Questionnaire.

†Study quality was downgraded for the hospital readmissions outcomes because of serious limitations in many of the studies including: unknown or inadequate allocation concealment (4 of 5 studies); unclear randomization process based on published trials (3 of 5 studies); unclear or no blinded outcome assessors (single blind) (3 of 5 studies); lack of a priori power calculations (2 of 5 studies); inadequately powered studies (1 of 5 studies); withdrawals/dropouts > 20% (1 of 5 studies); and intention-to-treat (ITT) analysis not used (2 of 5 studies).

‡Study quality was downgraded for the HRQL outcome because of serious limitations in many of the studies including: unknown or inadequate allocation concealment (CRQ, 4 of 4 studies; SGRQ, 2 of 3 studies); unclear randomization process based on published trials (CRQ, 2 of 4 studies; SGRQ, 2 of 3 studies); unclear or no blinded outcome assessors (single blind) (CRQ, 3 of 4 studies; SGRQ, 2 of 3 studies); lack of a priori power calculations (CRQ, 1 of 4 studies; SGRQ, 1 or 3 studies); inadequately powered studies (CRQ, 1 of 4 studies); withdrawals/dropouts > 20% (CRQ, 1 of 4 studies); and intention-to-treat (ITT) analysis not used (CRQ, 1 of 4 studies; SGRQ, 1 of 3 studies).

Table A9: GRADE Quality of Evidence for Studies Examining Pulmonary Rehabilitation Maintenance Programs*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: Exercise Capacity – 6MWT							
2	RCT	Serious limitations†	Serious limitations†	No serious limitations	No serious limitations	n/a	Low
Outcome: HRQL – SGRQ							
2	RCT	Very serious limitations‡	No serious limitations	No serious limitations	No serious limitations	n/a	Low

*Abbreviations: 6MWT, Six Minute Walking Test; HRQOL, health-related quality of life; n/a, not applicable; RCT, randomized controlled trial; SGRQ, St. George's Respiratory Questionnaire; WMD, weighted mean difference.

†Study quality was downgraded for the exercise capacity outcome because of serious limitations in many of the studies including: unknown or inadequate allocation concealment (1 of 2 studies); unclear randomization process based on published trials (2 of 2 studies); unclear whether assessor was blinded (single blind) (1 of 2 studies); lack of a priori power calculations (1 of 2 studies); inadequately powered studies (2 of 2 studies); and intention-to-treat (ITT) analysis not used (1 of 2 studies). The study quality was also downgraded because of inconsistent findings for the WMD of the 6MWT.

‡Study quality was downgraded for the HRQOL outcome because of very serious limitations in many of the studies including: unknown or inadequate allocation concealment (2 of 2 studies); unclear randomization process based on published trials (2 of 2 studies); unclear whether assessor was blinded (single blind) (1 of 2 studies); lack of a priori power calculations (1 of 2 studies); and intention-to-treat (ITT) analysis not used (1 of 2 studies). The study quality was also downgraded because of missing data reported for the effect size and associated *P* values.

Appendix 4: Forest Plots

Studies of Stable COPD

Quality of Life (St. George's Respiratory Questionnaire)

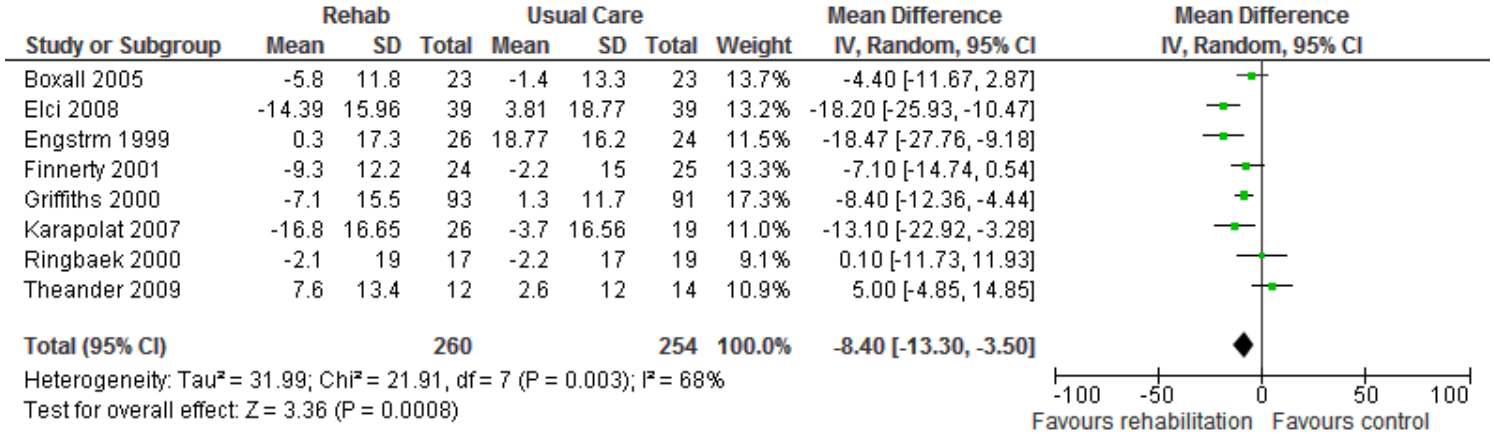


Figure A1: Forest Plot of Pooled Quality of Life Data Measured by the Total Score of the St. George's Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

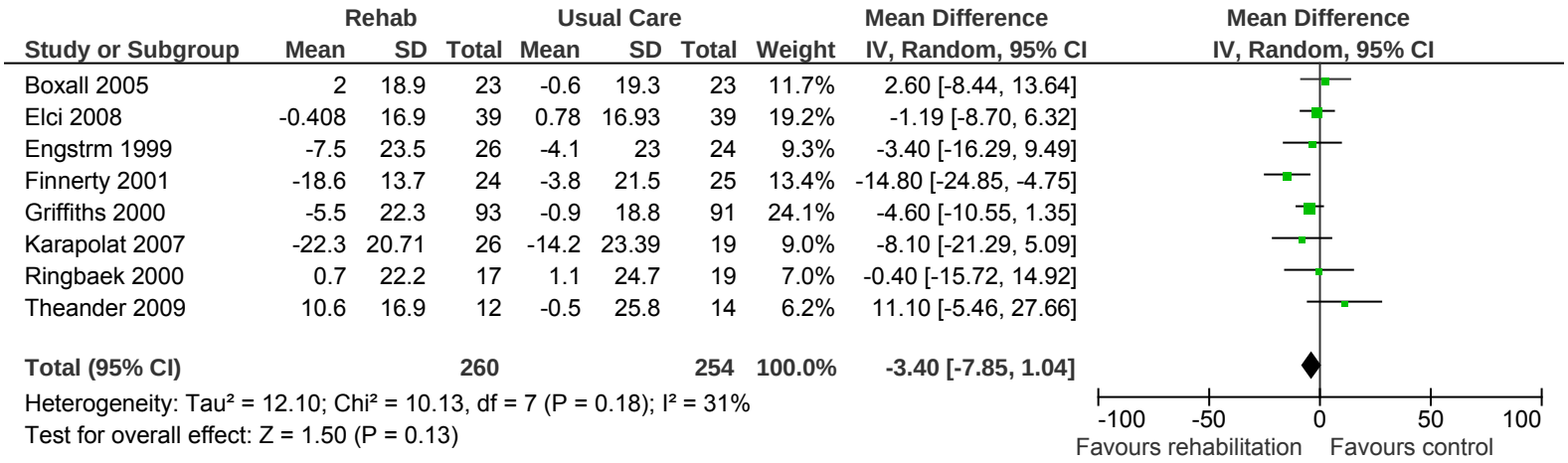


Figure A2: Forest Plot of Pooled Quality of Life Data Measured by the Symptom Score of the St. George's Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

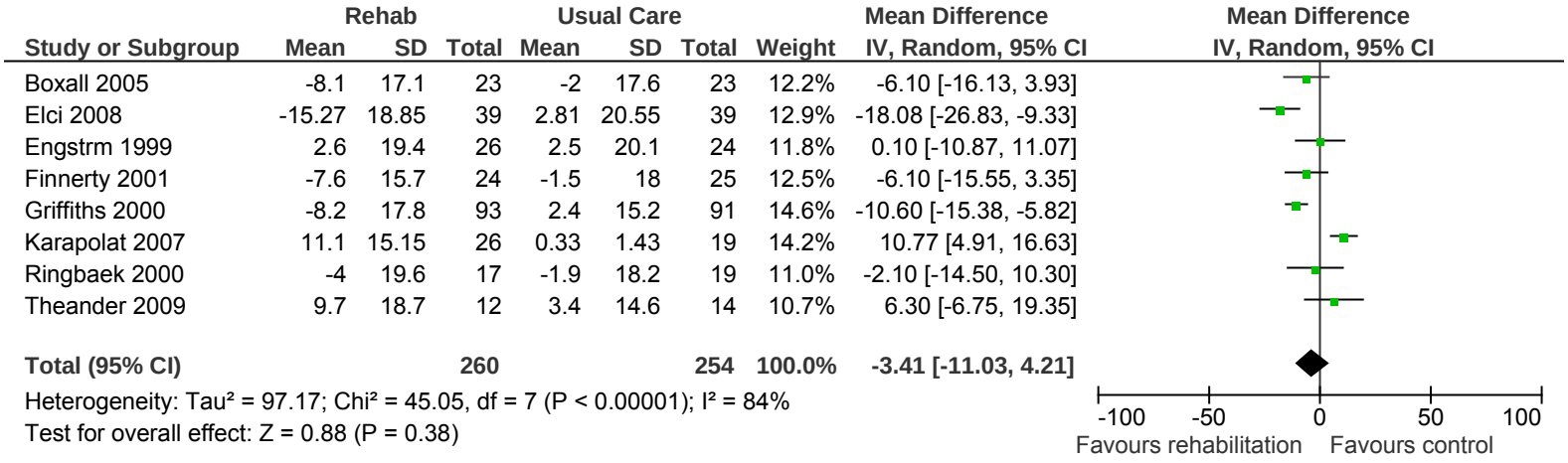


Figure A3: Forest Plot of Pooled Quality of Life Data Measured by the Impacts Score of the St. George's Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

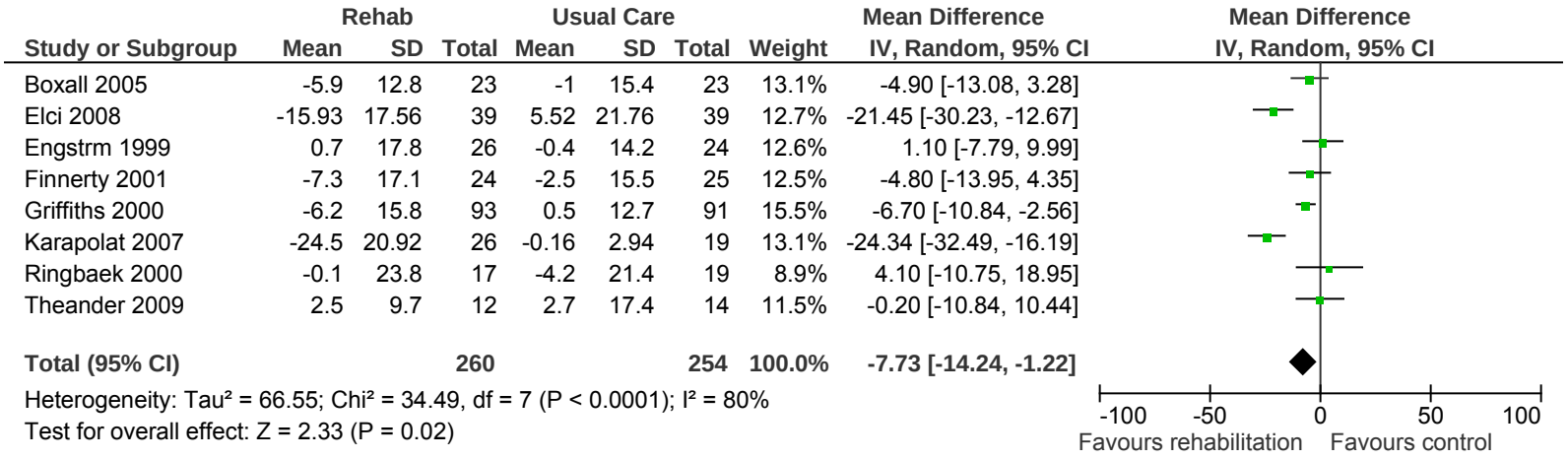


Figure A4: Forest Plot of Pooled Quality of Life Data Measured by the Activity Score of the St. George's Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

Quality of Life (Chronic Respiratory Questionnaire)

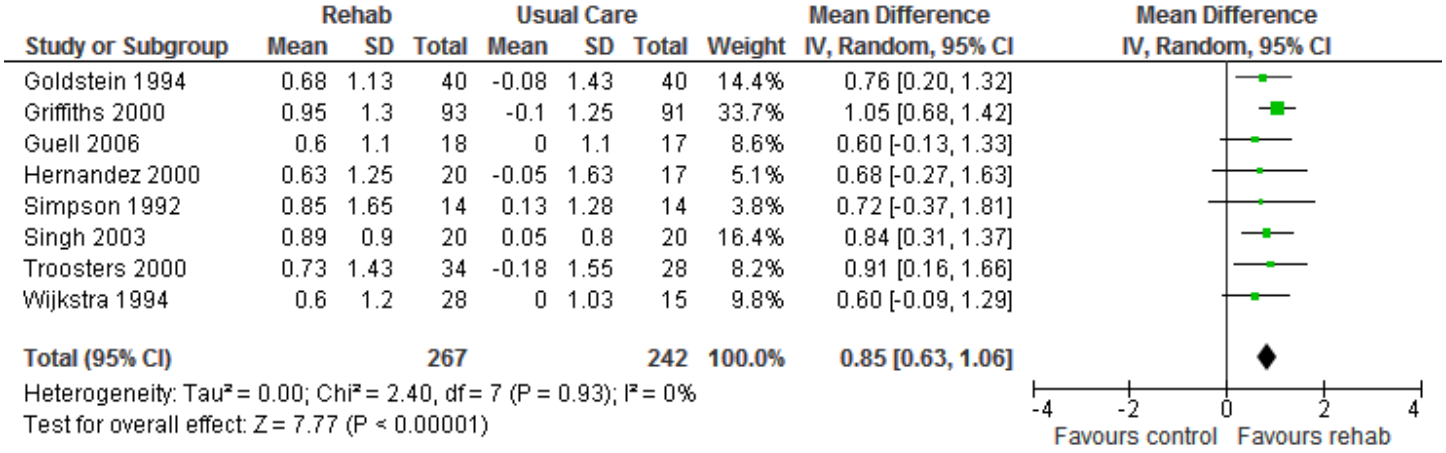


Figure A5: Forest Plot of Pooled Quality of Life Data Measured by the Mastery Score of the Chronic Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

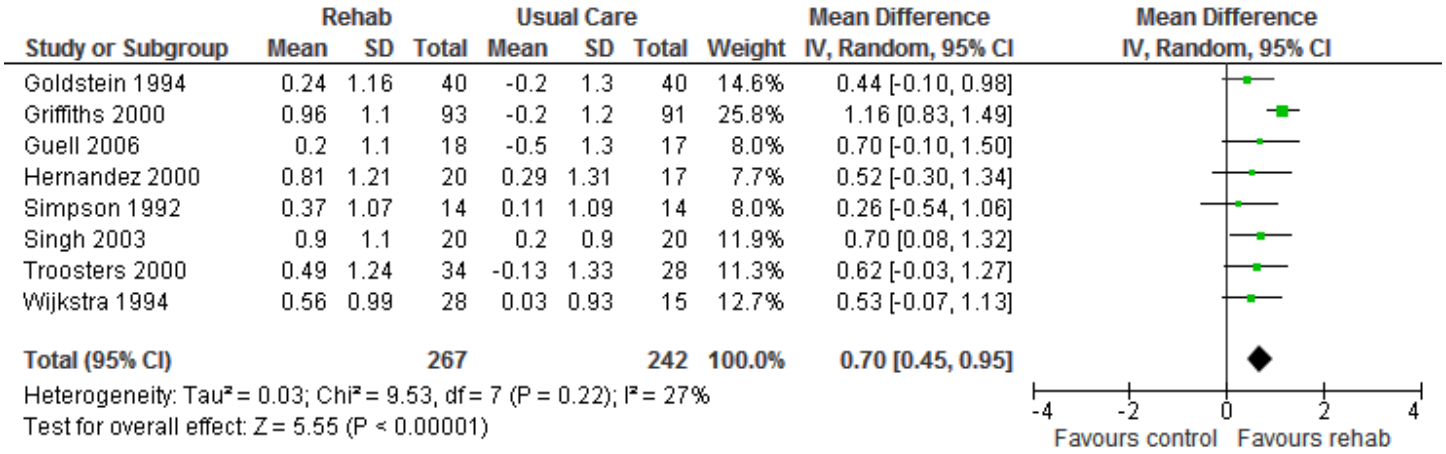


Figure A6: Forest Plot of Pooled Quality of Life Data Measured by the Emotional Function Score of the Chronic Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

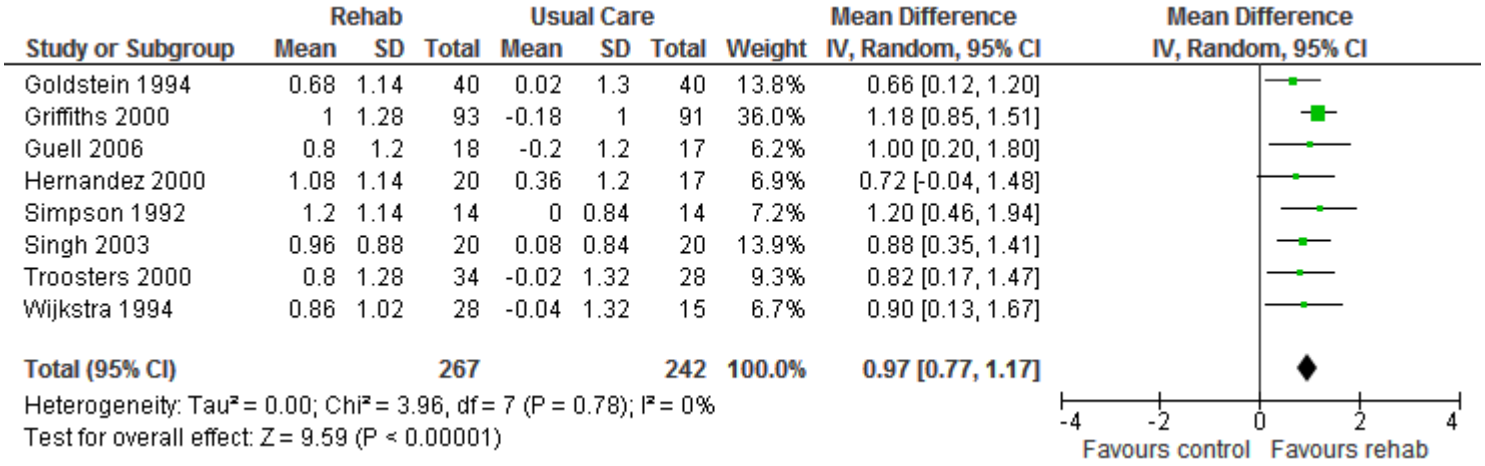


Figure A7: Forest Plot of Pooled Quality of Life Data Measured by the Dyspnea Score of the Chronic Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

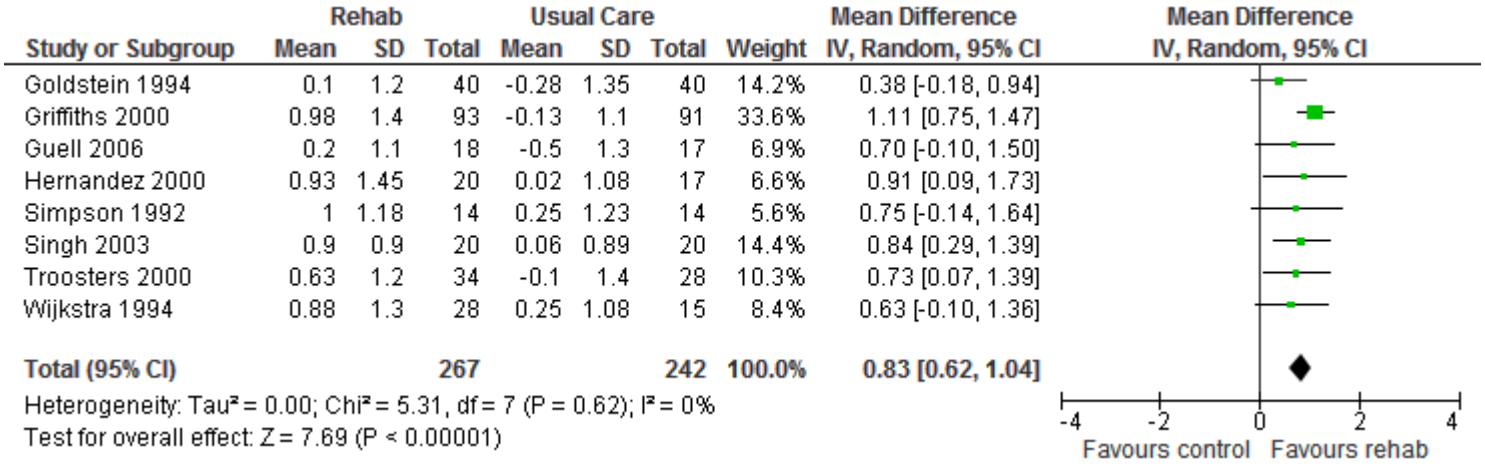


Figure A8: Forest Plot of Pooled Quality of Life Data Measured by the Fatigue Score of the Chronic Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

Functional Exercise Capacity (6 Minute Walking Test)

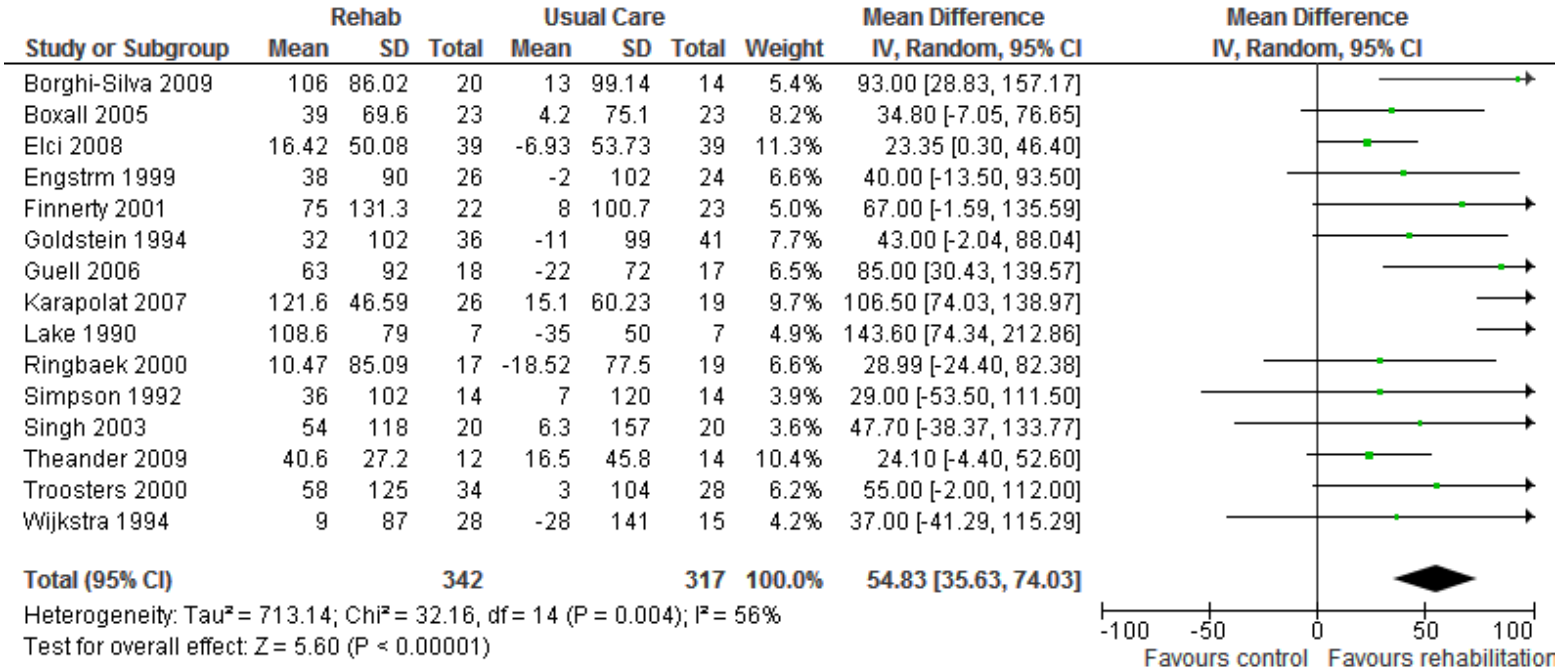


Figure A9: Forest Plot of Pooled Data on Functional Exercise Capacity Measured by the Six Minute Walking Test

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

Studies Examining Pulmonary Rehabilitation Within One Month of an Acute Exacerbation

Hospital Readmissions

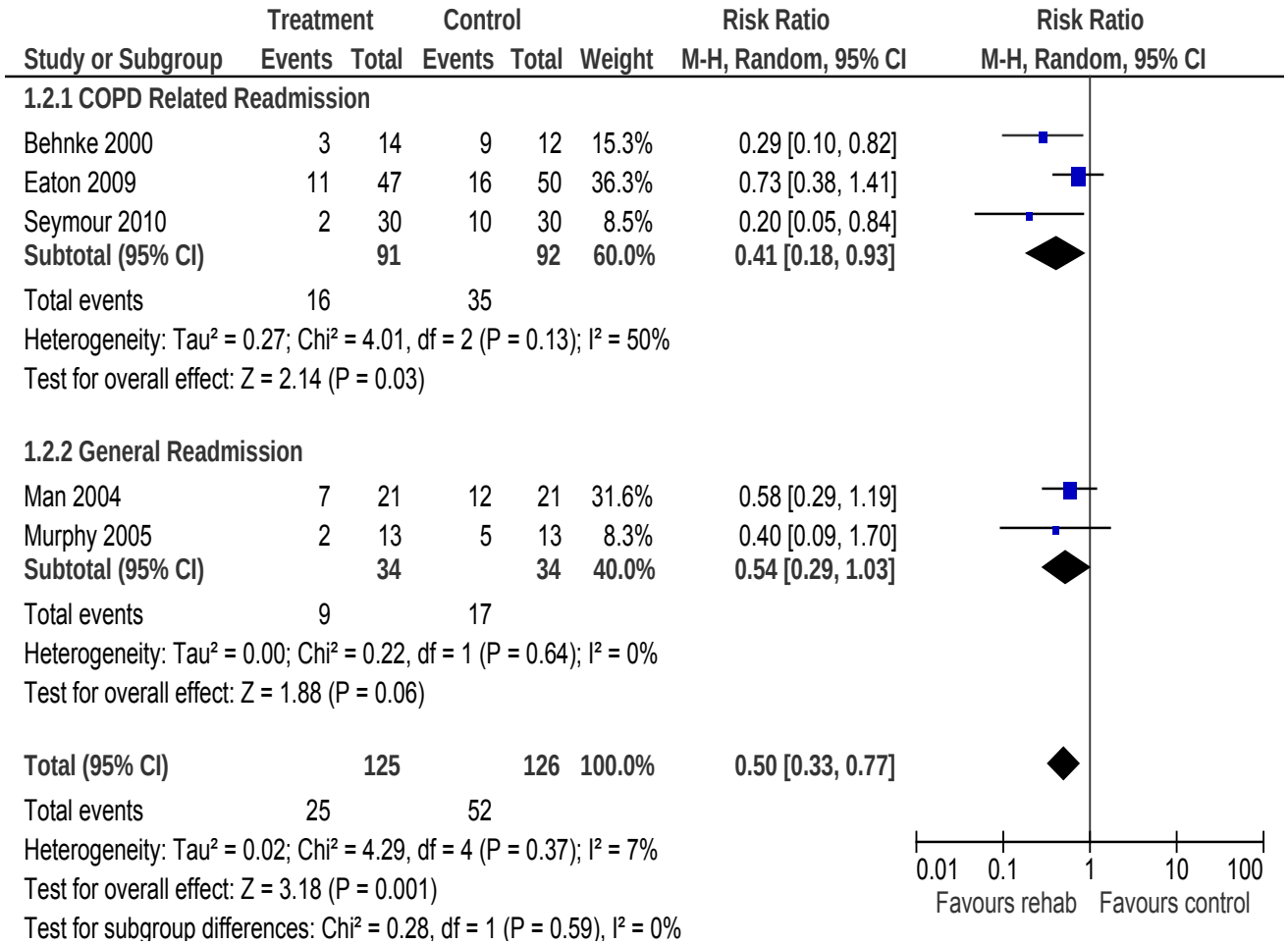


Figure A10: Forest Plot of Pooled Data on Hospital Readmissions Subgrouped by Type of Readmission

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; M–H, Mantel–Haenszel.

Health-Related Quality of Life (Chronic Respiratory Questionnaire)

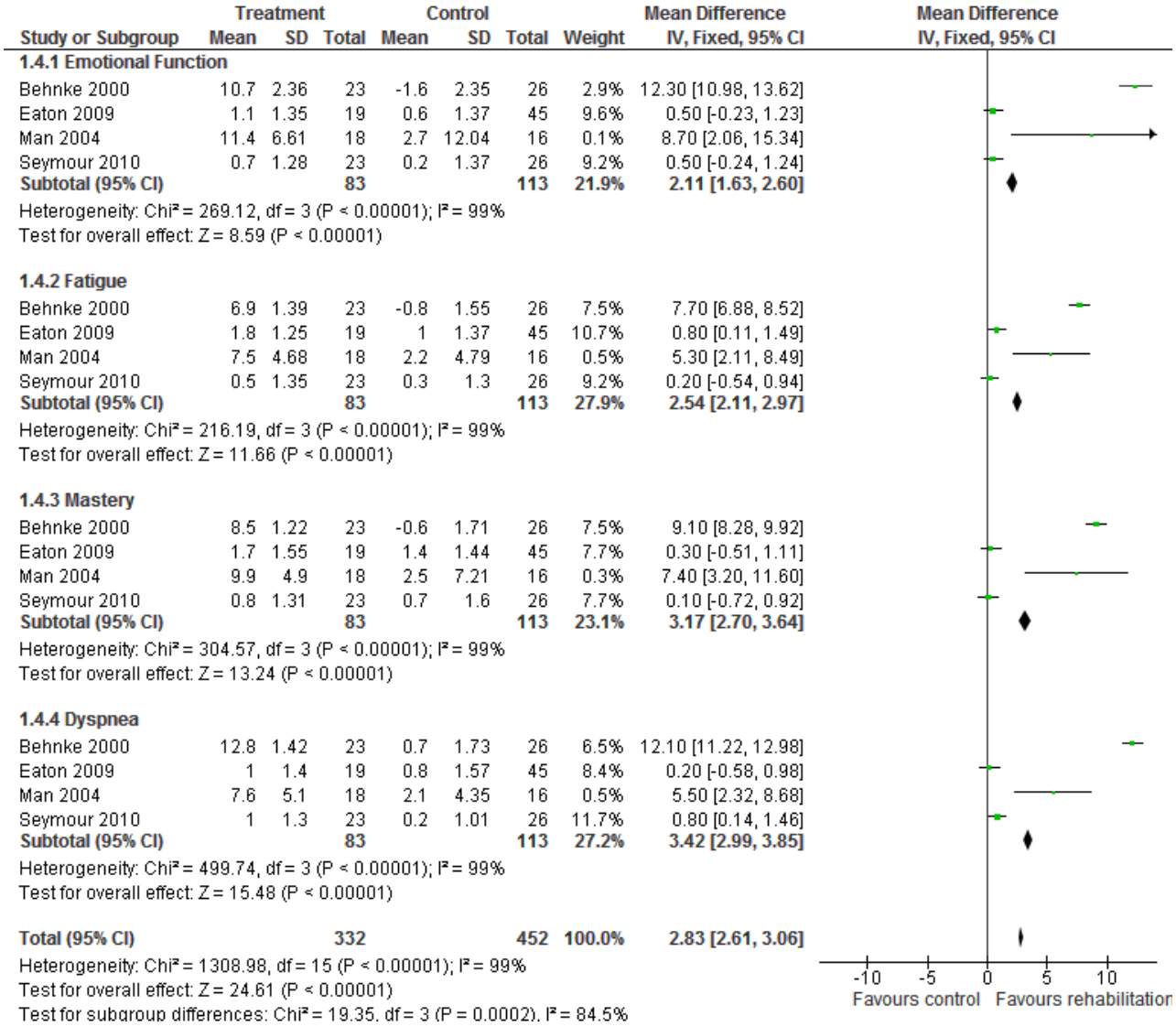


Figure A11: Forest Plot of Pooled Data on Health-Related Quality of Life as Measured by the CRQ, Subgrouped by Components of the CRQ

*Abbreviations: CI, confidence interval; CRQ, Chronic Respiratory Questionnaire; SD, standard deviation.

Health-Related Quality of Life (St. George's Respiratory Questionnaire)

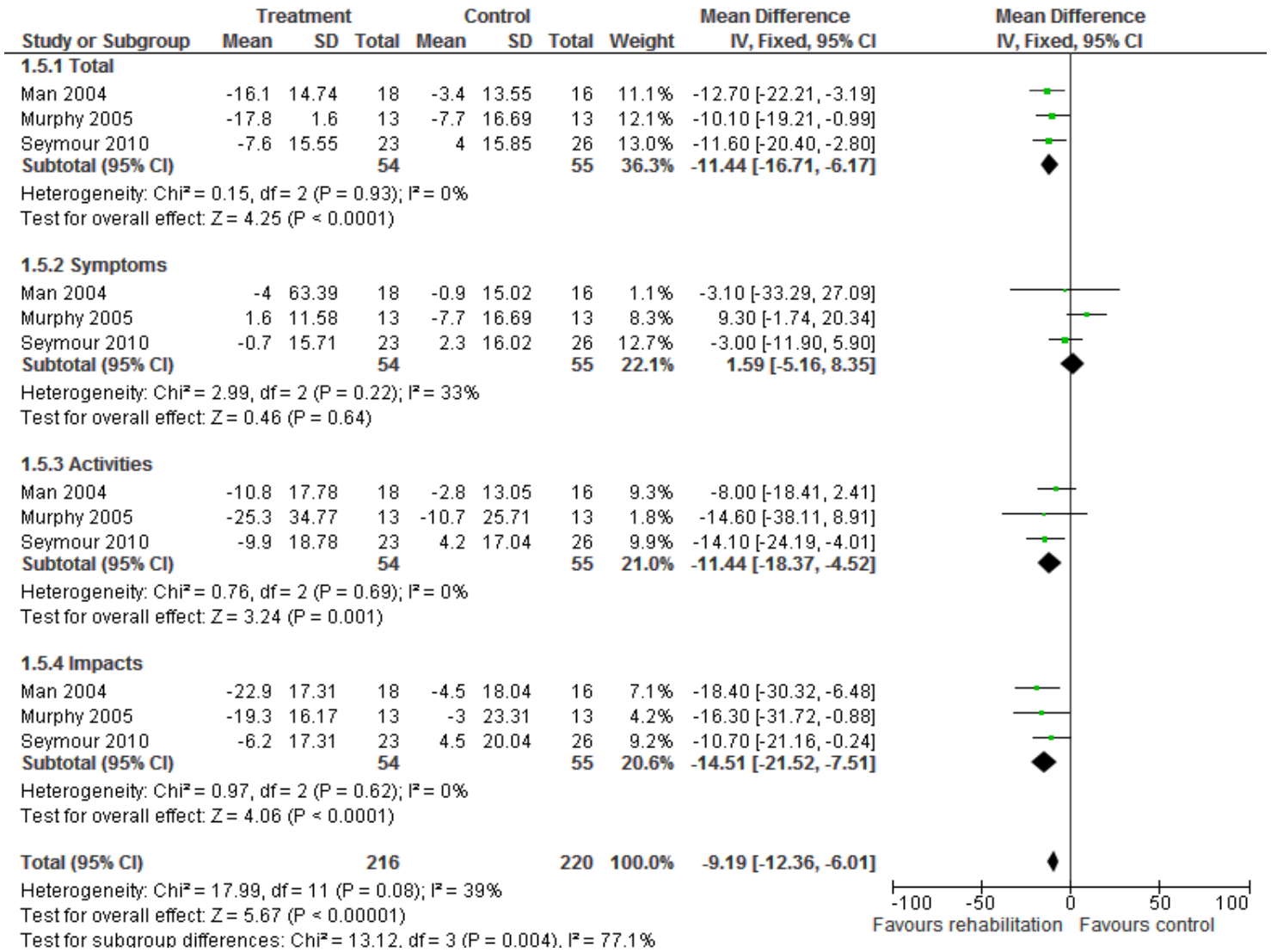


Figure A12: Forest Plot of Pooled Data on Health-Related Quality of Life as Measured by the SGRQ, Subgrouped by Components of SGRQ

*Abbreviations: CI, confidence interval; SD, standard deviation; SQRQ, St. George's Respiratory Questionnaire.

Exercise Capacity

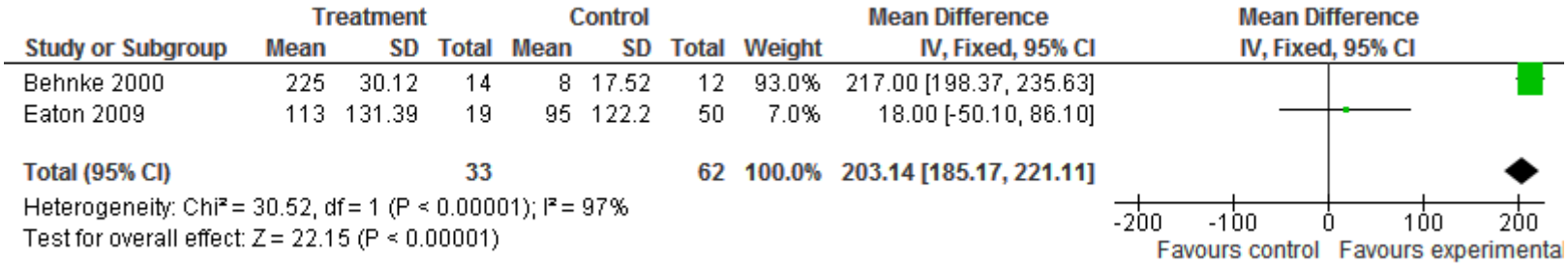


Figure A13: Forest Plot of Pooled Data on Exercise Capacity as Measured by the Six Minute Walking Test

*Abbreviations: CI, confidence interval; SD, standard deviation.

Emergency Department Visits

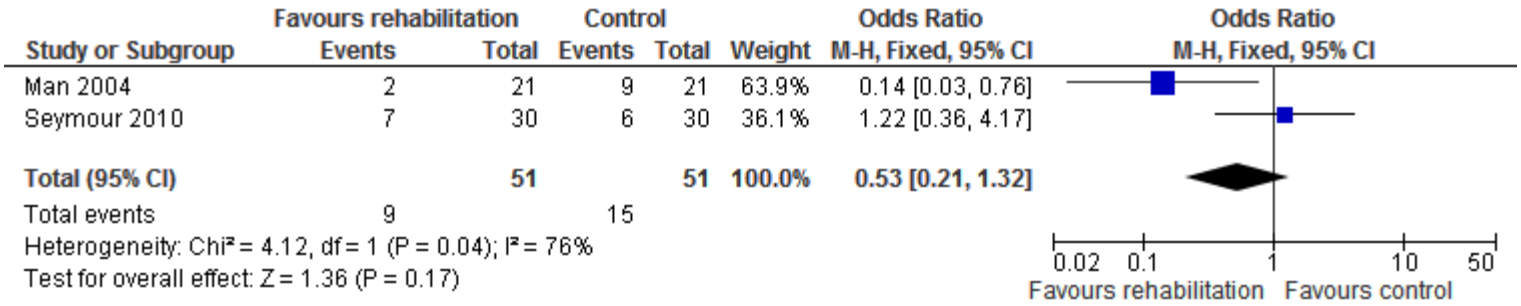


Figure A14: Forest Plot of Pooled Data on Emergency Department Visits

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.

Mortality

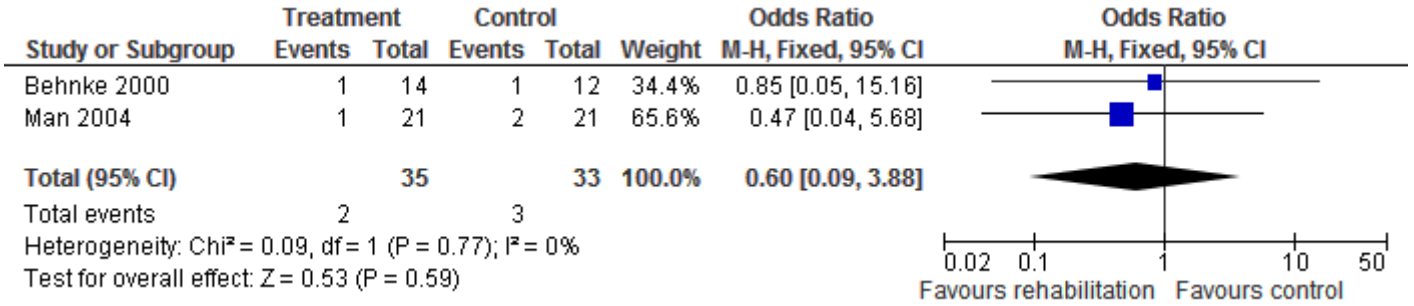


Figure A15: Forest Plot of Pooled Data on Mortality

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.

Studies Examining Pulmonary Rehabilitation Maintenance Programs

Exercise Capacity

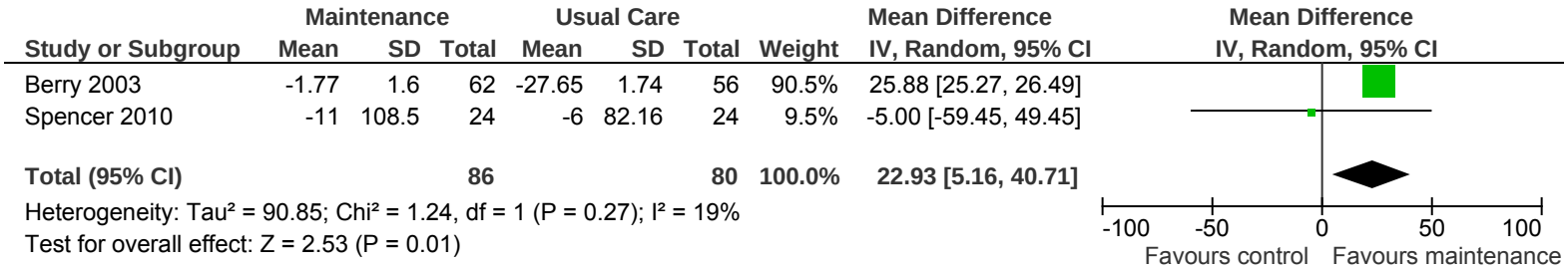


Figure A16: Forest Plot of Pooled Data on Exercise Capacity as Measured by the Six Minute Walking Test

*Abbreviations: CI, confidence interval; SD, standard deviation.

References

(1) Lacasse Y, Maltais F, Goldstein RS. Smoking cessation in pulmonary rehabilitation: goal or prerequisite? J Cardpulm Rehabil. 2002 May;22(3):148-53.

(2) Furukawa TA, Barbui C, Cipriani A, Brambilla P, Wantanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol. 2006 Jan 1;59(1):7-10.

(3) Thiessen PH, Barrowman N, Garg AX. Imputing variance estimates do not alter the conclusions of a meta-analysis with continuous outcomes: a case study of changes in renal function after living kidney donation. J Clin Epidemiol. 2007 Jan 1;60(3):228-40.

(4) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490.

(5) Goodman, C. Literature searching and evidence interpretation for assessing health care practices. Stockholm, Sweden: Swedish Council on Technology Assessment in Health Care; 1996 81 p. SBU Report No. 119E.

(6) Hailey D, Jacobs P, Stickland M, Chuck A, Marciniuk DD, Mayers I, Mierzwinsky-Urban M. Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease: Clinical, Economic, and Budget Impact Analysis [Technology report number 126]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010.

(7) Vieira DS, Maltais F, Bourbeau J. Home-based pulmonary rehabilitation in chronic obstructive pulmonary disease patients. Curr Opin Pulm Med. 2010 Mar;16(2):134-43.

(8) Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2006;(4).

(9) Behnke M, Taube C, Kirsten D, Lehnigk B, Jorres RA, Magnussen H. Home-based exercise is capable of preserving hospital-based improvements in severe chronic obstructive pulmonary disease. Respir Med. 2000 Dec;94(12):1184-91.

(10) Behnke M, Jorres RA, Kirsten D, Magnussen H. Clinical benefits of a combined hospital and home-based exercise programme over 18 months in patients with severe COPD. Monaldi Arch Chest Dis. 2003;59(1):44-51.

(11) Borghi-Silva A, Arena R, Castello V, Simoes RP, Martins LE, Catai AM, et al. Aerobic exercise training improves autonomic nervous control in patients with COPD. Respir Med. 2009 Oct;103(10):1503-10.

(12) Boxall A, Barclay L, Sayers A, Caplan GA. Managing chronic obstructive pulmonary disease in the community: a randomized controlled trial of home-based pulmonary rehabilitation for elderly housebound patients. J Cardpulm Rehabil. 2005 Nov;25(6):378-85.

(13) Elci A, Borekci S, Ovayolu N, Elbek O. The efficacy and applicability of a pulmonary rehabilitation programme for patients with COPD in a secondary-care community hospital. Respirology. 2008 Sep;13(5):703-7.

(14) Engstrom CP, Persson LO, Larsson S, Sullivan M. Health-related quality of life in COPD: why both disease-specific and generic measures should be used. Eur Respir J. 2001 Jul;18(1):69-76.

(15) Finnerty JP, Keeping I, Bullough I, Jones J. The effectiveness of outpatient pulmonary rehabilitation in chronic lung disease: a randomized controlled trial. Chest. 2001 Jun;119(6):1705-10.

(16) Goldstein RS, Gort ES, Stubbing D, Avendano MA, Guyatt GH. Randomised controlled trial of respiratory rehabilitation. Lancet. 1994 Jan 19;344(8934):1394.

(17) Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet. 2000 Jan 29;355(9201):362-8.

(18) Guell R, Resqueti V, Sangenis M, Morante F, Martorell B, Casan P, et al. Impact of pulmonary rehabilitation on psychosocial morbidity in with severe COPD. Chest. 2006;129(4):899-904.

(19) Hernandez MT, Rubio TM, Ruiz FO, Riera HS, Gil RS, Gomez JC. Results of a home-based training program for patients with COPD. Chest. 2000 Jul;118(1):106-14.

(20) Karapolat H, Atasever A, Atamaz F, Kirazli Y, Elmas F, Erdinc E. Do the benefits gained using a short-term pulmonary rehabilitation program remain in COPD patients after participation? Lung. 2007 Jul;185(4):221-5.

(21) Lake FR, Henderson K, Briffa T, Openshaw J, Musk AW. Upper-limb and lower-limb exercise training in patients with chronic airflow obstruction. Chest. 1990;97:1077-82.

(22) Ringbaek TJ, Broendum E, Hemmingsen L, Lybeck K, Nielsen D, Andersen C, et al. Rehabilitation of patients with chronic obstructive pulmonary disease. Exercise twice a week is not sufficient! Respir Med. 2000 Feb;94(2):150-4.

(23) Theander K, Jakobsson P, Jorgensen N, Unosson M. Effects of pulmonary rehabilitation on fatigue, functional status and health perceptions in patients with chronic obstructive pulmonary disease: a randomized controlled trial. Clin Rehabil. 2009 Feb;23(2):125-36.

(24) Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Am J Med. 2000 Aug 15;109(3):207-12.

(25) Simpson AC, Rocker GM. Advanced chronic obstructive pulmonary disease: rethinking models of care. Qjm. 2008 Sep;101(9):697-704.

(26) Singh S. Chronic obstructive pulmonary disease. Curr Anaesth Crit Care. 2003;14(2):74-80.

(27) Wijkstra PJ, Altena RV, Kraan J, Otten V, Postma DS, Koeter GH. Quality of life in patients with chronic obstructive pulmonary disease improves after rehabilitation at home. Eur Respir J. 1994 Jan 1;7:269-73.

(28) Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. Arch Phys Med Rehabil. 2010 Feb;91(2):221-5.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-7012-1 (PDF)

Ontario
Health Quality Ontario
Qualité des services de santé Ontario

Long-Term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis

COPD Working Group

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 7, pp. 1–64, March 2012

Suggested Citation

This report should be cited as follows:

COPD Working Group. Long-term oxygen therapy for patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2012 Mar;12(7):1–64. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_LTOT_March.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to: MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

CI	Confidence interval(s)
CO_2	Carbon dioxide
CRQ	Chronic Respiratory Questionnaire
CT	Control group
FVC	Forced vital capacity (also referred to as vital capacity in this report)
FEV_1	Forced expiratory volume in 1 second
HRQOL	Health-related quality of life
kPa	Kilopascal (1 kPa = 7.5 mm Hg)
LTOT	Long-term oxygen therapy
MAS	Medical Advisory Secretariat
MCID	Minimal clinically important difference
MD	Mean difference
mm Hg	Millimetre of mercury
O_2	Oxygen
OR	Odds ratio
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
RCT	Randomized controlled trial
RR	Relative risk
SpO_2	Oxygen saturation level of arterial blood measured by pulse oximetry
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
VC	Vital capacity (used interchangeably with forced vital capacity in this report)

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective

The objective of this health technology assessment was to determine the effectiveness, cost-effectiveness, and safety of long-term oxygen therapy (LTOT) for chronic obstructive pulmonary disease (COPD).

Clinical Need: Condition and Target Population

Oxygen therapy is used in patients with COPD with hypoxemia, or very low blood oxygen levels, because they may have difficulty obtaining sufficient oxygen from inspired air.

Technology

Long-term oxygen therapy is extended use of oxygen. Oxygen therapy is delivered as a gas from an oxygen source. Different oxygen sources are: 1) oxygen concentrators, electrical units delivering oxygen converted from room air; 2) liquid oxygen systems, which deliver gaseous oxygen stored as liquid in a tank; and 3) oxygen cylinders, which contain compressed gaseous oxygen. All are available in portable versions. Oxygen is breathed in through a nasal cannula or through a mask covering the mouth and nose. The treating clinician determines the flow rate, duration of use, method of administration, and oxygen source according to individual patient needs. Two landmark randomized controlled trials (RCTs) of patients with COPD established the role of LTOT in COPD. Questions regarding the use of LTOT, however, still remain.

Research Question

What is the effectiveness, cost-effectiveness, and safety of LTOT compared with no LTOT in patients with COPD, who are stratified by severity of hypoxemia?

Research Methods

Literature Search

Search Strategy

A literature search was performed on September 8, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, CINAHL, the Cochrane Library, and INAHTA for studies published from January 1, 2007 to September 8, 2010.

A single clinical epidemiologist reviewed the abstracts, obtained full-text articles for studies meeting the eligibility criteria, and examined reference lists for additional relevant studies not identified through the literature search. A second clinical epidemiologist and then a group of epidemiologists reviewed articles with an unknown eligibility until consensus was established.

Inclusion Criteria

- patients with mild, moderate, or severe hypoxemia;
- English-language articles published between January 1, 2007 and September 8, 2010;
- journal articles reporting on effectiveness, cost-effectiveness, or safety for the comparison of interest;
- clearly described study design and methods;
- health technology assessments, systematic reviews, RCTs, or prospective cohort observational studies;

- any type of observational study for the evaluation of safety.

Exclusion Criteria

- no hypoxemia
- non-English papers
- animal or in vitro studies
- case reports, case series, or case-case studies
- studies comparing different oxygen therapy regimens
- studies on nocturnal oxygen therapy
- studies on short-burst, palliative, or ambulatory oxygen (supplemental oxygen during exercise or activities of daily living)

Outcomes of Interest

- mortality/survival
- hospitalizations
- readmissions
- forced expiratory volume in 1 second (FEV_1)
- forced vital capacity (FVC)
- FEV_1/FVC
- pulmonary hypertension
- arterial partial pressure of oxygen (PaO_2)
- arterial partial pressure of carbon dioxide ($PaCO_2$)
- end-exercise dyspnea score
- endurance time
- health-related quality of life

Note: Outcomes of interest were formulated according to existing studies, with arterial pressure of oxygen and carbon dioxide as surrogate outcomes.

Summary of Findings

Conclusions

- Based on low quality of evidence, LTOT (~ 15 hours/day) decreases all-cause mortality in patients with COPD who have severe hypoxemia (PaO_2 ~ 50 mm Hg) and heart failure.
- The effect for all-cause mortality had borderline statistical significance when the control group was no LTOT: one study.
- Based on low quality of evidence, there is no beneficial effect of LTOT on all-cause mortality at 3 and 7 years in patients with COPD who have mild-to-moderate hypoxemia (PaO_2 ~ 59–65 mm Hg).[1]
- Based on very low quality of evidence, there is some suggestion that LTOT may have a beneficial effect over time on FEV_1 and $PaCO_2$ in patients with COPD who have severe hypoxemia and heart failure: improved methods are needed.

[1] The mild-to-moderate classification was created for the purposes of the report.

- Based on very low quality of evidence, there is no beneficial effect of LTOT on lung function or exercise factors in patients with COPD who have mild-to-moderate hypoxemia, whether survivors or nonsurvivors are assessed.
- Based on low to very low quality of evidence, LTOT does not prevent readmissions in patients with COPD who have severe hypoxemia. Limited data suggest LTOT increases the risk of hospitalizations.
- Limited work has been performed evaluating the safety of LTOT by severity of hypoxemia.
- Based on low to very low quality of evidence, LTOT may have a beneficial effect over time on health-related quality of life in patients with COPD who have severe hypoxemia. Limited work using disease-specific instruments has been performed.
- Ethical constraints of not providing LTOT to eligible patients with COPD prohibit future studies from examining LTOT outcomes in an ideal way.

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this health technology assessment was to determine the effectiveness, cost-effectiveness, and safety of long-term oxygen therapy (LTOT) for chronic obstructive pulmonary disease (COPD).

Clinical Need and Target Population

Patients With COPD and Hypoxemia and Respiratory Failure: Need for LTOT

Airflow limitation in COPD may cause very low arterial blood oxygen levels, or hypoxemia. (1) Hypoxemia increases respiratory drive to maintain adequate oxygen delivery to tissues. Prolonged hypoxemia may lead to tissue hypoxia and permanent damage as a result of adverse effects on organ function and structure. Short-term effects of hypoxemia include increased breathing difficulty, peripheral vascular dilation with increased heart rate and cardiac output, regional pulmonary vasoconstriction, high erythropoietin levels, and increased blood viscosity. Long-term effects include pulmonary hypertension, right ventricular failure, and polycythemia. (2)

Respiratory failure is found only in stage 4, very severe COPD, where the arterial partial pressure of oxygen (PaO_2) is less than 60 mm Hg, and it may be accompanied by a forced expiratory volume in 1 second (FEV_1) less than 30% predicted. Respiratory failure in the absence of such severely decreased lung function is a criterion for very severe COPD. Respiratory failure may lead to secondary effects on the heart, known as cor pulmonale, or right heart failure. The clinical signs of cor pulmonale include jugular venous pressure elevation and pitting ankle edema. Patients at this very severe stage have end-organ dysfunction related to COPD, and exacerbations may be life-threatening. (3)

Respiratory failure is classified as type I (hypoxemic) respiratory failure or type II (hypercapnic) respiratory failure. In hypoxemic respiratory failure, PaO_2 is decreased to less than 60 mm Hg, and the arterial pressure of carbon dioxide ($PaCO_2$) is normal or low. (4) Clinical signs of hypoxemia include restlessness, confusion, and coma. In hypercapnic respiratory failure, PaO_2 is also low, but $PaCO_2$ is increased. Clinical signs of hypercapnia include drowsiness, flapping tremor, warm peripheries, headaches, and a bounding pulse. (5) About 10 to 15% of patients with COPD have type II respiratory failure. (4)

The normal range for PaO_2 is 80 to 100 mm Hg, and the normal range for $PaCO_2$ is 35 to 45 mm Hg. (5) Normally, elevated $PaCO_2$ stimulates respiratory drive to reduce these levels through increased breathing. This stimulation is diminished, however, in type II respiratory failure, and low PaO_2 triggers hypoxic drive instead. (4)

The management goal in treating respiratory failure is to reverse hypoxemia while preventing further increases in hypercapnia, which can be fatal in people who retain carbon dioxide (CO_2). Hypoxic drive is needed to maintain respiration in CO_2 retainers. (5) A clinical safety dilemma arises because oxygen therapy may decrease respiration in type II respiratory failure, but withholding oxygen from a patient with COPD who is hypoxemic may be detrimental. (4)

Oxygen therapy can reverse hypoxemia. (2) Indications for oxygen therapy include respiratory failure and an increased respiratory rate. The following conditions, which are associated with hypoxemia, may require oxygen therapy: cardiac respiratory arrest, acute myocardial infarction with reduced cardiac output, severe trauma, anemia, infection, general anesthesia, and surgical procedures. (4) Patients with COPD may have difficulty obtaining enough oxygen from inspired air and may benefit from oxygen therapy. (1) The purpose of oxygen therapy is to correct the deficiency of oxygen in arterial blood and prevent tissue hypoxia. (6)

Long-term oxygen therapy is extended use of oxygen. Oxygen therapy needs vary depending on activity levels. Patients with daytime resting hypoxemia may need LTOT during sedentary periods, when they are typically resting at home or performing nonstressful domiciliary activities of daily living. Increased activity levels, such as casual walking, may require ambulatory or supplemental oxygen to meet higher systemic demands. Patients with COPD have decreased sensitivity to the normal neurochemical control of breathing during sleep, which results in nocturnal oxygen desaturation. As a result, nocturnal oxygen therapy may be needed. Some guidelines recommend increasing the oxygen dose during periods of extended exercise and during sleep. (7;8)

At higher altitudes, decreased atmospheric pressure reduces the partial pressure of oxygen in the air. Patients living at or travelling to higher altitudes may also require supplemental oxygen. Episodes of breathlessness in patients with COPD may require short-burst oxygen therapy, or palliative oxygen therapy. (7;8) Long-term oxygen therapy may be given after an acute exacerbation of COPD, and the need for LTOT should be reassessed after an exacerbation. Home LTOT is a potential risk factor for relapse after acute exacerbation. (9) When acute exacerbations are treated in hospital, oxygen therapy is titrated to achieve a PaO_2 above 60 mm Hg (> 8 kilopascals [kPa]) or oxygen saturation measured by pulse oximetry (SpO_2) greater than 90%. The goal is to achieve adequate oxygenation without promoting CO_2 retention or acidosis. (3)

The role of LTOT in COPD is based on 2 landmark randomized controlled trials (RCTs) of patients with COPD. In the first trial, (10) LTOT for 15 hours per day, including nocturnal therapy, was compared with no LTOT in patients with COPD, who had severe airflow limitation (FEV_1: 0.58–0.76 L), severe hypoxemia (PaO_2: 49–52 mm Hg), hypercapnia ($PaCO_2$: 53–60 mm Hg), and mild pulmonary hypertension. The oxygen flow rate was at least 2 L/minute but sufficient to achieve a PaO_2 above 60 mm Hg. Study findings demonstrated that LTOT improved survival, a primary outcome. No between-group differences were seen in pulmonary hemodynamics, among secondary outcomes of the trial. The 15-hour period was based on its ability to reduce pulmonary arterial pressure. (11) In a second trial, (12) continuous use of LTOT was compared with nocturnal oxygen therapy in patients with COPD who had severe hypoxemia (PaO_2 < 56 mm Hg) or moderate hypoxemia (PaO_2 < 60 mm Hg) with edema, polycythemia (hematocrit > 54%), or P pulmonale, an electrocardiographic finding. The relative risk (RR) of death for nocturnal oxygen was about twice that for continuous LTOT (RR, 1.94: 95% confidence interval [CI], 1.17–3.24). Continuous LTOT was associated with a beneficial clinical profile, decreased hematocrit levels, and reduced pulmonary vascular resistance compared with nocturnal use. Mean daily duration of oxygen use was 17.7 hours in the continuous LTOT group and 12 hours in the nocturnal oxygen therapy group. (13)

The results of these trials indicate that some oxygen is better than none, and that when oxygen is given, continuous use is better than nocturnal use. The way in which oxygen prolongs survival is not known. (2) A remaining question is whether LTOT confers a survival advantage in mild-to-moderate hypoxemia[2] (PaO_2: 56-65 mm Hg) and during exercise or sleep. (13)

Canadian Context

The Canadian Thoracic Society recommends patients with stable COPD and severe hypoxemia ($PaO_2 \leq$ 55 mm Hg), or less severe hypoxemia (PaO_2 < 60 mm Hg) with at least 1 additional factor of bilateral ankle edema, cor pulmonale, or hematocrit above 56%, receive LTOT for at least 15 hours per day to achieve an oxygen saturation of at least 90%. (14) The number of people using LTOT in Canada is not known.

[2] The mild-to-moderate classification was created for the purposes of the report.

Ontario Context

The Assistive Devices Program administers oxygen therapy in Ontario. Eligibility criteria for LTOT under the Ministry of Health and Long-Term Care are consistent with Canadian guidelines ($PaO_2 \leq 55$ mm Hg or $PaO_2 < 60$ mm Hg with comorbidities). Patients with persistent hypoxemia (PaO_2: 56–60 mm Hg), exercise-limiting hypoxemia documented to improve with supplemental oxygen, or nocturnal hypoxemia, are also eligible for LTOT, as are patients with exertional hypoxemia without hypoxemia at rest. In summary, the eligibility criteria for LTOT in Ontario are: 1) severe hypoxemia, 2) mild-to-moderate hypoxemia with specific comorbidities, 3) mild-to-moderate hypoxemia plus exercise-limiting hypoxemia or nocturnal hypoxemia, 4) exertional hypoxemia without hypoxemia at rest. (15;16)

To confirm eligibility for LTOT, oximetry testing is required for applicants younger than 18 years, and arterial blood gas determination is required for applicants older than 19 years. Oximetry testing for application renewal for Ontario's home oxygen program is required at the 90-day period and 12-month period to determine whether eligibility criteria are being met. Oximetry test results are required for patients renewing their funding annually. The oximetry tests must monitor the oxygen level for at least 5 continuous minutes and demonstrate hypoxemia for at least 2 continuous minutes. Uncertain oximetry test results must be confirmed with arterial blood gases. (15;16)

Oxygen prescription in Ontario is based on oxygen titration at a pulmonary function laboratory or assessment in the person's home by the oxygen vendor. The method used depends on the prescribing physician and availability of the pulmonary function laboratory (Personal communication, expert, November 7, 2011). Titration determines oxygen needed at rest and while walking to achieve an SpO_2 of about 90% with a flow rate that prevents CO_2 build-up in people prone to retaining CO_2. The flow rate at rest is used as the nocturnal flow rate. Either the respirologist or the family physician completes the required prescription, and the respirologist may contact the oxygen company. Reassessment occurs as necessary (Personal communication, clinical expert, November 4, 2010).

Patient need determines the choice of oxygen delivery system. Until April 2010, the Home Oxygen Program funded any combination of oxygen supply delivery systems, such as home oxygen concentrator and portable compressed gas cylinder, or home oxygen concentrator and portable liquid oxygen, without tracking the system that patients received. After April 2010, the vendor was required to provide the details of the oxygen delivery system that patients used. As a result, the provincial government is now able to track the systems patients in Ontario are using. Most patients receive a home oxygen concentrator and a second portable system (Personal communication, expert, January 19, 2011).

Technology

An oxygen source delivers oxygen as a gas. The different oxygen sources are: 1) oxygen concentrators, electrical units delivering oxygen that has been converted from room air; 2) liquid oxygen systems, delivering gaseous oxygen stored as liquid in a tank; and 3) oxygen cylinders, which contain compressed gaseous oxygen. All have portable versions. Oxygen is breathed in through a nasal cannula or through a mask covering the mouth and nose. The treating physician determines the flow rate, duration of use, method of administration, and oxygen source according to individual needs. A critical point with oxygen therapy is that the therapy is only effective while it is being used. (17)

Safety

Limited work has been performed on the safety of oxygen therapy. Oxygen itself is not flammable, but it accelerates a fire source, such as a lit cigarette. Patient safety education includes the hazards of oxygen use and initial training on equipment, including demonstration of skills needed to operate the equipment safely and independently. Another hazard is falls due to oxygen tubing. (18;19) Underuse of oxygen is

also a safety issue, and it is responsible for deaths and permanent disability. A small risk is associated with high-dose oxygen among CO_2 retainers. (5)

Evidence-Based Analysis

Research Questions

What is the effectiveness, cost-effectiveness, and safety of LTOT compared with no LTOT in patients with COPD, who are stratified by severity of hypoxemia?

Research Methods

Literature Search

Search Strategy

A literature search was performed on September 8, 2010 using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2007 until September 8, 2010.

A single clinical epidemiologist reviewed the abstracts, obtained full-text articles for studies meeting the eligibility criteria, and examined reference lists for additional relevant studies not identified through the literature search. A second clinical epidemiologist and then a group of epidemiologists reviewed articles with an unknown eligibility until consensus was established.

Inclusion Criteria

- patients with mild, moderate, or severe hypoxemia;
- English-language articles published between January 1, 2007 and September 8, 2010;
- journal articles reporting on effectiveness, cost-effectiveness, or safety for the comparison of interest;
- clearly described study design and methods;
- health technology assessments, systematic reviews, randomized controlled trials, or prospective cohort observational studies;
- any type of observational study for the evaluation of safety.

Exclusion Criteria

- no hypoxemia
- non-English papers
- animal or in vitro studies
- case reports, case series, or case-case studies
- studies comparing different oxygen therapy regimens
- studies on nocturnal oxygen therapy
- studies on short-burst, palliative, or ambulatory oxygen (supplemental oxygen during exercise or activities of daily living)

Outcomes of Interest

- mortality/survival
- hospitalizations

- readmissions
- FEV_1
- forced vital capacity (FVC)
- FEV_1/FVC
- pulmonary hypertension
- PaO_2
- $PaCO_2$
- end-exercise dyspnea score
- endurance time
- health-related quality of life (HRQOL)

Note: Outcomes of interest were formulated according to existing studies, with arterial pressure of oxygen and carbon dioxide as surrogate outcomes.

Statistical Analysis

An analysis of individual studies was performed using Review Manager version 5. The analysis section describes details of the analyses. No formal meta-analysis was performed. Mean difference was calculated for continuous data, and RR was calculated for dichotomous RCT data. A change value was calculated for continuous variables with available mean baseline and follow-up data as the difference between these 2 mean values. Standard deviation (SD) accounting for baseline and follow-up SD was calculated from 3 parameters: baseline SD, follow-up SD, and a correlation coefficient, which represents the strength of the relationship between the 2 SDs. A correlation coefficient of 0.5 was used for this analysis. Forest plots were also examined.

Quality of Evidence

The quality of each included study was assessed taking into consideration the following 7 study design characteristics:

- adequate allocation concealment,
- randomization (study must include a description of the randomization procedure used and must be a proper method),
- power/sample size (adequate sample size based on a priori calculations, underpowered studies were identified, when possible, using post hoc sample size power calculations),
- blinding (if double blinding is not possible, a single blind study with unbiased assessment of outcome was considered adequate for this criterion),
- < 20% withdrawals/dropouts,
- intention-to-treat analysis conducted and done properly (withdrawals/dropouts considered in analysis), and
- other criteria as appropriate for the particular research question and study design.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (20) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding, and follow-up.

- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

The database search yielded 1,096 citations published between January 1, 2007 and September 8, 2010 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded in the analysis. Three systematic reviews met the inclusion criteria.

For each included study, the study design was identified and is summarized below in Table 1, which is a modified version of a hierarchy of study design by Goodman. (21)

Table 1: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
Randomized Controlled Trials	
Systematic review of RCTs	2
Large RCT†	-
Small RCT	-
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	1
Non-RCT with contemporaneous controls	-
Systematic review of non-RCTs with historical controls	-
Non-RCT with historical controls	-
Database, registry, or cross-sectional study	-
Case series	-
Retrospective review, modelling	-
Studies presented at an international conference or other sources of grey literature	-
Expert opinion	-
Total	3

*Abbreviation: RCT, randomized controlled trial.

†Large RCT ≥ 150 subjects.

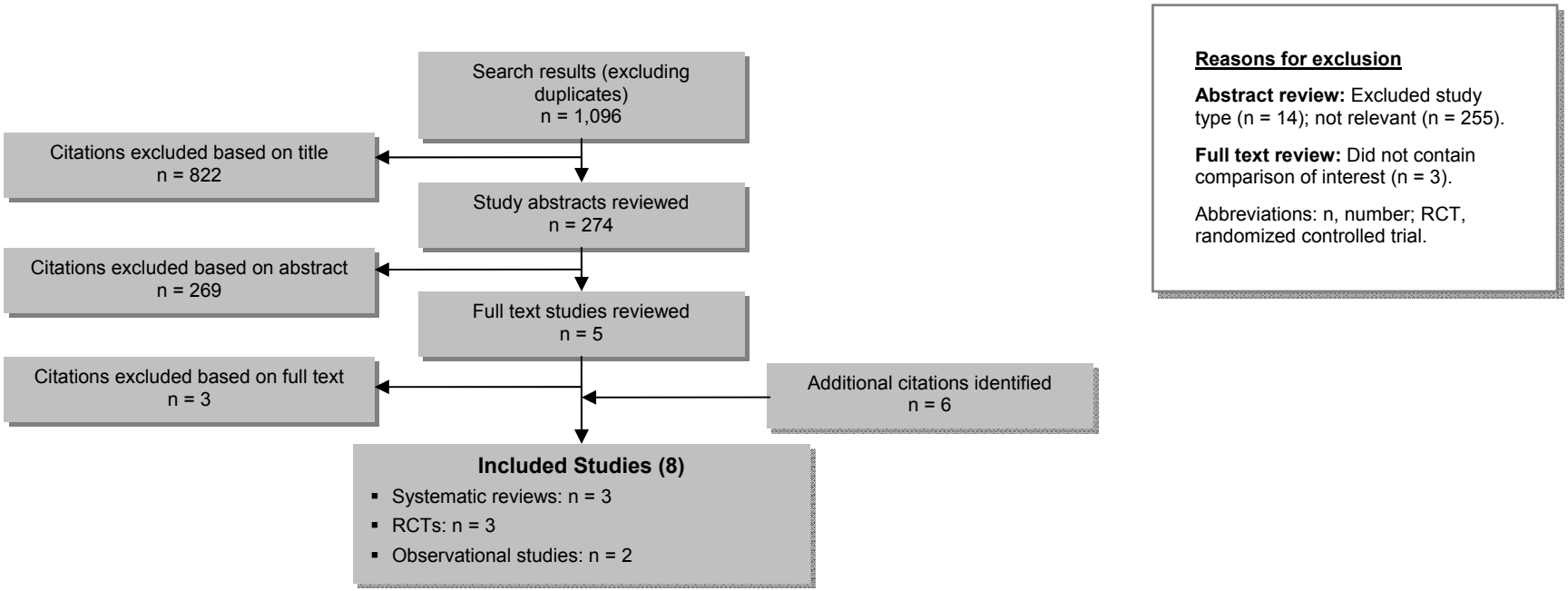


Figure 1: Citation Flow Chart*

Randomized Controlled Trials

Long-Term Oxygen Treatment Trial

The Long-Term Oxygen Treatment Trial sponsored by the National Heart, Lung, and Blood Institute and Centers for Medicare & Medicaid Services is an ongoing phase 3 trial. This multicentre RCT is being performed in the United States and is following 1,134 patients with moderate resting hypoxemia for up to 4.5 years and comparing continuous LTOT (24 hours/day) with no LTOT to determine whether continuous LTOT prolongs time to all-cause mortality or hospitalization. Among other secondary outcome measures, the trial is evaluating HRQOL.

The intervention includes oxygen at rest and during sleep at 2 L/min via nasal cannula. Supplemental oxygen is used for people with normal blood oxygen levels at rest but low or very low blood oxygen levels during exercise. The supplemental oxygen dose aims to achieve an SpO_2 of at least 90% for at least 2 minutes during walking. Participants with resting hypoxemia are instructed to use oxygen 24 hours per day, whereas those with normal resting blood oxygen levels but low or very low blood oxygen levels during exercise are instructed to use oxygen during physical activity and sleep. Eligible individuals are older than 39 years, have COPD defined as postbronchodilator FEV_1 less than 66% predicted or FEV_1/FVC less than 0.70, and have dyspnea. It is estimated the study will be completed by May 2013. (13;22) Results of this trial may provide information about safety, efficacy, and cost-effectiveness of LTOT.

Cochrane Review

One of the largest systematic reviews and meta-analyses of LTOT RCTs was published as a Cochrane review. (23) The objective of the review was to examine the effect of domiciliary LTOT on survival, quality of life, and physiological measures. The review included articles published up to January 2007. Six identified RCTs are summarized individually and in Appendix 3, Tables A8 and A9, and reviewed by severity of hypoxemia according to standard definitions (Existing Guidelines for Long-term Oxygen Therapy). The studies on nocturnal oxygen therapy and the study on patients with COPD without hypoxemia were not eligible for this evidence-based analysis and are not included.

Severe Hypoxemia

Survival

A multicentre RCT performed by the Medical Research Council (MRC) Working Group (10) in the United Kingdom compared the effect of LTOT with no LTOT on survival in 87 patients with stable COPD (chronic bronchitis or emphysema with irreversible airway obstruction) and severe hypoxemia (40–60 mm Hg). Inclusion criteria included patient age less than 70 years and at least 1 episode of heart failure with ankle edema. Patients taking drug therapy and current smokers were included. Exclusion criteria included fibrotic or infiltrative lung disease, pneumoconiosis, severe kyphoscoliosis, pulmonary embolism, hypertension, coronary artery disease, or other unspecified life-threatening diseases. A random numbers table randomly allocated participants. Oxygen sources were oxygen from a concentrator, liquid oxygen, and oxygen from cylinders. The 3 study sites measured adherence differently: weighing cylinders, recording time of use, or performing random visits.

Duration of follow-up was 5 years. One participant in the treatment group withdrew from the study. Baseline age and clinical and physiological factors were comparable between groups. Overall, 19 of 42 (45.2%) patients in the treatment (LTOT) group died and 30 of 45 (66.7%) patients in the control (CT) group died (*P* not given). Examination of the results by sex for the 66 men and 21 women in the trial found a lower risk of death for women in the LTOT group (5.7%) compared with the CT group (36.5%, $P < 0.05$). A mortality difference between the groups for men emerged only after 500 days (LTOT 12% vs. CT 29%, $P = 0.04$). Rates of change for PaO_2, $PaCO_2$, and pulmonary vascular resistance were favourable

for survivors receiving LTOT. The authors concluded that LTOT confers a survival advantage for both men and women with severe hypoxemia and cor pulmonale.

Mild-to-Moderate Hypoxemia

Survival

A multicentre RCT performed by Gorecka et al (24) in Poland compared the effect of LTOT with no LTOT on survival in 135 patients with stable COPD and moderate hypoxemia (56–65 mm Hg). Participants were aged 40 to 80 years, were not smokers, and received usual or conventional medical treatment. Exclusion criteria included serious organ disease other than lung disease. Centrally developed randomization schedules randomly allocated patients to treatment assignments using computer-generated random numbers. An oxygen concentrator provided oxygen, and a built-in meter monitored adherence.

Follow-up duration was at least 3 years or until death. There were no dropouts. Baseline data were comparable between the treatment (LTOT) and CT groups, except for mean PaO_2, which was slightly lower in the LTOT group (mean PaO_2 59.5 mm Hg, SD 2.7) than in the CT group (PaO_2 61.3 mm Hg, SD 2.7, $P < 0.05$). The preliminary sensitivity analysis, however, found no effect of PaO_2 on survival. With up to 7 years' follow-up, no difference was seen in survival between the LTOT group (38/68, 55.9%) and the CT group (32/67, 47.8%, $P = 0.89$). Among surviving participants, mean PaO_2 levels were lower in the LTOT group (mean PaO_2 59.6 mm Hg, SD 2.9) than in the CT group (PaO_2 61.2 mm Hg, SD 2.7, $P < 0.05$). No differences were seen among surviving participants between the LTOT and CT groups in $PaCO_2$, FEV_1 percent predicted, vital capacity (VC) percent predicted, or FEV_1/VC. The authors concluded that LTOT does not provide a survival advantage in patients with COPD who have chronic airflow obstruction and moderate hypoxemia.

Survival and Exercise Parameters

A randomized single-institution study by Haidl et al (25) in Germany compared the effect of LTOT with no LTOT on survival and exercise parameters in 28 patients with stable COPD and mild hypoxemia ($PaO_2 > 55$ mm Hg). Patients had been admitted for an acute exacerbation of COPD that included reversible hypercapnia ($PaCO_2 > 45$ mm Hg). Exclusion criteria were malignant disease, left heart failure, or other severe comorbidities, such as advanced renal failure or severe diabetes. Patients were randomly allocated to treatment groups, but randomization details were not provided. An oxygen concentrator provided oxygen. Patients' self-reported duration of oxygen use from the built-in meter determined adherence.

Duration of follow-up was up to 3 years. Only 13 of the original 28 patients (46.4%) remained at the end of 3 years. Baseline data were comparable in both groups except for mean body mass index (BMI), which was slightly higher in the LTOT group (BMI 26.2 kg/m^2, SD 3.7) than in the CT group (BMI 23.7 kg/m^2, SD 3.8, $P = 0.05$). At the start of the study, each group included 3 smokers (21.4%). Survival was comparable in both groups: over 3 years, 4 of the original 14 patients (28.6%) in the LTOT group and 3 of the 14 patients (21.4%, *P* not given) in the CT group died.

At 1 year, mean endurance time in the LTOT group (7.1 minutes, SD 4.1) was greater than in the CT group (4.9 min, SD 3.8 minutes, $P = 0.04$) and mean perceived end-exercise dyspnea was lower in the LTOT group (4.5 minutes, SD 1.5) than in the CT group (5.7 minutes, SD 1.9, $P = 0.03$). No differences were seen for $PaCO_2$, PaO_2, or FEV_1 percent predicted between the groups at 1 year. The authors concluded that LTOT in patients with COPD who have mild hypoxemia and reversible hypercapnia helped to stop the natural decline in exercise performance and reduced dyspnea. The biological basis of this effect is not known.

Results of the Cochrane Review

The objective of the Cochrane review was to determine the effect of domiciliary LTOT on survival and quality of life in patients with COPD and hypoxemia. The literature search identified 6 studies for inclusion. (10;12;24-27) The authors scored the methodological quality of 5 of the 6 studies as moderate (10;12;24;26;27) and of the remaining study as low. (25) Data analysis was performed by degree of hypoxemia. Data from 2 studies on mild-to-moderate hypoxemia and nocturnal oxygen therapy were analyzed together (26;27), and data from 2 studies on mild-to-moderate hypoxemia and LTOT were analyzed together. (24;25) Although the 2 remaining studies both evaluated patients with severe hypoxemia, they were analyzed separately, due to differences in interventions and study populations. (10;12)

Standard meta-analysis was performed, including calculating a Peto odds ratio (OR) for dichotomous data. Detailed results are presented (Appendix 3, Table A9) only for studies relevant for this evidence-based analysis. Study design characteristics included in the Cochrane review and relevant for this evidence-based analysis are summarized in Appendix 3, Tables A8 to A11. A discussion of results for studies from the Cochrane review that are relevant for this evidence-based analysis follows.

Severe Hypoxemia: Mortality and Physiological Factors

Analysis of the MRC study (10) compared the effect of LTOT on mortality and physiological factors with no LTOT in highly selected patients with severe hypoxemia and possible episodes of heart failure and ankle edema. After 5 years of follow-up, patients receiving LTOT were less likely to die than patients receiving no LTOT (OR 0.42, 95% CI, 0.18–0.98; $P = 0.045$).

Rates of change for a subset of physiological factors were analyzed for men who died at 500 days or less and for men surviving more than 500 days, as in the original article. Factors discussed here include weight, FEV_1, FVC, PaO_2, and $PaCO_2$. Rates of change for FEV_1 (mean difference [MD] 0.08 L, 95% CI 0.04, 0.12; $P < 0.001$), FVC (MD 0.56 L, 95% CI 0.12, 1.00; $P < 0.012$), and $PaCO_2$ (MD −2.16 mm Hg, 95% CI: −4.04 to −0.28; $P < 0.03$) favoured LTOT. Therefore, among patients surviving more than 500 days, patients receiving LTOT had increased FEV_1 and decreased $PaCO_2$ compared with patients not receiving LTOT. An improvement in FVC was shown among nonsurvivors. The remaining physiological factors were similar in both groups. Change data were determined from 2 monthly values in the original article; the timing of the values was not described. Pulmonary arterial pressure was not analyzed in the Cochrane review, as no patients with data on pulmonary arterial pressure died. No data were available for FEV_1/FVC.

Mild-to-Moderate Hypoxemia: Mortality and Exercise Factors

The studies by Gorecka et al (24) and Haidl et al (25) were analyzed together, because both included patients with mild-to-moderate hypoxemia and compared LTOT with no LTOT. Analysis identified no difference between groups for mortality (OR, 1.39; 95% CI, 0.74–2.59), with an index of heterogeneity of 0%. Only Gorecka et al (24) performed a survival analysis and only Haidl et al (25) compared the effect of continuous LTOT with no LTOT on exercise factors in patients with mild-to-moderate hypoxemia. At 1 year, the groups were similar in end-exercise dyspnea score (MD, −1.20; 95% CI, −2.47 to 0.07) and endurance time (MD, 2.20 minutes; 95% CI, −0.73 to 5.13), in contrast to the original study, which showed small differences at 1-year follow-up in mean dyspnea between the LTOT group (4.5, SD 1.5) and the CT group (5.7, SD 1.9, $P = 0.03$) and in mean endurance time between the LTOT group (7.1 minutes, SD 4.1) and the CT group (4.9 minutes, SD: 3.8, $P = 0.04$).

The authors of the Cochrane review concluded that LTOT improved survival in selected patients with COPD with severe hypoxemia but did not improve survival in patients with COPD with mild-to-moderate hypoxemia. (23)

Additional Studies, Systematic Reviews, and Meta-Analyses

Mortality

Wilt et al (28) performed a second systematic review and meta-analysis of RCTs of LTOT that identified 8 RCTs and 1 systematic review published up to March 2007. This review included articles that have already been discussed in the Cochrane review. (10;12;24;27) Sin et al (29) performed an earlier systematic review that identified 7 RCTs, most of which were also discussed in the Cochrane review (10;12;24;26;27) and the Wilt et al review. (10;12;24;27;30-32) The other studies included in the Wilt et al review investigated ambulatory oxygen therapy (30-33) and are not relevant for this evidence-based analysis.

Wilt et al concluded that LTOT for at least 15 hours daily to maintain a PaO_2 greater than 60 mm Hg reduces mortality among patients with COPD, who have an FEV_1 less than 30% predicted and a mean resting PaO_2 less than or equal to 55 mm Hg. This conclusion is based on good evidence with a Mantel-Haenszel relative risk ratio summary estimate of 0.61 (95% CI, 0.46–0.82) for the 2 studies on severe hypoxemia combined. (10;12) The 2 studies of patients with PaO_2 greater than 60 mm Hg demonstrated no benefit for LTOT (RR, 1.16; 95% CI, 0.85–1.58). (24;27)

Hospitalization and Readmissions

A systematic review of observational studies (34) of risk factors for hospital admission or readmission among patients experiencing COPD exacerbations identified and included 17 studies published up to October 2006. Two prospective cohort studies, 2 retrospective cohort studies, 1 case-control study, and 1 cross-sectional study examined LTOT. The authors of the systematic review concluded that the evidence related to hospital admission and readmission is equivocal and requires further study. The 2 prospective studies were not analyzed together because they described different outcomes (readmission vs. hospitalization), nor were they individually analyzed, as suitable data were lacking.

Among the cohort studies, only 1 prospective cohort study included an adjusted analysis for hospital readmissions. (35) Analysis found no statistically significant difference between LTOT and no LTOT for the risk of hospital readmission (hazard ratio, 1.26; 95% CI, 0.87–1.84; $P = 0.22$). This multicentre prospective study, conducted in Barcelona, examined the association between readmission for a COPD exacerbation and several modifiable risk factors. The sampling scheme, diagnosis of COPD, exacerbation, readmission, death, analysis, and follow-up were well defined. The population was mostly men with a mean age of 69 years, severe COPD (mean FEV_1 36% predicted), and mild-to-moderate hypoxemia (mean PaO_2 64 mm Hg). Mean follow-up was 1.1 years. Sensitivity analyses had no effect on the results. The authors concluded that no association existed between readmission and factors relating to medical care. The main limitations of the study are the potential for confounding by unmeasured factors in observational studies and the potential for heterogeneity in the comparison, with individuals using LTOT having severe hypoxemia and those not using LTOT having mild-to-moderate hypoxemia, although this was not well described.

The second prospective cohort study was a single-centre study (36) that used well-defined parameters to examine predictive factors for hospitalization for acute exacerbation in a stable COPD population. The study recruited consecutive patients and followed them for an exacerbation, defined by American Thoracic Society criteria and using quarterly visits and hospitalization. The population was mostly men with a mean age of 64 years, severe COPD (mean FEV_1 39% predicted), and mild-to-moderate hypoxemia (mean PaO_2 66 mm Hg). Ten of 64 patients with COPD, who had severe hypoxemia, were receiving LTOT. This study found that the cumulative proportion of patients using home LTOT at 1-year follow-up, who were free of hospitalization due to an exacerbation (38.5%), was lower than the proportion of patients not using LTOT (77%, $P = 0.01$). Limitations of the study include its small sample

size, lack of a random sampling scheme, unmeasured confounders, absence of multivariable analysis for home LTOT, and heterogeneity in the comparison.

An additional prospective cohort study identified by the systematic search, which examined factors associated with revisiting the emergency department for an exacerbation, was excluded because the authors considered all patients to be using oxygen therapy and did not describe the nature of the oxygen therapy. (37)

Safety

Only 1 study included in the Cochrane review described a lack of evidence for toxicity of LTOT. (10) No other individual study mentioned adverse effects of LTOT by severity of hypoxemia.

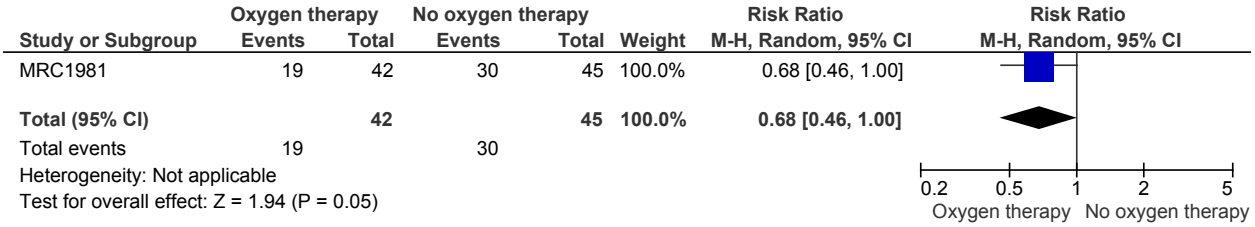
Analysis

Examination of the research question of effectiveness of LTOT compared with no LTOT in patients with COPD by severity of hypoxemia analyzed mortality, lung function, and exercise factors. Analysis of lung function and exercise factors uses change values, which include the maximum amount of data compared with analysis of follow-up data only and show the difference between mean baseline and follow-up values.

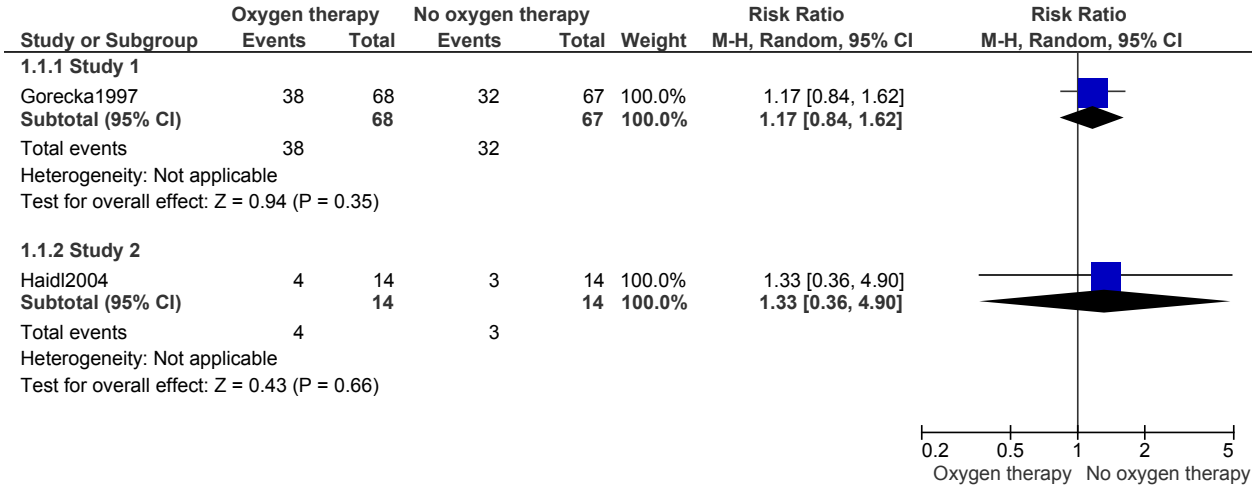
No data were available for exercise factors in patients with COPD who had severe hypoxemia. (10) Gorecka et al (24) followed patients for 7 years but did not specify the time at which lung function factors were measured. Haidl et al (25) measured lung function and exercise factors at 1 year. Lung function data are presented by survivors and nonsurvivors separately, as shown in the study by Gorecka et al, (24) and consistent with the presentation of data in the Cochrane review. (23) Presentation of results by survivors and nonsurvivors is a limitation of the published data on lung function. The results on lung function presented here are not combined with data from the Cochrane review, as the study populations differed in degree of hypoxemia. Exercise data in the study by Haidl et al (25) are not presented by survivors and nonsurvivors, but for survivors only.

Data from the 2 studies evaluating mild-to-moderate hypoxemia patients with COPD are not combined. A formal meta-analysis was not performed, nor was a summary estimate calculated, due to different follow-up lengths (7 vs. 3 years for mortality, and up to 7 years vs. 1 year for lung function), and the potential for clinical heterogeneity. Estimates for lung function and exercise factors are interpreted as the change over time for a given factor. Interpretation of the results differs based on the direction of change and the factor. A positive change over time is favourable for FEV_1, FEV_1/FVC, FVC, PaO_2, and endurance time, suggesting an increase in lung function or exercise capacity. A negative change over time is favourable for $PaCO_2$ and the dyspnea score, suggesting a decrease in adverse factors.

Results of the mortality analysis define a beneficial effect of LTOT compared with no LTOT as decreased risk, or an RR less than 1.0. Results of the lung function and exercise analysis results define a beneficial effect of LTOT compared with no LTOT as a mean difference that is a negative number less than 1.0. Authors were contacted for additional data as necessary. Measures of PaO_2 and $PaCO_2$ are considered indirect surrogate measures. The analyses are presented consistently in Figures 2-11 below.



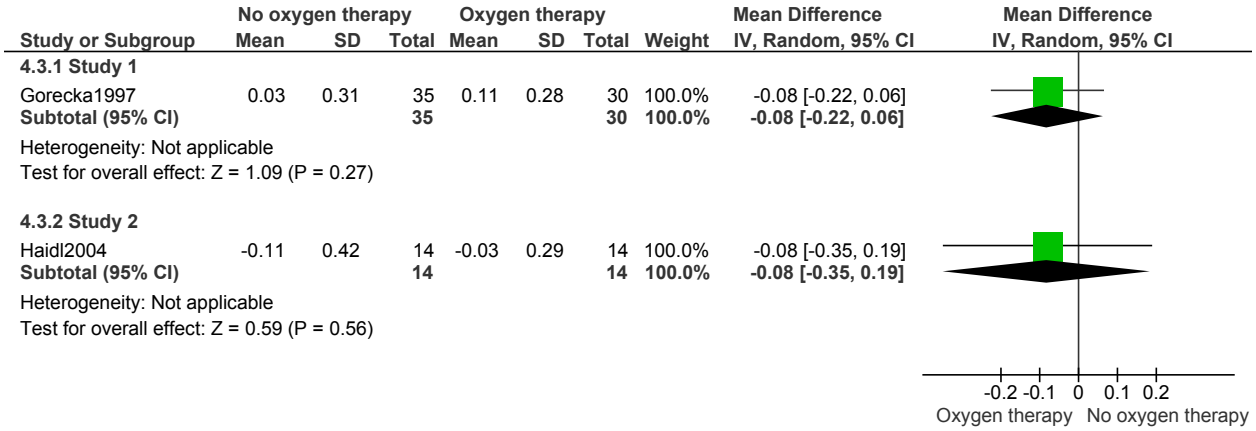
a) Severe Hypoxemia



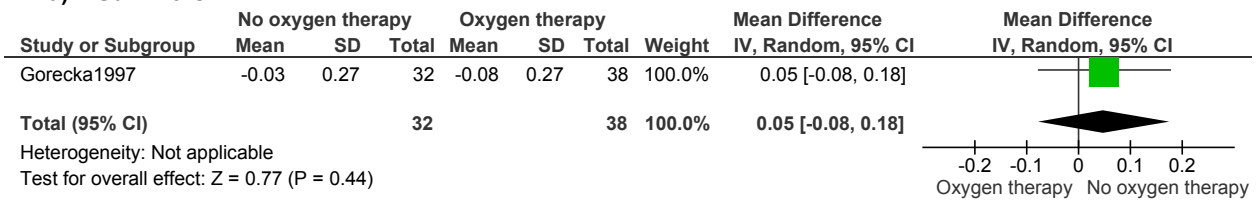
b) Mild-to-Moderate Hypoxemia†

Figure 2: Mortality (Number of Events)*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.
†Study 1 reports 7 years' follow-up and study 2 reports 3 years' follow-up.



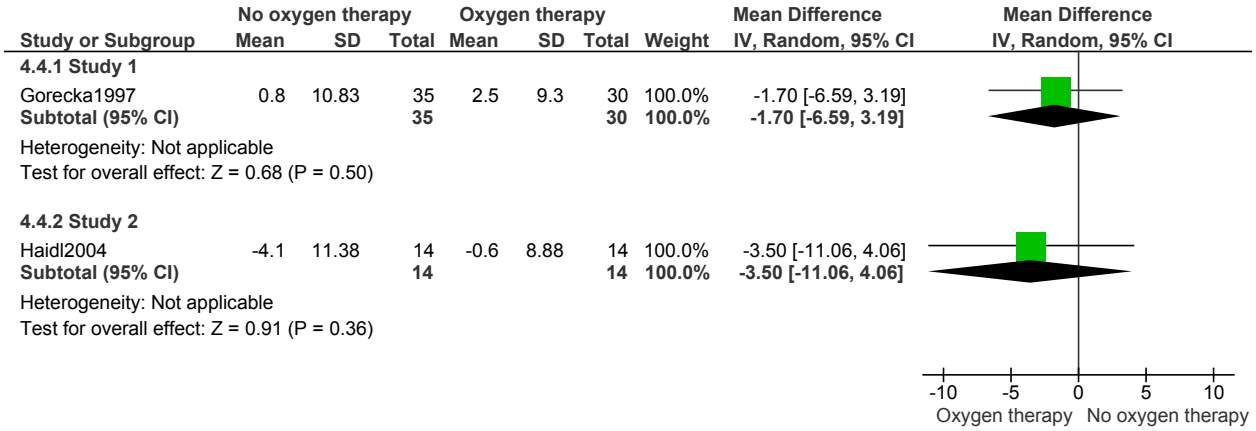
a) Survivors†



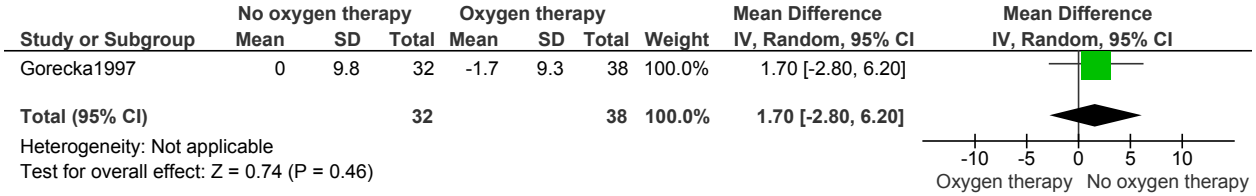
b) Nonsurvivors‡

Figure 3: Forced Expiratory Volume in One Second (Litres)*

*Abbreviations: CI, confidence interval; SD, standard deviation.
†Study 1 reports up to 7 years' follow-up and study 2 reports 1 year's follow-up.
‡Gorecka et al (24) reports 7 years' follow-up.



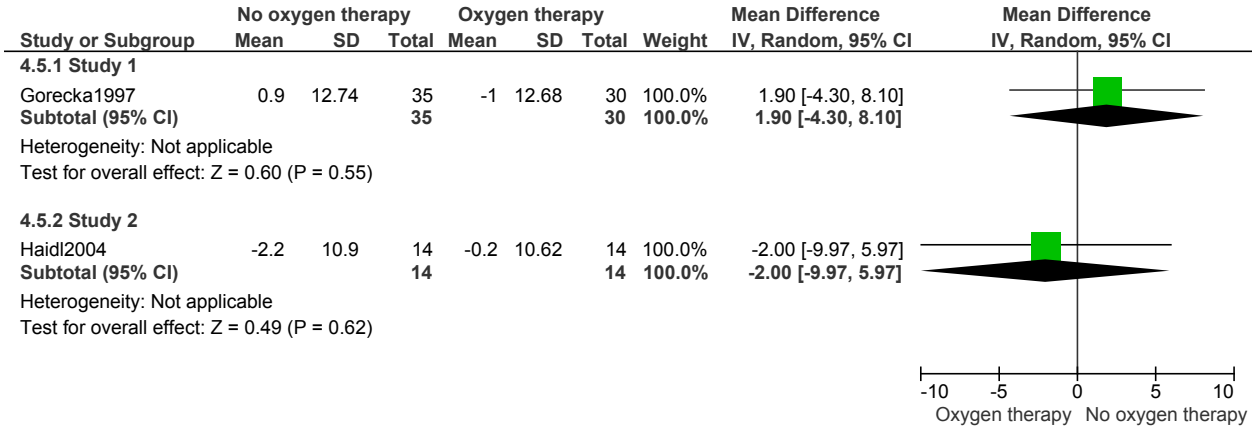
a) Survivors†



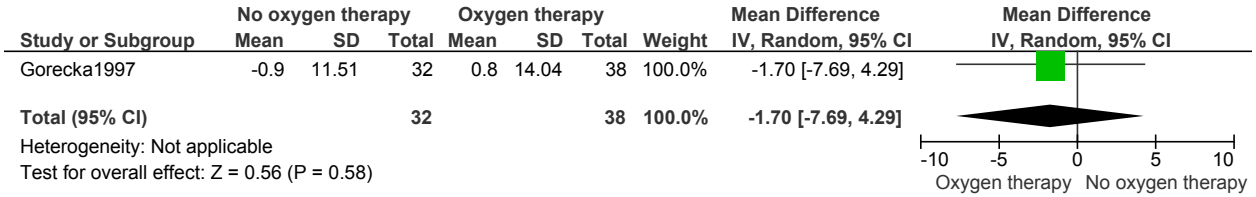
b) Nonsurvivors‡

Figure 4: Forced Expiratory Volume in One Second (% Predicted)*

*Abbreviations: CI, confidence interval; SD, standard deviation.
†Study 1 reports up to 7 years' follow-up and study 2 reports 1 year's follow-up.
‡Gorecka et al (24) reports 7 years' follow-up.



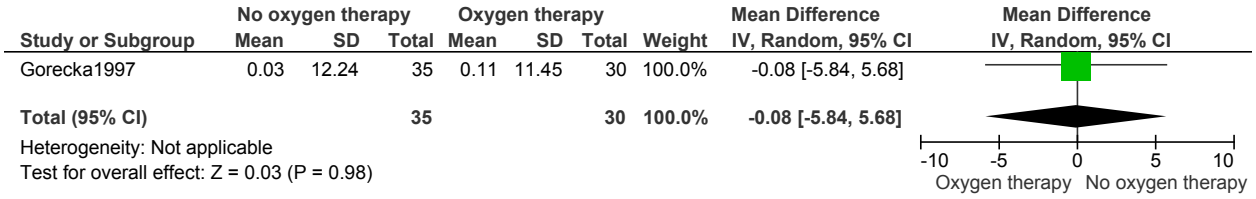
a) Survivors†



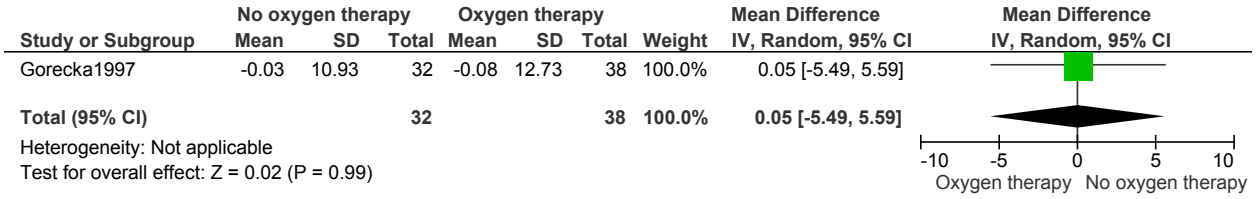
b) Nonsurvivors‡

Figure 5: Forced Expiratory Volume in One Second by Forced Vital Capacity (%)*

*Abbreviations: CI, confidence interval; SD, standard deviation.
†Study 1 reports up to 7 years' follow-up and study 2 reports 1 year's follow-up.
‡Gorecka et al reports 7 years' follow-up.



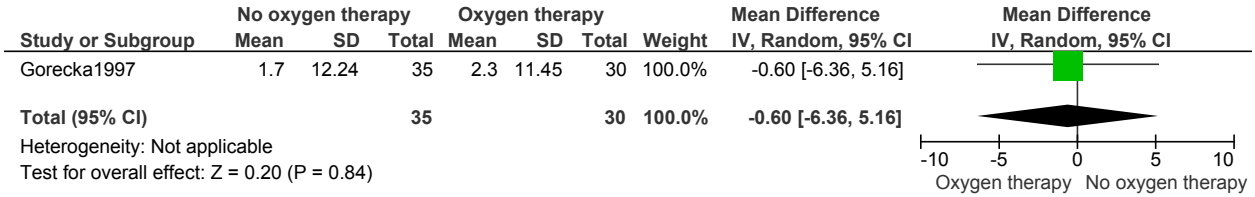
a) Survivors†



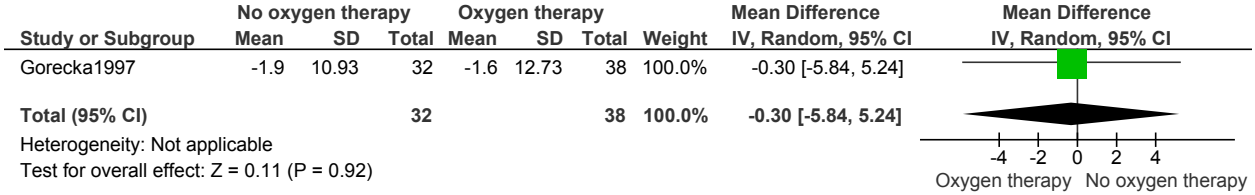
b) Nonsurvivors†

Figure 6: Forced Vital Capacity (Litres)*

*Abbreviations: CI, confidence interval; SD, standard deviation.
†Gorecka et al (24) reports up to 7 years' follow-up.



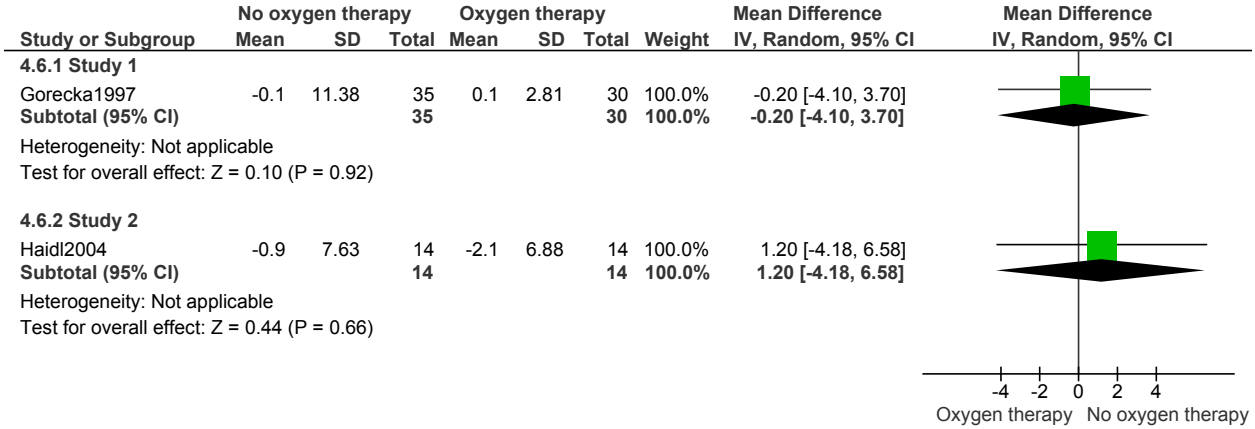
a) Survivors†



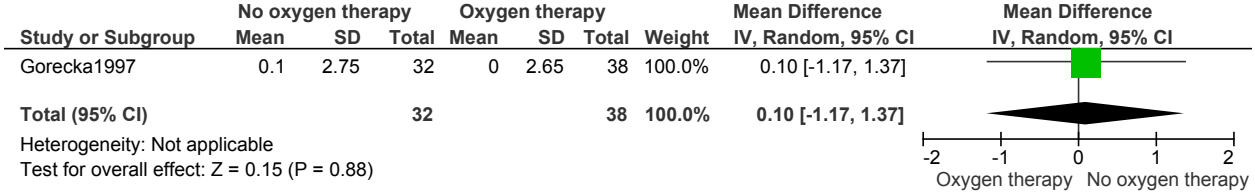
b) Nonsurvivors†

Figure 7: Forced Vital Capacity (% Predicted)*

*Abbreviations: CI, confidence interval; SD, standard deviation.
†Gorecka et al (24) reports up to 7 years' follow-up.



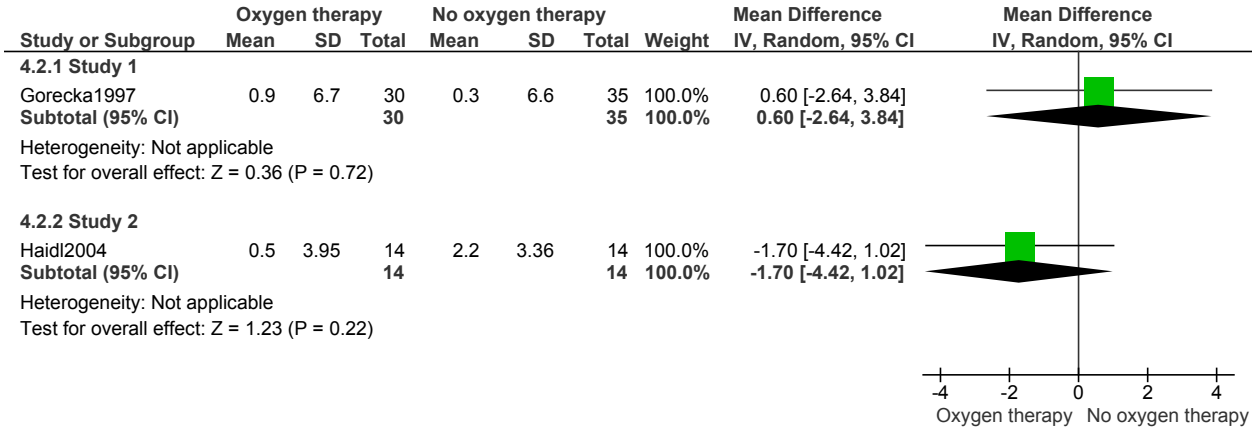
a) Survivors‡



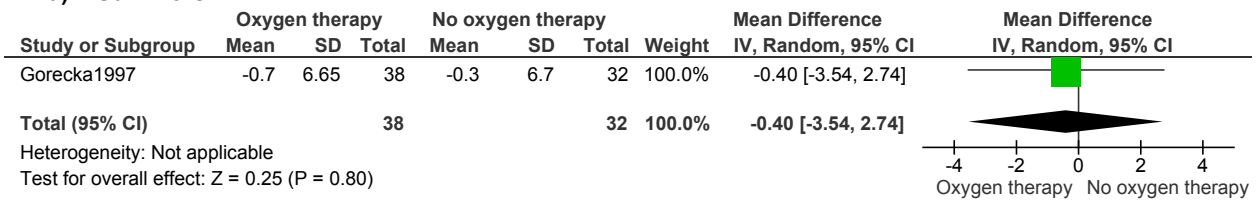
b) Nonsurvivors§

Figure 8: Arterial Pressure of Oxygen (mm Hg)*,†

*Abbreviations: CI, confidence interval; SD, standard deviation.
†Surrogate outcome.
‡Study 1 reports up to 7 years' follow-up and study 2 reports 1 year's follow-up.
§Gorecka et al reports (24) 7 years' follow-up.



a) Survivors†



b) Nonsurvivors‡

Figure 9: Arterial Pressure of Carbon Dioxide (mm Hg)*

*Abbreviations: CI, confidence interval; SD, standard deviation.
†Study 1 reports up to 7 years' follow-up and study 2 reports 1 year's follow-up.
‡Gorecka et al (24) reports 7 years' follow-up.

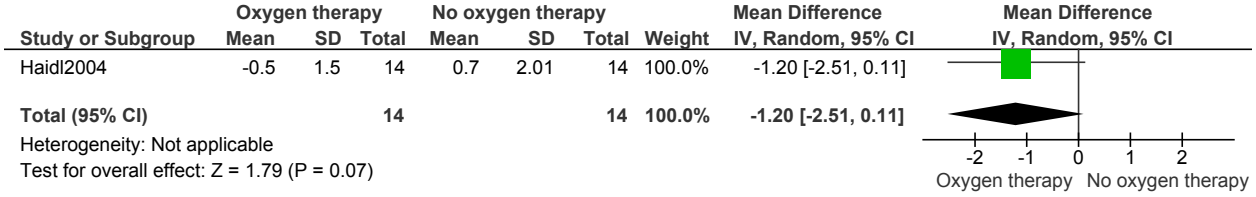


Figure 10: Dyspnea (Borg Scale)*,†

*Abbreviations: CI, confidence interval; SD, standard deviation.
†Haidl et al (25) reports 1 year's follow-up.

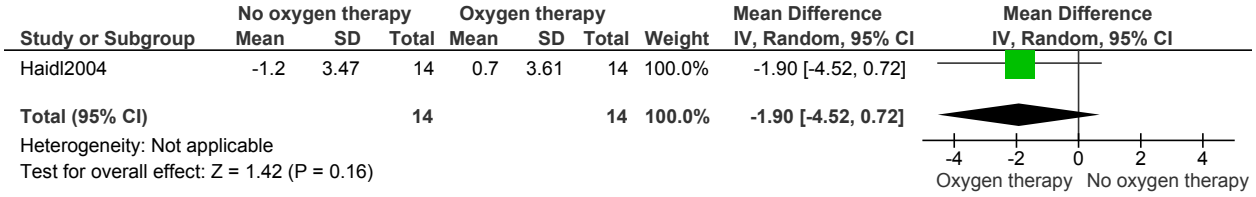


Figure 11: Endurance Time (Minutes)*,†

*Abbreviations: CI, confidence interval; SD, standard deviation.
†Haidl et al (25) reports 1 year's follow-up.

Results of Analysis

Analysis of mortality data found a 32% decreased risk of mortality for patients with COPD who had severe hypoxemia and heart failure and used LTOT compared with patients not using LTOT (RR, 0.68; 95% CI, 0.46–1.00; $P = 0.05$). It is important to note, however, that the CI includes 1.0 and the statistical significance level is 0.05, suggesting no effect.

Analysis of data on lung function and exercise factors found no difference in change values over time for patients with COPD who had mild-to-moderate hypoxemia and received LTOT compared with those who did not receive LTOT. No clinical benefit of LTOT for patients with COPD and mild-to-moderate hypoxemia was seen for FEV_1, FEV_1/FVC, FVC, PaO_2, $PaCO_2$, dyspnea, or endurance time. Significant results for FEV_1 and $PaCO_2$ for patients with COPD and severe hypoxemia and heart failure have been discussed previously.

Summary of Literature Review

The methods used in the Cochrane review helped to address the research question in this evidence-based analysis. (23) Of the 2 studies of patients with severe hypoxemia, only 1 study examined continuous LTOT compared with no LTOT. (10) This study was analyzed separately. (10) Two studies comparing patients with mild-to-moderate hypoxemia who received LTOT with those who received no LTOT were analyzed separately from the 2 studies on nocturnal oxygen use. (24-27) Overall, 3 studies provided data that were useful for the analysis. (10;24;25) The results from the systematic review by Wilt et al (28) were consistent with the Cochrane review, (23) but the analysis aggregated the 2 studies of patients with severe hypoxemia. (10;12) In this evidence-based analysis, the 3 eligible studies identified in the Cochrane review were analyzed separately, due to heterogeneity in length of follow-up and severity of hypoxemia. (10;24;25)

Mortality

The Cochrane review (23) found a beneficial effect of continuous LTOT on survival compared with no LTOT in patients with severe hypoxemia and heart failure when considering the MRC (10) study. Study strengths were the RCT design, successful randomization with no baseline differences, definition of irreversible airway obstruction consistent with a diagnosis of COPD, and low attrition rate over the 5-year follow-up. Study limitations were the absence of survival analysis for the main comparison of interest (LTOT vs. no LTOT), non-standardized measurement of adherence across the 3 study sites, lack of information on the mean number of hours of oxygen therapy used, and the non-blinded nature of the study.

Adherence in the treatment group is difficult to assess and may have affected the results. It is not known if patients received at least 15 hours of oxygen. If adherence was less than ideal, the magnitude of effect may be greater than shown in the meta-analysis. Alternatively, given adequate adherence and no control group receiving LTOT, the effect shown in the Cochrane meta-analysis is a true effect, and continuous LTOT produced a 60% reduction in the risk of all-cause mortality for continuous LTOT compared with no LTOT (OR, 0.42; 95% CI, 0.18–0.98). (23)

Similarly, the analysis in this report showed a decreased risk of mortality, but the magnitude of effect was attenuated and the result was not significant, with a CI that included 1.0 and a statistical significance value of 0.05. Closer examination of the result from the Cochrane review indicates a borderline statistically significant result. A post hoc power calculation shows that a type 2 error occurred, as the study had only 46% power to detect a 20% difference between treatment and control groups with 43 patients per arm. Conversely, had there been 100 patients per group, the study would have had 81% power to detect the same difference.

Smoking is related to COPD mortality, (38;38) but a post hoc analysis found no difference between the number of smokers in the treatment and control groups at baseline and at the end of the study, where some patients had quit smoking ($P > 0.05$). (10) Similarly, acute exacerbations are related to accelerated decline in lung function and increased mortality, with the typical patient with COPD experiencing 2 exacerbations per year. (14) The authors reported no between-group differences in the number of days hospitalized due to exacerbations. (10)

Meta-analysis results of the Cochrane review found no difference in mortality between continuous LTOT and no LTOT in patients with mild-to-moderate hypoxemia, based on data from the Gorecka et al (24) and Haidl et al (25) studies. Individual analysis of these studies similarly found no between-group differences in mortality, although the study by Haidl et al (25) had a small sample size (N = 28), the randomization process was less detailed than in Gorecka et al (24), and 5 of 14 subjects in the control group required LTOT over the 3 years of follow-up. Mean use of LTOT was less than 15 hours/day in both studies, and exclusion criteria were not adequately detailed. Gorecka et al (24) did not state whether any patients in the control group began using LTOT over the 7-year follow-up period. Although study participants were not smoking at the start of the study, some patients resumed smoking by the end of the study; this information was known only for participants in the treatment group. A post hoc power calculation indicates a type 2 error due to small sample sizes.

An important difference between the study of severe hypoxemia (10) and the studies of mild-to-moderate hypoxemia (24;25) is the inclusion of patients with heart failure in the severe hypoxemia study. The severe hypoxemia study included patients with a severe cardiovascular comorbidity, whereas the mild-to-moderate hypoxemia studies may have included patients with less severe comorbidities. In addition, the mild-to-moderate hypoxemia studies included patients that were less severe than those defining eligibility for LTOT according to existing guidelines. The biological cause-effect link between some comorbidities, COPD, and mortality is not clear, and the inaccurate recording of cause of death in patients with COPD may be a limiting factor. (39)

The cause of death of most patients in the MRC (10) study who died was respiratory failure. The benefit of LTOT can therefore perhaps be described as preventing COPD-related deaths. (38) Most deaths in the study by Gorecka et al (24) were due to COPD. Analysis for all-cause and COPD-related mortality, with well-defined exclusion criteria, would help to clarify pulmonary versus extrapulmonary benefits of LTOT in COPD. In addition, studies should include well-defined mortality endpoints and methods of ascertainment, such as use of death certificates or number and type of International Classification of Diseases codes used. (40) Appendix 3 summarizes quality assessment according to GRADE Evidence. The evidence for mortality among patients with COPD who had severe hypoxemia and among those with mild-to-moderate hypoxemia was graded as low quality.

Lung Function and Exercise Factors

Pathological changes characteristic of COPD include chronic inflammation and structural changes from repeated injury and repair. Affected sites include proximal and peripheral airways, lung parenchyma, and pulmonary vasculature. (3) Standard spirometry measures of pulmonary function can be used to assess the efficacy of treatment on lung function. Changes in arterial blood gases are important measures for interventions that affect respiratory drive, such as oxygen therapy, but arterial blood gases are considered surrogate outcomes. It is suggested that a change of 10 mm Hg for PaO_2 and $PaCO_2$ is clinically significant (Personal communication, clinical expert, April 13, 2011).

The analyses for change in lung function factors FEV_1 and $PaCO_2$ showed improvement over time in patients with COPD who had severe hypoxemia and survived more than 500 days. (10) No other differences among survivors were shown. No differences were shown for lung function factors among those dying within 500 days of the start of the study, except for FVC.

Analysis found no differences in lung function or exercise factors for patients with COPD with mild-to-moderate hypoxemia among survivors or nonsurvivors. (24) The main limitations in interpreting these analyses are the nonspecific time point at which lung function was measured and the subset analysis, which does not maintain successful randomization. Only the study by Haidl et al, (25) which assessed lung function and exercise factors at 1 year's follow-up for all subjects, maintained randomization. In addition, measurement of exercise variables was not described in detail. Dyspnea was measured using the Borg scale, which is a validated and reproducible 10-point scale that assesses either perceived dyspnea or effort required during a formal exercise test. The exercise test in Haidl et al (25) was a formal laboratory-based test using a stationary bicycle. Ascertainment of maximal workload was not described in detail. (41) In Appendix 3, GRADE Quality Assessment graded the evidence for all lung function factors among patients with COPD who had severe hypoxemia as very low quality. No data were available for exercise factors for patients with COPD who had severe hypoxemia. The evidence for all lung function and exercise factors among patients with COPD who had mild-to-moderate hypoxemia was graded as very low quality.

Hospitalizations and Readmissions

Two prospective studies, 1 study for readmission and 1 study for hospitalization, were evaluated. The readmission study, (35) a well-designed prospective cohort study, found no effect of LTOT on risk of readmission. The observational nature of the study resulted in grading as low-quality evidence (Appendix 3). The prospective study on hospitalization, (36) an adequately designed study, found that LTOT increased the risk of hospitalization. The observational nature of the study, heterogeneity in the comparison (10 of 64 patients with severe hypoxemia used LTOT), and limited analysis resulted in grading as very low quality evidence (Appendix 3).

Health-Related Quality of Life

The concern about LTOT and quality of life in COPD patients is that home LTOT equipment, such as oxygen concentrators, may reduce quality of life by restricting mobility and producing noise. The relation between dyspnea, exercise limitation, anxiety and depression, muscle wasting, quality of life, and disability is complex in COPD patients with severe hypoxemia. Long-term oxygen therapy may have little effect on health status but may reduce anxiety. Reduced independence in patients with COPD may also be related to the degree of airflow obstruction, depression, and poor health status. (42)

Analysis of HRQOL is also an objective of this report. A modified literature search of MEDLINE only with no limits on date or study design identified 91 articles on quality of life outcomes in patients with COPD who used LTOT. Hand-searching reference lists also identified potentially appropriate studies. One health technology assessment on a related topic, portable oxygen therapy, was also identified.

Studies were included in the analysis if:

- study design and methods were clearly described,
- the study assessed HRQOL using the St. George's Respiratory Questionnaire (SGRQ) or the Chronic Respiratory Questionnaire (CRQ), and
- the study was a health technology assessment, systematic review, RCT, or observational study.

Studies that did not meet the inclusion criteria were excluded. Studies were also excluded from analysis for the following reasons:

- nonrelevant outcome measures, such as psychiatric measures or non-standardized measures (n = 4),
- nonrelevant comparison, such as different oxygen delivery systems or nocturnal oxygen (n = 2),

- heterogeneity in the comparison, such as patients with COPD, severe hypoxemia, and LTOT compared with patients with mild-to-moderate hypoxemia and no LTOT (n = 4),
- no information on LTOT (n = 1),
- previously used LTOT (n = 1).

Summary of the Evidence

Nine studies were reviewed in detail and 3 observational studies were eligible and appropriate for review. One health technology assessment of portable oxygen therapy was also identified, but it was not considered relevant. (43) A review of the references of this study did not provide any additional studies. None of the 91 citations identified in the modified literature search were eligible and included. From 2 of the 3 observational studies identified, relevant LTOT information was abstracted, providing a before-and-after comparison for patients with COPD using LTOT, which were reviewed and are summarized in Appendix 3, Table A12.

Chronic Respiratory Questionnaire

A prospective study of 68 consecutive patients with COPD, who were referred to a regional oxygen service in New Zealand for assessment for LTOT, evaluated changes in HRQOL with a 6-month follow-up. (44) The study compared patients who were eligible for LTOT to those who were not eligible (no LTOT) for changes in HRQOL. Eligible patients were clinically stable for at least 2 months. Patients were ineligible if they had major but unspecified comorbidities, were smokers, or were unable to complete the questionnaire. Ambulatory oxygen was not provided. A total of 43 patients used LTOT for a mean 14.6 hours daily by meter reading. Mean baseline PaO_2 was 51.8 mm Hg for the LTOT group and 66 mm Hg for the no-LTOT group ($P < 0.001$). The percent predicted FEV_1 was 31.7% for the LTOT group and 29.6% for the no-LTOT group.

The Chronic Respiratory Questionnaire measured HRQOL at baseline and at 2 and 6 months. The mean change of the total score (possible score 20–140) from baseline was calculated. Increasing CRQ scores indicate improvements in HRQOL. Patients using LTOT had statistically significant improvements in HRQOL at 2 and 6 months. Mean change scores at 2 months were 2.36 (95% CI, 0.48–4.23) for dyspnea, 2.00 (95% CI, 0.57–3.43) for fatigue, 2.43 (95% CI, 0.36–4.50) for emotional function, and 1.55 (95% CI, 0.21–2.88) for mastery. Mean change scores at 6 months were similar, with only emotional function lacking statistical significance. The mean change total CRQ score for the LTOT group was 8.10 (95% CI, 3.02–13.17) at 2 months and 9.26 (95% CI, 2.37–16.15) at 6 months. Health-related quality of life improved with LTOT. The authors also concluded that the benefits of LTOT should be expanded to include HRQOL. (44)

A prospective study in Australia (45) followed 114 patients (59 men and 55 women) with COPD, who used LTOT including ambulatory oxygen, and assessed changes in CRQ at 3, 6, and 12 months. No exclusions were made for concomitant disease. Patients used LTOT for a mean 19 hours per day (Personal communication, January 17, 2011). At baseline, mean PaO_2 was 54 mm Hg in men and 53.3 mm Hg in women, and mean FEV_1 was 0.5 L in men and 0.4 L in women.

The minimal clinically important difference (MCID) in CRQ scores is 0.5. (46) In men, fatigue improved by at least 0.5 from baseline at 3, 6, and 12 months, a statistically significant improvement. A trend toward improvement was also seen for emotional function and mastery, but the results were not statistically significant. In women, mastery improved by at least 0.5 from baseline at 3, 6, and 12 months, which are statistically significant changes. Emotional function and fatigue also significantly improved by at least 0.5 from baseline at 3 and 6 months. (45) Improvements in emotional function and fatigue at 12 months were not significant, possibly due to reductions in sample size.

During the first 12 months of the study, 17 patients had not completed the 12-month follow-up, and 36 patients were lost to follow-up. Of the 36 total patients lost to follow-up, 16 men (44.4%) and 8 women (22.2%) were reported to have died, with remaining differences in loss to follow-up not reported by sex. These reasons included cessation of LTOT use, mental deterioration, refusal to continue, and transfer to another hospital. Overall, men and women using LTOT experienced statistically significant and clinically relevant improvements in HRQOL. (45)

St. George's Respiratory Questionnaire

A prospective study in the United Kingdom (47) examined changes in HRQOL among 36 patients with COPD who were referred to outpatient chest clinics for assessment for LTOT, comparing patients who were eligible for LTOT with those who were not eligible (no LTOT). Exclusion criteria were age less than 45 years and inability to understand or complete the quality-of-life questionnaires. Included patients were free from acute exacerbations for at least 3 weeks. Ambulatory oxygen was not provided. Follow-up duration was 6 months. Mean PaO_2 at baseline was 52.5 mm Hg for the LTOT group and 62.3 mm Hg for the no-LTOT group ($P < 0.001$). The percent predicted FEV_1 was 40% for the LTOT group and 43% for the no-LTOT group. The 19 patients in the LTOT group used oxygen for a mean 16.7 hours per day according to meter readings.

The St. George's Respiratory Questionnaire measured HRQOL at baseline, at 2 weeks, and at 3 and 6 months. A higher SGRQ score indicates poorer HRQOL (Table 2). A negative mean change in SGRQ score from baseline to follow-up indicates better HRQOL (Table 3). For the SGRQ, the MCID is 4 (Table 3). (48)

The LTOT group had statistically significantly higher SGRQ total scores at all time points than did the no-LTOT group (Table 2), indicating poorer quality of life. At 2 weeks, there was no statistically significant difference in improvement from baseline in SGRQ score between the LTOT group (6.8, SD 12.7) and the no-LTOT group (4.0, SD 10.7, $P = 0.48$). Similarly, at 6 months, the improvement from baseline in HRQL in the LTOT group (1.3, SD 14.5) did not differ significantly from that in the no-LTOT group (2.9, SD 13.4, $P = 0.38$). The authors concluded from the nonsignificant differences in changes in SGRQ total over time between LTOT and no-LTOT that LTOT does not adversely affect quality of life. (47)

Table 2: Comparison of Health-Related Quality of Life Between LTOT and No-LTOT Groups (St. George's Respiratory Questionnaire)*,†

	LTOT Group		No-LTOT Group		*P* Value
	Mean Total SGRQ Score	Standard Deviation	Mean Total SGRQ Score	Standard Deviation	
Baseline	61.8	18.3	45.8	15.5	0.008
2 Weeks	55.0	13.7	41.8	17.7	?
3 Months	55.9	12.1	44.3	17.4	?
6 Months	60.5	16.5	48.7	17.3	?

*Abbreviations: LTOT, long-term oxygen therapy; SGRQ, St. George's Respiratory Questionnaire; ?, unknown information.
†Source: Okubadejo et al, 1996 (47)

The analysis in this report uses a before-and-after design to examine the LTOT cohort by itself and to calculate the mean change in SGRQ total score; mean change in the SGRQ domains of symptoms, activities, and impacts; and mean change SD, using a correlation of 0.5 (Table 3).

Table 3: Change in Health-Related Quality of Life Results From Baseline (St. George's Respiratory Questionnaire)*,†

	Change From Baseline to Follow-Up: Mean (SD)		
SGRQ	**2 Weeks**	**3 Months**	**6 Months**
SGRQ Total	-6.8 (16.5)	-5.9 (16.1)	-1.3 (17.5)
Symptoms	3.3 (18.3)	3.0 (17.5)	4.1 (18.1)
Activities	1.7 (18.3)	-4.2 (16.9)	1.8 (18.1)
Impacts	-14.1 (22.7)	-9.0 (22.8)	-4.1 (23.9)

*Abbreviations: SGRQ, St. George's Respiratory Questionnaire; SD, standard deviation.
†Source: Okubadejo et al, 1996 (47)

When examining change scores and SGRQ, a negative mean change from baseline to follow-up indicates better HRQL, and for SGRQ, the MCID is four. (48) The analysis demonstrates that LTOT use produces clinically important and statistically significant improvements in the SGRQ domain of impacts at 2 weeks, based on calculation of 95% CIs, which are not shown. Use of LTOT is also associated with a trend for clinically important improvement in at least 1 of the SGRQ domains of symptoms, activities, or impacts at 2 weeks and 3 and 6 months, and for SGRQ total score at 2 weeks and 3 months.

In summary, HRQOL results for observational studies are graded as low quality of evidence for CRQ and as very low quality of evidence for SGRQ. Quality assessment uses GRADE Evidence (Appendix 3). It is important to note that ethical constraints of not providing LTOT to eligible patients with COPD prohibit future studies from examining LTOT outcomes in an ideal way.

Economic Analysis

The results of the economic analysis are summarized in issue 12 of the COPD series entitled *Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model*. This report can be accessed at: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Economic_March.pdf.

Conclusions

- Based on low quality of evidence, LTOT (~ 15 hours/day) decreases all-cause mortality in patients with COPD who have severe hypoxemia (PaO_2 ~ 50 mm Hg) and heart failure.
- The effect for all-cause mortality had borderline statistical significance when the control group was no LTOT: one study.
- Based on low quality of evidence, there is no beneficial effect of LTOT on all-cause mortality at 3 and 7 years in patients with COPD who have mild-to-moderate hypoxemia (PaO_2 ~ 59–65 mm Hg).
- Based on very low quality of evidence, there is some suggestion that LTOT may have a beneficial effect over time on FEV_1 and $PaCO_2$ in patients with COPD who have severe hypoxemia and heart failure: improved methods are needed.
- Based on very low quality of evidence, there is no beneficial effect of LTOT on lung function or exercise factors in patients with COPD who have mild-to-moderate hypoxemia, whether survivors or nonsurvivors are assessed.
- Based on low to very low quality of evidence, LTOT does not prevent readmissions in patients with COPD who have severe hypoxemia. Limited data suggest LTOT increases the risk of hospitalization.
- Limited work has been performed evaluating the safety of LTOT by severity of hypoxemia.
- Based on low to very low quality of evidence, LTOT may have a beneficial effect over time on HRQOL in patients with COPD who have severe hypoxemia. Limited work using disease-specific instruments has been performed.
- Ethical constraints of not providing LTOT to eligible patients with COPD prohibit future studies from examining LTOT outcomes in an ideal way.

Existing Guidelines for Long-Term Oxygen Therapy

International guidelines for use of LTOT for stable COPD, (2) which are based on the severity of hypoxemia, differ (Table 4).

Table 4: International Guidelines for Use of Long-term Oxygen Therapy in Patients with Stable Chronic Obstructive Pulmonary Disease*

Guideline	Severe Hypoxemia	Moderate Hypoxemia	No Hypoxemia
Ministry of Health and Long-Term Care (15)	PaO_2 ≤ 55 mm Hg *or* SpO_2 ≤ 88%	PaO_2 56–60 mm Hg plus cor pulmonale, pulmonary hypertension, persistent erythrocytosis, exercise-limiting hypoxemia documented to improve with supplemental oxygen, or nocturnal hypoxemia	Funding assistance is provided to individuals who are not hypoxemic at rest but who exhibit exertional hypoxemia on room air and improved exercise tolerance with oxygen
ATS-ERS (49)	PaO_2 < 55 mm Hg *or* SpO_2 < 88%	PaO_2 55–59 mm Hg or SpO_2 of 89% plus at least one of cor pulmonale, peripheral edema, or hematocrit > 55%	PaO_2 ≥ 60 mm Hg or SpO_2 > 90% with severe nocturnal desaturation and lung-related dyspnea responsive to oxygen
GOLD (50)	PaO_2 ≤ 55 mm Hg *or* SpO_2 ≤ 88%, with or without hypercapnia	PaO_2 56–59 mm Hg or SpO_2 of 88% with evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%)	No recommendation
NICE (51)	PaO_2 < 55 mm Hg	PaO_2 56–59 mm Hg plus secondary polycythemia, nocturnal hypoxemia (SpO_2 < 90% for >30% of the time), peripheral edema, or pulmonary hypertension	No recommendation
TSA-NZ (52)	PaO_2 ≤ 55 mm Hg	PaO_2 56–59 mm Hg, plus evidence of hypoxic organ damage including right heart failure, pulmonary hypertension, or polycythemia	Nocturnal oxygen may be indicated if SpO_2 ≤ 88% for > 30% sleep time, or hypoxia-related sequelae
AIPO (2)	PaO_2 < 55 mm Hg	PaO_2 55–60 mm Hg, plus at least one of hematocrit > 55%, signs of pulmonary hypertension, signs of hypoxia such as peripheral edema or right heart failure or mental decline, and ischemic heart failure	Intermittent oxygen may be indicated for SpO_2 < 90% for > 30% sleep time or exercise-related desaturation

*Abbreviations: AIPO, Associazione Italiana Pneumologi Ospedalieri; ATS-ERS, American Thoracic Society and European Respiratory Society; GOLD, Global Initiative for Obstructive Lung Disease; mm Hg, millimetres of mercury; NICE, National Institute for Health and Clinical Excellence; $PaCO_2$, arterial pressure of carbon dioxide; PaO_2, arterial pressure of oxygen; SpO_2, oxygen saturation level measured by pulse oximetry TSA-NZ, Thoracic Society of Australia and New Zealand.

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity (FVC)	The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.

Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.
Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[3]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.
Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.

[3] The mild-to-moderate classification was created for the purposes of the report.

Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.
Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Medical Information Officer

Kellee Kaulback

Editorial Staff

Joanna Gorski
Irina Alecu

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

Appendices

Appendix 1: Literature Search Strategies

Search date: September 8, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1996 to August Week 4 2010>
Search Strategy:
---
1 exp Pulmonary Disease, Chronic Obstructive/ (13896)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (14772)
3 (copd or coad).ti,ab. (13084)
4 chronic airflow obstruction.ti,ab. (110)
5 exp Emphysema/ (2921)
6 ((chronic adj2 bronchitis) or emphysema).ti,ab. (8434)
7 or/1-6 (29825)
8 exp Oxygen Inhalation Therapy/ (6948)
9 exp Oxygen/ (56003)
10 (oxygen adj2 (therap* or supplement* or portab* or ambulatory)).ti,ab. (5161)
11 or/8-10 (63799)
12 7 and 11 (1875)
13 limit 12 to (english language and humans and yr="2007 -Current") (399)

Database: EMBASE <1980 to 2010 Week 35>
Search Strategy:
---
1 exp chronic obstructive lung disease/ (47610)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (25725)
3 (copd or coad).ti,ab. (20981)
4 chronic airflow obstruction.ti,ab. (549)
5 exp emphysema/ (25443)
6 exp chronic bronchitis/ (6546)
7 ((chronic adj2 bronchitis) or emphysema).ti,ab. (25378)
8 or/1-7 (87489)
9 exp oxygen therapy/ (26313)
10 exp OXYGEN/ (112232)
11 (oxygen adj2 (therap* or supplement* or portab* or ambulatory)).ti,ab. (10687)
12 or/9-11 (135284)
13 8 and 12 (5682)
14 limit 13 to (human and english language and yr="2007 -Current") (946)

****

CINAHL

#	Query	Results
S12	S6 and S10 Limiters - Published Date from: 20070101-20101231;	151
S11	S6 and S10	573
S10	S7 or S8 or S9	6119
S9	oxygen therap* or supplement* oxygen or therapeutic oxygen or portab* oxygen or ambulatory oxygen	3585
S8	(MH "Oxygen+")	2379
S7	(MH "Oxygen Therapy+")	3501
S6	S1 or S2 or S3 or S4 or S5	7364
S5	chronic bronchitis or emphysema	1575
S4	(MH "Emphysema+")	964
S3	copd or coad	4065
S2	(chronic obstructive and (lung* or pulmonary or airway* or airflow or respiratory) and (disease* or disorder*))	5571
S1	(MH "Pulmonary Disease, Chronic Obstructive+")	4315

Appendix 2: GRADE Evidence Tables

Table A1: GRADE Evidence Table for Long-Term Oxygen Therapy and Mortality in Patients With Severe Hypoxemia*

LTOT Versus No LTOT: Severe Hypoxemia for Patients with COPD					
Outcomes	**Illustrative Comparative Risks (95% CI)**		**Relative Effect (95% CI)**	**No. of Participants (Studies)**	**Quality of Evidence (GRADE)†**
	Assumed Risk	Corresponding Risk			
Mortality MRC (10)	**Study Population**		RR 0.68 (0.46–1)	87 (1 study)	⊕⊕ Low‡,§,‖,¶,#
	667 per 1000	454 per 1000 (307–667)			
	Medium-Risk Population				
	667 per 1000	454 per 1000 (307–667)			

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; LTOT, long-term oxygen therapy; MRC, Medical Research Council; no., number; RR, relative risk.
†Specific weighting, for all (-2 overall).
‡Study design limitations include measurement and reporting of adherence, such as lack of standardized assessment of oxygen therapy and no information on mean hours of use. (-1/2)
§This study included a highly selected group of patients with COPD, heart failure, and severe hypoxemia. Ascertainment of death was not described in detail. (did not contribute to GRADE)
‖Allocation concealment was not addressed. (-1/2)
¶Not blinded. (did not contribute to GRADE for all-cause mortality)
#Sparse data. Type 2 error not excluded. (-1)

Table A2: GRADE Evidence Table for Long-Term Oxygen Therapy and Mortality in Patients With Mild-to-Moderate Hypoxemia*

LTOT Versus No LTOT: Mild-to-Moderate Hypoxemia for Patients with COPD					
Outcomes	**Illustrative Comparative Risks (95% CI)**		**Relative Effect (95% CI)**	**No of Participants (studies)**	**Quality of Evidence (GRADE)†**
	Assumed Risk	Corresponding Risk			
Mortality: Study 1 7 years' follow-up Gorecka et al (24)	**Study Population**		RR 1.17 (0.84–1.62)	135 (1 study)	⊕⊕ Low‡,§,‖,¶,#,††,‡‡
	478 per 1000	559 per 1000 (402–774)			
	Medium-Risk Population				
	478 per 1000	559 per 1000 (402–774)			
Mortality: Study 2 3 years' follow-up Haidl et al (25)	**Study Population**		RR 1.33 (0.36– 4.9)	28 (1 study)	⊕⊕ Low‡,§,‖,¶,**,††,‡‡, §§
	214 per 1000	285 per 1000 (77–1000)			
	Medium-Risk Population				
	214 per 1000	285 per 1000 (77–1000)			

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; LTOT, long-term oxygen therapy; no., number; RR, relative risk.
†Specific weighting, for all (-2 overall).
‡Oxygen use was inadequate according to study protocol. (-1/4 or -1/3)
§Allocation concealment was not addressed. (-1/4 or -1/3)
‖Exclusion criteria were not adequately detailed. (did not contribute to GRADE)
¶Ascertainment of mortality was not described in detail. (did not contribute to GRADE)
#It was not known whether or not individuals in the control arm received LTOT during follow-up. (-1/3)
**High numbers crossing over to LTOT in the control arm. (-1/4)
††Process of generating randomization not adequately described. (-1/4)
‡‡Not blinded. (did not contribute to GRADE for all-cause mortality)
§§Sparse data. (-1)

Table A3: GRADE Evidence Table for Long-Term Oxygen Therapy and Lung Function in Patients With Severe Hypoxemia (Survivors and Nonsurvivors)*,†

Outcomes		Illustrative Comparative Risks (95% CI)	No. of Participants (Studies)	Quality of Evidence (GRADE)‡
		Corresponding Risk: Intervention Groups		
Mean FEV_1 (L)	**Nonsurvivors**	0.11 lower (0.27 lower to 0.05 higher)	21 (1 study)	⊕ Very low§,‖,¶,#,**,††
	Survivors	0.08 higher (0.04 to 0.12 higher)	40 (1 study)	⊕ Very low§,‖,¶,#,**,††
Mean FVC (L)	**Nonsurvivors**	0.56 higher (0.12 to 1.00 higher)	21 (1 study)	⊕ Very low§,‖,¶,#,**,††
	Survivors	0.05 higher (0.89 lower to 0.99 higher)	40 (1 study)	⊕ Very low§,‖,¶,#,**,††
Mean PaO_2 (mm Hg)	**Nonsurvivors**	4.56 higher (1.04 lower to 10.16 higher)	19 (1 study)	⊕ Very low§,‖,¶,#,**,††
	Survivors	1.07 higher (1.24 lower to 3.38 higher)	40 (1 study)	⊕ Very low§,‖,¶,#,**,††
Mean $PaCO_2$ (mm Hg)	**Nonsurvivors**	0.96 lower (8.53 lower to 6.61 higher)	19 (1 study)	⊕ Very low§,‖,¶,#,**,††
	Survivors	2.16 lower (4.04 to 0.28 lower)	39 (1 study)	⊕ Very low§,‖,¶,#,**,††

*Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mm Hg, millimetres of mercury; no., number; $PaCO_2$, arterial pressure of carbon dioxide; PaO_2, arterial pressure of oxygen; RR, relative risk.
†MRC et al (10).
‡Specific weighting, for all (-3 overall).
§Study design limitations include the measurement and reporting of compliance such as the lack of standardized assessment of oxygen therapy and no information on the mean hours of use. (-1/3)
‖Subgroup analysis on men lacks the benefits of randomization. (-1)
¶Time point of lung function measurements not specified in detail. (-1/3)
#Standard spirometry not described in detail. (did not contribute to GRADE)
**Not blinded. (-1/3)
††Sparse data. (-1)

Table A4: GRADE Evidence Table for Long-Term Oxygen Therapy and Lung Function in Survivors, Mild-to-Moderate Hypoxemia*

Outcomes		Illustrative Comparative Risks (95% CI)	No. of Participants (studies)	Quality of Evidence (GRADE)†
		Corresponding Risk: Intervention Groups		
Mean FVC %	**Study 1**	0.6 lower (6.36 lower to 5.16 higher)	65 (1 study)	⊕ Very low‖,¶,#,**,††,‡‡,§§
Mean $PaCO_2$ (mm Hg)	**Study 1**	0.6 higher (2.64 lower to 3.84 higher)	65 (1 study)	⊕ Very low‖,¶,#,**,††,‡‡,§§
	Study 2	1.7 lower (4.42 lower to 1.02 higher)	28 (1 study)	⊕ Very low#,**,††,§§,‖ ‖
Mean FEV_1 (L)	**Study 1**	0.08 lower (0.22 lower to 0.06 higher)	65 (1 study)	⊕ Very low‖,¶,#,**,††,‡‡,§§
	Study 2	0.08 lower (0.35 lower to 0.19 higher)	28 (1 study)	⊕ Very low#,**,††,§§,‖ ‖
Mean FEV_1 % Predicted	**Study 1**	1.7 lower (6.59 lower to 3.19 higher)	65 (1 study)	⊕ Very low‖,¶,#,**,††,‡‡,§§
	Study 2	3.5 lower (11.06 lower to 4.06 higher)	28 (1 study)	⊕ Very low#,**,††,§§,‖ ‖
Mean FEV_1/FVC	**Study 1**	1.9 higher (4.3 lower to 8.1 higher)	65 (1 study)	⊕ Very low‖,¶,#,**,††,‡‡,§§
	Study 2	2 lower (9.97 lower to 5.97 higher)	28 (1 study)	⊕ Very low#,**,††,§§,‖ ‖
Mean PaO_2 (mm Hg)	**Study 1**	0.2 lower (4.1 lower to 3.7 higher)	65 (1 study)	⊕ Very low‖,¶,#,**,††,‡‡,§§
	Study 2	1.2 higher (4.18 lower to 6.58 higher)	28 (1 study)	⊕ Very low#,**,††,§§,‖ ‖
Mean FVC (L)	**Study 1**	0.08 lower (5.84 lower to 5.68 higher)	65 (1 study)	⊕ Very low‖,¶,#,**,††,‡‡,§§
Mean Endurance Time (minutes)	**Study 2**	1.9 lower (4.52 lower to 0.72 higher)	28 (1 study)	⊕ Very low#,††,‖ ‖,¶¶
Mean Dyspnea (Borg Scale)	**Study 2**	1.2 lower (2.51 lower to 0.11 higher)	28 (1 study)	⊕ Very low#,††,‖ ‖,¶¶

*Abbreviations: CI, confidence interval; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; mm Hg, millimetres of mercury; no., number; $PaCO_2$, arterial pressure of carbon dioxide; PaO_2, arterial pressure of oxygen.
†Specific weighting, for all (-3 overall).
‡Study 1, 7 years' follow-up in Gorecka et al (24).
§Study 2, 1-year follow-up in Haidl et al (25).
‖Randomization not maintained. (-1 and with the remaining items below contributing equal amounts)
¶Time point of lung function measurement not described in detail.
#Oxygen use was inadequate according to study protocol.
**Not blinded.
††Sparse data. (-1 and with the remaining items below contributing equal amounts)
‡‡It is unknown if individuals in the control arm began using oxygen therapy.
§§Measurement of spirometry was not described in detail. (did not contribute to GRADE)
‖ ‖Allocation concealment was not addressed.
¶¶Measurement of exercise data was not described in detail. (did not contribute to GRADE)

Table A5: GRADE Evidence Table for Long-Term Oxygen Therapy and Lung Function in Nonsurvivors, Mild-to-Moderate Hypoxemia*

Outcomes	Illustrative Comparative Risks (95% CI)	Quality of Evidence (GRADE)†
	Corresponding Risk: Intervention Groups	
Mean FVC %	0.3 lower (5.84 lower to 5.24 higher)	⊕ Very low‡,§,‖,¶,#,**,††
Mean $PaCO_2$ (mm Hg)	0.4 lower (3.54 lower to 2.74 higher)	⊕ Very low‡,§,‖,¶,#,**,††
Mean FEV_1 (L)	0.05 higher (0.08 lower to 0.18 higher)	⊕ Very low‡,§,‖,¶,#,**,††
Mean FEV_1 % Predicted	1.7 higher (2.8 lower to 6.2 higher)	⊕ Very low‡,§,‖,¶,#,**,††
Mean FEV_1/FVC	1.7 lower (7.69 lower to 4.29 higher)	⊕ Very low‡,§,‖,¶,#,**,††
Mean PaO_2 (mm Hg)	0.1 higher (1.17 lower to 1.37 higher)	⊕ Very low‡,§,‖,¶,#,**,††
Mean FVC (L)	0.05 higher (5.49 lower to 5.59 higher)	⊕ Very low‡,§,‖,¶,#,**,††

*Abbreviations: CI, confidence interval; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; mm Hg, millimetres of mercury; $PaCO_2$, arterial pressure of carbon dioxide; PaO_2, arterial pressure of oxygen.
†Gorecka et al (24); 70 participants; specific weighting, for all (-3 overall).
‡Randomization not maintained. (-1)
§Time point of lung function measurement not described in detail. (-1/4)
‖Oxygen use was inadequate according to study protocol. (-1/4)
¶It is unknown if individuals in the control arm began using oxygen therapy. (-1/4)
#Measurement of spirometry not described in detail. (did not contribute to GRADE)
**Not blinded. (-1/4)
††Sparse data. (-1)

Table A6: GRADE Evidence Table for Long-Term Oxygen Therapy and Hospital Readmissions and Hospitalizations, Severe Hypoxemia*,†,‡

LTOT Versus No LTOT: Hospital Readmission and Hospitalization for COPD			
Outcomes	**Relative Effect (95% CI)**	**No. of Participants (studies)**	**Quality of Evidence (GRADE)§**
Hospital Readmission	HR 1.26 (0.87–1.84)	312 (1 study)	⊕⊕ Low‖,#
Hospitalization	RR 0 (0–0)	64 (1 study)	⊕ Very low‖,¶,#,**

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LTOT, long-term oxygen therapy; no., number; RR, relative risk.
†Hospital readmission: Garcia-Aymerich et al (35); hospitalization: Kessler et al (36).
‡No meta-analysis.
§Specific weighting -1 overall; already low quality of evidence for observational studies.
‖Unmeasured confounders for non-RCT studies. (did not contribute to GRADE)
¶Sparse data. (did not contribute to GRADE, already very low quality of evidence)
#Heterogeneity in the comparison. (did not contribute to GRADE)
**Unadjusted analysis only. (-1)

Table A7: GRADE Evidence Table for Long-Term Oxygen Therapy and Health-Related Quality of Life, Severe Hypoxemia*

LTOT Only: Health-Related Quality of Life					
Population: Patients With COPD					
Outcomes	**Illustrative Comparative Risks (95% CI)**	**Relative Effect (95% CI)**	**No. of Participants (studies)**	**Quality of Evidence (GRADE)**	**Comments**
	Assumed Risk Corresponding Risk				
CRQ†	Meta-analysis not performed	Not estimable	157 (2 studies)	⊕⊕ Low§,‖,¶	LTOT only Observational
SGRQ‡	Meta-analysis not performed	Not estimable	19 (1 study)	⊕ Very low#	LTOT only Observational

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Questionnaire; LTOT, long-term oxygen therapy; no., number; SGRQ, St. George's Respiratory Questionnaire.
†Eaton et al (44) and Crockett et al (45).
‡Okubadejo et al (47).
§Ambulatory oxygen provided in 1 study. (did not contribute to GRADE)
‖Confounders not accounted for. (did not contribute to GRADE)
¶CRQ was characterized differently for each study. (did not contribute to GRADE)
#Sparse data. (-1)

Appendix 3: Summary Tables

The following studies were included in the Cochrane Review (23) and are relevant for this evidence-based analysis. The objective of the Cochrane Review was to determine the effect of domiciliary oxygen therapy on survival and quality of life in patients with COPD.

Table A8: Summary of Study Design Characteristics*

Author	Study Design: Comparison	Study Population	Intervention	Main Results (Original Study)	Comments
MRC (10)	MC RCT: LTOT vs. no LTOT	87 patients with CB/E, CS FEV_1 < 1.2 L, PaO_2 40–60 mm Hg ≥ 1 episode of heart failure + ankle edema FU: up to 5 years	LTOT (n = 42) vs. no LTOT (n = 45) FR 2 L/minute ≥ 15 hours/day including sleeping hours	Mean age ~58 years, mean PaO_2 ~50 mm Hg, FEV_1 ~0.65 L LTOT 19/42 (45.2%) vs. CT 30/45 (66.7%), *P* = ?, Men (n = 66) > 500 days, risk of death: LTOT 12% vs. CT 29% (*P* = 0.04) Women (n = 21), LTOT 5.7% vs. CT 36.5% (*P* < 0.05)	Severe hypoxemia, not blinded, differences in O_2 source, usage check not standardized (adherence), hours? 1 DO (O_2)
Gorecka et al (24)	MC RCT: LTOT vs. no LTOT	135 patients with COPD FEV_1/VC < 70%, PaO_2 56–65 mm Hg FU ≥ 3 years or death, NS	LTOT + UC (n = 68) vs. no LTOT + UC (n = 67) FR adjusted to > 65 mm Hg at rest ≥ 17 hours/day	Mean age ~60 years, mean PaO_2 60.4 mm Hg, mean O_2 use 13.5 hours/day, FEV_1 29.8%, 0 DO LTOT 38/68 (55.9%) vs. CT 32/67 (47.8%), no difference in survival (*P* = 0.982)	Moderate hypoxemia, not blinded, UC included drug therapies, concentrator, adherence check, crossover?
Haidl et al (25)	RCT: LTOT vs. no LTOT	28 patients with COPD + $PaCO_2$ > 45 mm Hg at rest or exercise test, CS FEV_1/VC < 70%, PaO_2 > 55 mm Hg FU 3 years	LTOT (n = 14) vs. no LTOT (n = 14) FR 2 L/minute, 15 hours/day	Mean age ~64 years, mean PaO_2 ~66 mm Hg, mean O_2 use 10.4 hours/day, FEV_1 ~40%, ↑ endurance time at 1 year (*P* = 0.04), ↓ dyspnea score at 1 year (*P* = 0.03), no difference in deaths after 3 years LTOT 4/14 (28.6%) vs. CT 3/14 (21.4%), *P* = ?	Mild hypoxemia, not blinded, concentrator, adherence check by O_2 meter, 5 CTs given LTOT

*Abbreviations: CB/E, chronic bronchitis and emphysema; CO_2, continuous oxygen therapy; COPD, chronic obstructive pulmonary disease; CS, current smokers; CT, control group; DO, dropouts; FEV_1, forced expiratory volume in 1 second; FR, flow rate; FS, former smokers; FU, follow-up; L, litres; LTOT, long-term oxygen therapy; MC, multicentre; mm Hg, millimetres of mercury; MRC, Medical Research Council; NS, not significant; O_2, oxygen; PaO_2, arterial pressure of oxygen; RCT, randomized controlled trial; UC, usual care.

Table A9: Summary of Relevant Outcomes*

Comparison	Studies Included	Outcome†		Results (Pooled Analysis)‡	Comments
LTOT vs. No LTOT: Severe Hypoxemia	MRC (10)	Mortality	60 months	OR: 0.42 (0.18, 0.98)	+
		FEV_1 change	≤ 500 days	MD: -0.11 (-0.27, 0.05)	NS
			> 500 days	MD: 0.08 (0.04, 0.12)	+
		FVC change	≤ 500 days	MD: 0.56 (0.12, 1.00)	+
			> 500 days	MD: 0.05 (-0.89, 0.99)	NS
		PaO_2 change	≤ 500 days	MD: 4.56 (-1.04, 10.16)	NS
			> 500 days	MD: 1.07 (-1.24, 3.38)	NS
		$PaCO_2$ change	≤ 500 days	MD: -0.96 (-8.53, 6.61)	NS
			> 500 days	MD: -2.16 (-4.04, -0.28)	+
LTOT vs. No LTOT: Mild-to-moderate Hypoxemia	Gorecka et al (24) Haidl et al (25)	Mortality		OR: 1.39 (0.74, 2.59)	NS
LTOT vs. No LTOT: Mild-to-moderate Hypoxemia	Haidl et al (25)	End-exercise dyspnea score		MD: -1.20 (-2.47, 0.07)	NS
		Endurance time		MD: 2.20 (-0.73, 5.13)	NS

*Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LTOT, long-term oxygen therapy; MD, mean difference; MRC, Medical Research Council; NS, not significant; OR, Peto odds ratio; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide.

†≤ 500 days, for men dying between 180 and 500 days; > 500 days, for men surviving more than 500 days. Excluded were results for changes in packed cell volume (≤ 500 and > 500 days), and mortality for oxygen use of >15 hours per day and <15 hours per day. Units for FEV_1 and FVC are litres, and units for PaO_2 and $PaCO_2$ are mm Hg. Borg scale was used for dyspnea and minutes for endurance time.

‡OR < 1 favours LTOT (+). A positive MD value favours LTOT (+). The reverse is true for $PaCO_2$ in which a negative MD favours LTOT (+).

Source: Cranston et al, 2005 (23)

Table A10: Study Design Strengths and Limitations by Severity of Hypoxemia for Relevant Studies From the Cochrane Review*

Study	COPD Study Population	Adequate Sample Size	Exclusions Detailed	Randomization Achieved	Blinding	Adequately Measured Adherence	All-cause Mortality	Survival Analysis	Intent-to-Treat Analysis†	Minimal Attrition
Severe Hypoxemia										
MRC (10), ‡,§,‖	✓		✓	✓			✓		✓	✓
Mild-to-moderate Hypoxemia										
Gorecka et al (24), ‡	✓			✓		✓	✓	✓	✓	✓
Haidl et al (25), ‡	✓			✓		✓	✓		✓	✓

*Abbreviations: COPD, chronic obstructive pulmonary disease; MRC, Medical Research Council; checkmark (✓) refers to the presence of study design strengths.
†Considering mortality/survival as the main comparison of interest.
‡Allocation concealment was adequate for none of the above studies and the process of generating randomized schedules was adequate for MRC (10) and Gorecka et al (24).
§Survival analysis was not shown for the primary comparison of interest.
‖A larger proportion of patients in the treatment group smoked; however a post hoc analysis showed that this difference was not statistically significant ($P > 0.05$).
Source: Cranston et al, 2005 (23)

Table A11: Summary of Key Study Characteristics*

Study	Baseline FEV_1 % Predicted (L) (Mean)†			Baseline PaO_2 (mm Hg)(Mean)‡			Baseline $PaCO_2$ (mm Hg) (Mean)§			Follow-up
	Total‖	LTOT	Control	Total‖	LTOT	Control	Total‖	LTOT	Control	Mean (SD) or Range (Years)
Severe Hypoxemia										
MRC (10)	0.66	0.67	0.64	50.8	49.9	51.7	54.4	54.9	53.9	0–5
Mild-to-moderate Hypoxemia										
Gorecka et al (24)	29.8	29.7	29.8	60.4	59.5	61.3	44.1	45.3	42.8	0.2–7
Haidl et al (25)	40.8	38.8	42.7	66.5	65.6	67.3	40.8	41.9	39.7	1–3
Garcia-Aymerich et al (35), ¶	36	-	-	64	?	-	-	-	-	1.1 (0.5)
Kessler et al (36), ¶	39	-	-	66	<60	-	46	-	-	0–1

*Abbreviations: FEV_1, forced expiratory volume in 1 second; LTOT, long-term oxygen therapy treatment group; mm Hg, millimetres of mercury; O_2, oxygen; PaO2, arterial partial pressure of oxygen; PaCO2, arterial partial pressure of carbon dioxide, SD, standard deviation.
†COPD Stage: mild, $FEV_1 \geq 80\%$ predicted; moderate, $FEV_1 \geq 50\%$ and < 80% predicted; severe, $FEV_1 \geq 30\%$ and < 50% predicted; very severe, $FEV_1 < 30\%$. Severe COPD defined as $FEV_1 < 1.5$ litres.
‡Hypoxemia: severe, ≤ 50 mm Hg; mild-to-moderate, ~ 50-65 mm Hg.
§Hypercapnia: > 45-60 mm Hg.
‖Total: study population as a whole including treatment and control groups, either taken from the original paper or calculated as the mean from the 2 arms of the trial.
¶Heterogeneity in the comparison: COPD patients using O_2 have severe hypoxemia and COPD patients not using O_2 (e.g., controls) have mild-to-moderate hypoxemia.

Table A12: Summary of Key Study Characteristics for the Three Studies on Health-related Quality of Life*

Author	Study Design	Study Population	Intervention	Main Results†	Comments
Eaton et al (44)	Prospective follow-up: baseline to 2 and 6 months	68 patients with COPD, NS LTOT need assessed by standard criteria: severe hypoxemia or mild-to-moderate hypoxemia with a COPD-related condition Clinically stable ≥ 2 months	LTOT vs. no LTOT (43/25)	Baseline: significant differences‡ in PaO_2 (LTOT 51.8 vs. no LTOT 66 mm Hg), $PaCO_2$ (LTOT 48.8 vs. no LTOT 42.8 mm Hg), and CRQ (fatigue, emotional function, mastery, total); FEV_1 % predicted (LTOT: 31.7; no LTOT, 29.6) Mean O_2 use 14.6 hours At 2 months CRQ total: LTOT 8.10 (3.02–13.17); no LTOT -0.28 (-5.98 to 5.42), significant increases for domains in LTOT At 6 months, CRQ total: LTOT 9.26 (2.37–16.15); no LTOT -2.56 (-8.31 to 3.19), significant increases for domains in LTOT	>50% men Age ~70 years CRQ analyzed as total scores Other factors affecting HRQOL? Ambulatory O_2 not provided
Crockett et al (45)	Prospective follow-up: baseline to 3, 6, and 12 months	114 COPD patients LTOT need determined by standard criteria	LTOT only (M 59/W 55)	Baseline, PaO_2 ~53.7 mm Hg, $PaCO_2$ 49.2 mm Hg, FEV_1 0.5 L (men and women combined); mean O_2 use ~19 hours Men: CRQ at all time points, emotional function and mastery: nonsignificant increase; fatigue: significant increase > 0.5 Women: CRQ mastery, significant increase > 0.5 at all time points; emotional function and fatigue: significant increase > 0.5 at 3 and 6 months	~52% men Age ~70 years CRQ analysis mean score, 7-point scale Other factors affecting HRQOL? Ambulatory O_2 provided MCID 0.5 units
Okubadejo et al (47)	Prospective follow-up: baseline to 2 weeks, and 3 and 6 months	36 patients with COPD LTOT need assessed by standard criteria: severe hypoxemia or mild-to-moderate hypoxemia with a COPD-related condition Clinically stable ≥ 3 weeks	LTOT vs. no LTOT (19/17)	Baseline: LTOT, PaO_2 ~52.5 mm Hg, $PaCO_2$ 50.3 mm Hg, FEV_1 40% predicted; mean O_2 use ~17 hours; no LTOT, PaO_2 ~62.3 mm Hg, $PaCO_2$ ~45 mm Hg, FEV_1 43% predicted Significant differences between LTOT and no LTOT for SGRQ total at baseline (61.8 vs. 45.8, P = 0.008), no significant differences in improvement from baseline at 2 weeks and 3 and 6 months	% by sex unknown Age ~71 years Other factors affecting HRQOL Ambulatory O_2 not provided MCID 4 units

*Abbreviations: CRQ, Chronic Respiratory Questionnaire; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; HRQOL, health-related quality of life; LTOT, long-term oxygen therapy; M, men; MCID, minimal clinically important difference; mm Hg, millimetres of mercury; NS, nonsmokers; O2, oxygen; PaCO2, arterial pressure of carbon dioxide; PaO2, arterial pressure of oxygen; SGRQ, St. George's Respiratory Questionnaire; W, women.

†Data are reported as means and 95% confidence intervals, or mean alone.

‡Significant at < 0.05.

References

(1) Public Health Agency of Canada. Chronic Obstructive Pulmonary Disease (COPD) [Internet]. [updated 2008 Oct 7; cited 2010 Oct 27]. Available from: http://www.phac-aspc.gc.ca/cd-mc/crd-mrc/copd-mpoc-eng.php

(2) Corrado A, Renda T, Bertini S. Long-term oxygen therapy in COPD: evidences and open questions of current indications. Monaldi Arch Chest Dis. 2010;73(1):34-43.

(3) Global Initiative for Chronic Obstructive Pulmonary Disease. Global Initiative for Chronic Obstructive Pulmonary Disease [Internet]. Unknown: Medical Communications Resources Inc. 2009 Jan 1 [cited: 2010 Oct 27]. 109 p. Available from: http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003

(4) McGloin S. Administration of oxygen therapy. Nurs Stand. 2008;22(21):46-8.

(5) Henderson Y. Delivering oxygen therapy to acutely breathless adults. Nurs Stand. 2008;22(35):46-8.

(6) Lynes D, Kelly C. Domiciliary oxygen therapy: assessment and management. Nurs Stand. 2009;23(20):50-6.

(7) Dunne PJ. The clinical impact of new long-term oxygen therapy technology. Respir Care. 2009;54(8):1100-11.

(8) Uronis H, McCrory DC, Samsa G, Currow D, Abernethy A. Palliative oxygen for non-hypoxaemic chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CDD006429. DOI: 10.1002/14651858.CD006429. 2007

(9) Osthoff M, Leuppi JD. Management of chronic obstructive pulmonary disease patients after hospitalization for acute exacerbation. Respiration. 2010;79(3):255-61.

(10) Report of the Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet. 1981;1(8222):681-6.

(11) Stark RD, Finnegan P, Bishop JM. Long-term domiciliary oxygen in chronic bronchitis with pulmonary hypertension. Br Med J. 1973;3(5878):467-70.

(12) Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93(3):391-8.

(13) Stoller JK, Panos RJ, Krachman S, Doherty DE, Make B. Oxygen therapy for patients with COPD: Current evidence and the long-term oxygen treatment trial. Chest. 2010;138(1):179-87.

(14) O'Donnell DE, Hernandez P, Kaplan A, Aaron S, Bourbeau J, Marciniuk D, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update - Highlights for primary care. Can Respir J. 2008;15(SUPPL. A):1A-8A.

(15) Ministry of Health and Long-Term Care. Home Oxygen Program - Physician [Internet]. [Toronto, ON]: Government of Ontario. 2004 Jul 1 [cited: 2010 Oct 28]. 3 p. Available from: http://www.health.gov.on.ca/english/public/pub/adp/pdf/oxyphys.pdf

(16) Ministry of Health and Long-Term Care. Home Oxygen Program Policy and Administration Manual [Internet]. [Toronto, ON]: Government of Ontario. 2011 May 1 [cited: 2011 Nov 7]. 54 p. Available from: http://www.health.gov.on.ca/en/pro/programs/adp/information_technology/docs/home_oxygen_manual.pdf

(17) Canadian Lung Association. Fact sheet: What you need to know about oxygen [Internet]. Ottawa: Canadian Lung Association. 2005 Aug 1 [cited: 2010 Oct 28]. 6 p. Available from: http://www.lung.ca/_resources/Oxygen_COPD_LungAssoc.pdf

(18) Make B, Krachman S, Panos RJ, Doherty DE, Stoller JK. Oxygen therapy in advanced COPD: In whom does it work? Semin Respir Crit Care Med. 2010;31(3):334-42.

(19) Brinkerhoff S. Oxygen therapy in the home: safety precautions and implications for home healthcare clinicians. Home Healthc Nurse. 2009;27(7):417-20.

(20) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490.

(21) Goodman, C. Literature searching and evidence interpretation for assessing health care practices. Stockholm, Sweden: Swedish Council on Technology Assessment in Health Care. 1996. 81p. SBU Report No. 119E.

(22) United States National Institutes of Health. Effectiveness of Long-term Oxygen Therapy in Treating People With Chronic Obstructive Pulmonary Disease (The Long-term Oxygen Treatment Trial [LOTT]) [Internet]. [updated 2010 Sep 14; cited 2010 Oct 28]. Available from: http://clinicaltrials.gov/ct2/show/NCT00692198?term=oxygen+therapy&rank=6

(23) Cranston JM, Crockett A, Moss J, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD001744. DOI: 10.1002/14651858.CD001744.pub2.

(24) Gorecka D, Gorzelak K, Sliwinski P, Tobiasz M, Zielinski J. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. Thorax. 1997;52(8):674-9.

(25) Haidl P, Clement C, Wiese C, Dellweg D, Kohler D. Long-term oxygen therapy stops the natural decline of endurance in COPD patients with reversible hypercapnia. Respiration. 2004;71(4):342-7.

(26) Fletcher EC, Luckett RA, Goodnight-White S, Miller CC, Qian W, Costarangos-Galarza C. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO2 above 60 mm Hg. Am Rev Respir Dis. 1992;145(5):1070-6.

(27) Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Enrhart M, Schott R, et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. Eur Respir J. 1999;14(5):1002-8.

(28) Wilt TJ, Niewoehner D, MacDonald R, Kane RL. Management of stable chronic obstructive pulmonary disease: a systematic review for a clinical practice guideline. Ann Intern Med. 2007;147(9):639-53.

(29) Sin DD, McAlister FA, Man SF, Anthonisen NR. Contemporary management of chronic obstructive pulmonary disease: scientific review. JAMA. 2003;290(17):2301-12.

(30) Eaton T, Fergusson W, Kolbe J, Lewis CA, West T. Short-burst oxygen therapy for COPD patients: a 6-month randomised, controlled study. Eur Respir J. 2006;27(4):697-704.

(31) Eaton T, Garrett JE, Young P, Fergusson W, Kolbe J, Rudkin S et al. Ambulatory oxygen improves quality of life of COPD patients: a randomised controlled study. Eur Respir J. 2002;20(2):306-12.

(32) McDonald CF, Blyth CM, Lazarus MD, Marschner I, Barter CE. Exertional oxygen of limited benefit in patients with chronic obstructive pulmonary disease and mild hypoxemia. Am J Respir Crit Care Med. 1995;152(5 Pt 1):1616-9.

(33) Lacasse Y, Lecours R, Pelletier C, Begin R, Maltais F. Randomised trial of ambulatory oxygen in oxygen-dependent COPD. Eur Respir J. 2005;25(6):1032-8.

(34) Bahadori K, FitzGerald JM. Risk factors of hospitalization and readmission of patients with COPD exacerbation - Systematic review. Int J Chron Obstruct Pulmon Dis. 2007;2(3):241-51.

(35) Garcia-Aymerich J, Farrero E, Felez MA, Izquierdo J, Marrades RM, Anto JM. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. Thorax. 2003;58(2):100-5.

(36) Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;159(1):158-64.

(37) Goksu E, Oktay C, Kartal M, Oskay A, Sayrac AV. Factors affecting revisit of COPD exacerbated patients presenting to emergency department. Eur J Emerg Med. 2010;17(5):283-5.

(38) Viegi G, Pistelli F, Sherrill DL, Maio S, Baldacci S, Carrozzi L. Definition, epidemiology and natural history of COPD. Eur Respir J. 2007;30(5):993-1013.

(39) Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: Role of comorbidities. Eur Respir J. 2006;28(6):1245-57.

(40) Ekstrom M, Franklin KA, Strom KE. Increased relative mortality in women with severe oxygen-dependent COPD. Chest. 2010;137(1):31-6.

(41) Gross NJ. Chronic obstructive pulmonary disease outcome measurements: what's important? What's useful? Proc Am Thorac Soc. 2005;2(4):267-71.

(42) Wedzicha JA. Effects of long-term oxygen therapy on neuropsychiatric function and quality of life. Respir Care. 2000;45(1):119-24.

(43) Agence d'evaluation des technologies et des modes d'intervention en sante (AETMIS) (Report prepared by Susan Law and Pascale Lehoux). Hospital Technology at Home: Portable Oxygen Therapy in COPD [Internet]. Montreal: AETMIS. 2004 Jul 1 [cited: 2011 Jan 19]. 103 p.

AETMIS 04-03. Available from: http://www.aetmis.gouv.qc.ca/site/download.php?f=2c3728e0d8adac6eb66642754ecbdb9b

(44) Eaton T, Lewis C, Young P, Kennedy Y, Garrett JE, Kolbe J. Long-term oxygen therapy improves health-related quality of life. Respir Med. 2004;98(4):285-93.

(45) Crockett AJ, Cranston JM, Moss JR, Alpers JH. Effects of long-term oxygen therapy on quality of life and survival in chronic airflow limitation. Monaldi Arch Chest Dis. 1999;54(2):193-6.

(46) Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10(4):407-15.

(47) Okubadejo AA, Paul EA, Jones PW, Wedzicha JA. Does long-term oxygen therapy affect quality of life in patients with chronic obstructive pulmonary disease and severe hypoxaemia? Eur Respir J. 1996;9(11):2335-9.

(48) Jones PW. Health status measurement in chronic obstructive pulmonary disease. Thorax. 2001;56(11):880-7.

(49) Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23(6):932-46.

(50) Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176(6):532-55.

(51) The National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax. 2004;59(Suppl 1):1-232.

(52) McDonald CF, Crockett AJ, Young IH. Adult domiciliary oxygen therapy. Position statement of the Thoracic Society of Australia and New Zealand. Med J Aust. 2005;182(12):621-6.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-7013-8 (PDF)

Ontario
Health Quality Ontario
Qualité des services de santé Ontario

Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis

BR McCurdy

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 8, pp. 1–102, March 2012

Suggested Citation

This report should be cited as follows:

McCurdy BR. Noninvasive positive pressure ventilation for acute respiratory failure in patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2012 March; 12(8):1-102. Available from:
www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Ventilation_Acute_March.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to: MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit:
http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the *Ontario Health Technology Advisory Committee* and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ARF	Acute Respiratory Failure
BiPAP	Bilevel positive airway pressure
CI	Confidence interval(s)
cm H_2O	Centimetres of water
COPD	Chronic obstructive pulmonary disease
FEV_1	Forced expiratory volume in 1 second
FiO_2	Fraction of inspired oxygen
HRQOL	Health-related quality of life
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
LOS	Length of stay
MAS	Medical Advisory Secretariat
NPPV	Noninvasive positive pressure ventilation
$PaCO_2$	Partial pressure of carbon dioxide in the arterial blood
PaO_2	Partial pressure of oxygen in the arterial blood
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
UMC	Usual medical care
VAP	Ventilator-associated pneumonia
WMD	Weighted mean difference

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective

The objective of this evidence-based analysis was to examine the effectiveness, safety, and cost-effectiveness of noninvasive positive pressure ventilation (NPPV) in the following patient populations: patients with acute respiratory failure (ARF) due to acute exacerbations of chronic obstructive pulmonary disease (COPD); weaning of COPD patients from invasive mechanical ventilation (IMV); and prevention of or treatment of recurrent respiratory failure in COPD patients after extubation from IMV.

Clinical Need and Target Population

Acute Hypercapnic Respiratory Failure

Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute or chronic and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD, so this is the focus of this evidence-based analysis. Hypercapnic respiratory failure occurs due to a decrease in the drive to breathe, typically due to increased work to breathe in COPD patients.

Technology

There are several treatment options for ARF. Usual medical care (UMC) attempts to facilitate adequate oxygenation and treat the cause of the exacerbation, and typically consists of supplemental oxygen, and a variety of medications such as bronchodilators, corticosteroids, and antibiotics. The failure rate of UMC is high and has been estimated to occur in 10% to 50% of cases.

The alternative is mechanical ventilation, either invasive or noninvasive. Invasive mechanical ventilation involves sedating the patient, creating an artificial airway through endotracheal intubation, and attaching the patient to a ventilator. While this provides airway protection and direct access to drain sputum, it can lead to substantial morbidity, including tracheal injuries and ventilator-associated pneumonia (VAP).

While both positive and negative pressure noninvasive ventilation exists, noninvasive negative pressure ventilation such as the iron lung is no longer in use in Ontario. Noninvasive positive pressure ventilation provides ventilatory support through a facial or nasal mask and reduces inspiratory work. Noninvasive positive pressure ventilation can often be used intermittently for short periods of time to treat respiratory failure, which allows patients to continue to eat, drink, talk, and participate in their own treatment decisions. In addition, patients do not require sedation, airway defence mechanisms and swallowing functions are maintained, trauma to the trachea and larynx are avoided, and the risk for VAP is reduced. Common complications are damage to facial and nasal skin, higher incidence of gastric distension with aspiration risk, sleeping disorders, and conjunctivitis. In addition, NPPV does not allow direct access to the airway to drain secretions and requires patients to cooperate, and due to potential discomfort, compliance and tolerance may be low.

In addition to treating ARF, NPPV can be used to wean patients from IMV through the gradual removal of ventilation support until the patient can breathe spontaneously. Five to 30% of patients have difficultly weaning. Tapering levels of ventilatory support to wean patients from IMV can be achieved using IMV or NPPV. The use of NPPV helps to reduce the risk of VAP by shortening the time the patient is intubated.

Following extubation from IMV, ARF may recur, leading to extubation failure and the need for reintubation, which has been associated with increased risk of nosocomial pneumonia and mortality. To

avoid these complications, NPPV has been proposed to help prevent ARF recurrence and/or to treat respiratory failure when it recurs, thereby preventing the need for reintubation.

Research Questions

1. What is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of acute hypercapnic respiratory failure due to acute exacerbations of COPD compared with
   a. usual medical care, and
   b. invasive mechanical ventilation?
2. What is the effectiveness, cost-effectiveness, and safety of NPPV compared with IMV in COPD patients after IMV for the following purposes:
   a. weaning COPD patients from IMV,
   b. preventing ARF in COPD patients after extubation from IMV, and
   c. treating ARF in COPD patients after extubation from IMV?

Research Methods

Literature Search

A literature search was performed on December 3, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), Wiley Cochrane, and the Centre for Reviews and Dissemination/International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2004 until December 3, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Since there were numerous studies that examined the effectiveness of NPPV for the treatment of ARF due to exacerbations of COPD published before 2004, pre-2004 trials which met the inclusion/exclusion criteria for this evidence-based review were identified by hand-searching reference lists of included studies and systematic reviews.

Inclusion Criteria

- English language full-reports;
- health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials (RCTs);
- studies performed exclusively in patients with a diagnosis of COPD or studies performed with patients with a mix of conditions if results are reported for COPD patients separately;
- patient population: (Question 1) patients with acute hypercapnic respiratory failure due to an exacerbation of COPD; (Question 2a) COPD patients being weaned from IMV; (Questions 2b and 2c) COPD patients who have been extubated from IMV.

Exclusion Criteria

- < 18 years of age
- animal studies

- duplicate publications
- grey literature
- studies examining noninvasive negative pressure ventilation
- studies comparing modes of ventilation
- studies comparing patient-ventilation interfaces
- studies examining outcomes not listed below, such as physiologic effects including heart rate, arterial blood gases, and blood pressure

Outcomes of Interest

- mortality
- intubation rates
- length of stay (intensive care unit [ICU] and hospital)
- health-related quality of life
- breathlessness
- duration of mechanical ventilation
- weaning failure
- complications
- NPPV tolerance and compliance

Statistical Methods

When possible, results were pooled using Review Manager 5 Version 5.1, otherwise, the results were summarized descriptively. Dichotomous data were pooled into relative risks using random effects models and continuous data were pooled using weighted mean differences with a random effects model. Analyses using data from RCTs were done using intention-to-treat protocols; P values < 0.05 were considered significant. A priori subgroup analyses were planned for severity of respiratory failure, location of treatment (ICU or hospital ward), and mode of ventilation with additional subgroups as needed based on the literature. Post hoc sample size calculations were performed using STATA 10.1.

Quality of Evidence

The quality of each included study was assessed taking into consideration allocation concealment, randomization, blinding, power/sample size, withdrawals/dropouts, and intention-to-treat analyses.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. The following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Summary of Findings

NPPV for the Treatment of ARF due to Acute Exacerbations of COPD

NPPV Plus Usual Medical Care Versus Usual Medical Care Alone for First Line Treatment

A total of 1,000 participants were included in 11 RCTs[1]; the sample size ranged from 23 to 342. The mean age of the participants ranged from approximately 60 to 72 years of age. Based on either the Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD stage criteria or the mean percent predicted forced expiratory volume in 1 second (FEV_1), 4 of the studies included people with severe COPD, and there was inadequate information to classify the remaining 7 studies by COPD severity. The severity of the respiratory failure was classified into 4 categories using the study population mean pH level as follows: mild ($pH \geq 7.35$), moderate ($7.30 \leq pH < 7.35$), severe ($7.25 \leq pH < 7.30$), and very severe ($pH < 7.25$). Based on these categories, 3 studies included patients with a mild respiratory failure, 3 with moderate respiratory failure, 4 with severe respiratory failure, and 1 with very severe respiratory failure.

The studies were conducted either in the ICU (3 of 11 studies) or general or respiratory wards (8 of 11 studies) in hospitals, with patients in the NPPV group receiving bilevel positive airway pressure (BiPAP) ventilatory support, except in 2 studies, which used pressure support ventilation and volume cycled ventilation, respectively. Patients received ventilation through nasal, facial, or oronasal masks. All studies specified a protocol or schedule for NPPV delivery, but this varied substantially across the studies. For example, some studies restricted the amount of ventilation per day (e.g., 6 hours per day) and the number of days it was offered (e.g., maximum of 3 days); whereas, other studies provided patients with ventilation for as long as they could tolerate it and recommended it for much longer periods of time (e.g., 7 to 10 days). These differences are an important source of clinical heterogeneity between the studies. In addition to NPPV, all patients in the NPPV group also received UMC. Usual medical care varied between the studies, but common medications included supplemental oxygen, bronchodilators, corticosteroids, antibiotics, diuretics, and respiratory stimulators.

The individual quality of the studies ranged. Common methodological issues included lack of blinding and allocation concealment, and small sample sizes.

Need for Endotracheal Intubation

Eleven studies reported the need for endotracheal intubation as an outcome. The pooled results showed a significant reduction in the need for endotracheal intubation in the NPPV plus UMC group compared with the UMC alone group (relative risk [RR], 0.38; 95% confidence interval [CI], 0.28–0.50). When subgrouped by severity of respiratory failure, the results remained significant for the mild, severe, and very severe respiratory failure groups.
GRADE: moderate

Inhospital Mortality

Nine studies reported inhospital mortality as an outcome. The pooled results showed a significant reduction in inhospital mortality in the NPPV plus UMC group compared with the UMC group (RR, 0.53; 95% CI, 0.35–0.81). When subgrouped by severity of respiratory failure, the results remained significant for the moderate and severe respiratory failure groups.
GRADE: moderate

Hospital Length of Stay

Eleven studies reported hospital length of stay (LOS) as an outcome. The pooled results showed a significant decrease in the mean length of stay for the NPPV plus UMC group compared with the UMC

[1] Two of the RCTs reported results from the same study, so these papers were treated as 1 publication.

alone group (weighted mean difference [WMD], −2.68 days; 95% CI, −4.41 to −0.94 days). When subgrouped by severity of respiratory failure, the results remained significant for the mild, severe, and very severe respiratory failure groups.
GRADE: moderate

Complications
Five studies reported complications. Common complications in the NPPV plus UMC group included pneumonia, gastrointestinal disorders or bleeds, skin abrasions, eye irritation, gastric insufflation, and sepsis. Similar complications were observed in the UMC group including pneumonia, sepsis, gastrointestinal disorders or bleeds, pneumothorax, and complicated endotracheal intubations. Many of the more serious complications in both groups occurred in those patients who required endotracheal intubation. Three of the studies compared complications in the NPPV plus UMC and UMC groups. While the data could not be pooled, overall, the NPPV plus UMC group experienced fewer complications than the UMC group.
GRADE: low

Tolerance/Compliance
Eight studies reported patient tolerance or compliance with NPPV as an outcome. NPPV intolerance ranged from 5% to 29%. NPPV tolerance was generally higher for patients with more severe respiratory failure. Compliance with the NPPV protocol was reported by 2 studies, which showed compliance decreases over time, even over short periods such as 3 days.

NPPV Versus IMV for the Treatment of Patients Who Failed Usual Medical Care
A total of 205 participants were included in 2 studies; the sample sizes of these studies were 49 and 156. The mean age of the patients was 71 to 73 years of age in 1 study, and the median age was 54 to 58 years of age in the second study. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, patients in 1 study had very severe COPD. The COPD severity could not be classified in the second study. Both studies had study populations with a mean pH less than 7.23, which was classified as very severe respiratory failure in this analysis. One study enrolled patients with ARF due to acute exacerbations of COPD who had failed medical therapy. The patient population was not clearly defined in the second study, and it was not clear whether they had to have failed medical therapy before entry into the study.

Both studies were conducted in the ICU. Patients in the NPPV group received BiPAP ventilatory support through nasal or full facial masks. Patients in the IMV group received pressure support ventilation.

Common methodological issues included small sample size, lack of blinding, and unclear methods of randomization and allocation concealment. Due to the uncertainty about whether both studies included the same patient population and substantial differences in the direction and significance of the results, the results of the studies were not pooled.

Mortality
Both studies reported ICU mortality. Neither study showed a significant difference in ICU mortality between the NPPV and IMV groups, but 1 study showed a higher mortality rate in the NPPV group (21.7% vs. 11.5%) while the other study showed a lower mortality rate in the NPPV group (5.1% vs. 6.4%). One study reported 1-year mortality and showed a nonsignificant reduction in mortality in the NPPV group compared with the IMV group (26.1% vs. 46.1%).
GRADE: low to very low

Intensive Care Unit Length of Stay
Both studies reported LOS in the ICU. The results were inconsistent. One study showed a statistically significant shorter LOS in the NPPV group compared with the IMV group (5 ± 1.35 days vs. 9.29 ± 3

days; $P < 0.001$); whereas, the other study showed a nonsignificantly longer LOS in the NPPV group compared with the IMV group (22 ± 19 days vs. 21 ± 20 days; $P = 0.86$).
GRADE: very low

Duration of Mechanical Ventilation
Both studies reported the duration of mechanical ventilation (including both invasive and noninvasive ventilation). The results were inconsistent. One study showed a statistically significant shorter duration of mechanical ventilation in the NPPV group compared with the IMV group (3.92 ± 1.08 days vs. 7.17 ± 2.22 days; $P < 0.001$); whereas, the other study showed a nonsignificantly longer duration of mechanical ventilation in the NPPV group compared with the IMV group (16 ± 19 days vs. 15 ± 21 days; $P = 0.86$).
GRADE: very low

Complications
Both studies reported ventilator-associated pneumonia and tracheotomies. Both showed a reduction in ventilator-associated pneumonia in the NPPV group compared with the IMV group, but the results were only significant in 1 study (13% vs. 34.6%, $P = 0.07$; and 6.4% vs. 37.2%, $P < 0.001$, respectively). Similarly, both studies showed a reduction in tracheotomies in the NPPV group compared with the IMV group, but the results were only significant in 1 study (13% vs. 23.1%, $P = 0.29$; and 6.4% vs. 34.6%; $P < 0.001$).
GRADE: very low

Other Outcomes
One of the studies followed patients for 12 months. At the end of follow-up, patients in the NPPV group had a significantly lower rate of needing de novo oxygen supplementation at home. In addition, the IMV group experienced significant increases in functional limitations due to COPD, while no increase was seen in the NPPV group. Finally, no significant differences were observed for hospital readmissions, ICU readmissions, and patients with an open tracheotomy, between the NPPV and IMV groups.

NPPV for Weaning COPD Patients From IMV

A total of 80 participants were included in the 2 RCTs; the sample sizes of the studies were 30 and 50 patients. The mean age of the participants ranged from 58 to 69 years of age. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, both studies included patients with very severe COPD. Both studies also included patients with very severe respiratory failure (mean pH of the study populations was less than 7.23). Chronic obstructive pulmonary disease patients receiving IMV were enrolled in the study if they failed a T-piece weaning trial (spontaneous breathing test), so they could not be directly extubated from IMV.

Both studies were conducted in the ICU. Patients in the NPPV group received weaning using either BiPAP or pressure support ventilation NPPV through a face mask, and patients in the IMV weaning group received pressure support ventilation. In both cases, weaning was achieved by tapering the ventilation level.

The individual quality of the studies ranged. Common methodological problems included unclear randomization methods and allocation concealment, lack of blinding, and small sample size.

Mortality
Both studies reported mortality as an outcome. The pooled results showed a significant reduction in ICU mortality in the NPPV group compared with the IMV group (RR, 0.47; 95% CI, 0.23–0.97; $P = 0.04$).
GRADE: moderate

Intensive Care Unit Length of Stay
Both studies reported ICU LOS as an outcome. The pooled results showed a nonsignificant reduction in ICU LOS in the NPPV group compared with the IMV group (WMD, −5.21 days; 95% CI, −11.60 to 1.18 days).
GRADE: low

Duration of Mechanical Ventilation
Both studies reported duration of mechanical ventilation (including both invasive and noninvasive ventilation) as an outcome. The pooled results showed a nonsignificant reduction in duration of mechanical ventilation (WMD, −3.55 days; 95% CI, −8.55 to 1.44 days).
GRADE: low

Nosocomial Pneumonia
Both studies reported nosocominal pneumonia as an outcome. The pooled results showed a significant reduction in nosocomial pneumonia in the NPPV group compared with the IMV group (RR, 0.14; 95% CI, 0.03–0.71; $P = 0.02$).
GRADE: moderate

Weaning Failure
One study reported a significant reduction in weaning failure in the NPPV group compared with the IMV group, but the results were not reported in the publication. In this study, 1 of 25 patients in the NPPV group and 2 of 25 patients in the IMV group could not be weaned after 60 days in the ICU.

NPPV After Extubation of COPD Patients From IMV

The literature was reviewed to identify studies examining the effectiveness of NPPV compared with UMC in preventing recurrence of ARF after extubation from IMV or treating acute ARF which has recurred after extubation from IMV. No studies that included only COPD patients or reported results for COPD patients separately were identified for the prevention of ARF postextubation.

One study was identified for the treatment of ARF in COPD patients that recurred within 48 hours of extubation from IMV. This study included 221 patients, of whom 23 had COPD. A post hoc subgroup analysis was conducted examining the rate of reintubation in the COPD patients only. A nonsignificant reduction in the rate of reintubation was observed in the NPPV group compared with the UMC group (7 of 14 patients vs. 6 of 9 patients, $P = 0.67$). *GRADE: low*

Conclusions

NPPV Plus UMC Versus UMC Alone for First Line Treatment of ARF due to Acute Exacerbations of COPD

- Moderate quality of evidence showed that compared with UMC, NPPV plus UMC significantly reduced the need for endotracheal intubation, inhospital mortality, and the mean length of hospital stay.
- Low quality of evidence showed a lower rate of complications in the NPPV plus UMC group compared with the UMC group.

NPPV Versus IMV for the Treatment of ARF in Patients Who Have Failed UMC

- Due to inconsistent and low to very low quality of evidence, there was insufficient evidence to draw conclusions on the comparison of NPPV versus IMV for patients who failed UMC.

NPPV for Weaning COPD Patients From IMV

- Moderate quality of evidence showed that weaning COPD patients from IMV using NPPV results in significant reductions in mortality, nosocomial pneumonia, and weaning failure compared with weaning with IMV.
- Low quality of evidence showed a nonsignificant reduction in the mean LOS and mean duration of mechanical ventilation in the NPPV group compared with the IMV group.

NPPV for the Treatment of ARF in COPD Patients After Extubation From IMV

- Low quality of evidence showed a nonsignificant reduction in the rate of reintubation in the NPPV group compared with the UMC group; however, there was inadequate evidence to draw conclusions on the effectiveness of NPPV for the treatment of ARF in COPD patients after extubation from IMV.

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this evidence-based analysis was to examine the effectiveness, safety, and cost-effectiveness of noninvasive positive pressure ventilation (NPPV) in the following patient populations: patients with acute respiratory failure (ARF) due to acute exacerbations of chronic obstructive pulmonary disease (COPD); weaning of COPD patients from invasive mechanical ventilation (IMV); and prevention of or treatment of recurrent respiratory failure in COPD patients after extubation from IMV.

Clinical Need and Target Population

Acute Hypercapnic Respiratory Failure

Acute respiratory failure can lead to life-threatening changes in the arterial blood gases and acid-base status and develops quickly. (1) Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute or chronic and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD, so this is the focus of this evidence-based analysis.

Hypercapnic respiratory failure occurs due to a decrease in the drive to breathe, typically due to increased work to breathe in COPD patients. (2) Chronic obstructive pulmonary disease patients typically have impaired oxygenation due to loss of alveolar volume and impaired ventilation from dead space and poor respiratory mechanics. This puts COPD patients at high risk of developing respiratory failure when faced with additional pulmonary challenges such as an acute exacerbation. (3)

Technology

There are several treatment options for ARF. Usual medical care (UMC) attempts to facilitate adequate oxygenation and treat the cause of the exacerbation, and typically consists of supplemental oxygen, and a variety of medications such as bronchodilators, corticosteroids, and antibiotics. (4) The failure rate of UMC is high and has been estimated to occur in 10% to 50% of cases. (5)

The alternative treatment for ARF is mechanical ventilation, either invasive or noninvasive. Traditionally, IMV was the primary alternative, which involves sedating the patient, creating an artificial airway through endotracheal intubation, and attaching the patient to a ventilator. This provides airway protection and direct access to drain sputum. However, there are a number of common complications that may cause substantial morbidity and risk in patients receiving IMV, including tracheal injuries sustained during the intubation procedure as well as complications during the course of IMV, such as ventilator-associated pneumonia (VAP) and sinusitis. (4;6;7) Ventilator-associated pneumonia is associated with mortality rates of 30% or higher in the intensive care unit (ICU). (6)

Noninvasive ventilation is an alternative to IMV. While both positive and negative pressure noninvasive ventilation exists, noninvasive negative pressure ventilation such as the iron lung is no longer in use in Ontario. Noninvasive positive pressure ventilation provides ventilatory support through a facial or nasal mask attached to a flow generator or regular ventilator. (4) It reduces inspiratory work, recruits collapsed and poorly ventilated portions of the lung, and improves alveolar ventilation, enabling more efficient gas exchange. While there are different modes of NPPV possible, bilevel positive airway pressure ventilation (BiPAP) is the most common. Bilevel positive airway pressure ventilation uses alternating pressures, inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP), to enable improved ventilation and recruitment, respectively. (8)

There are numerous benefits to NPPV compared with IMV. Noninvasive positive pressure ventilation can often be used intermittently for short periods of time to treat respiratory failure, which allows patients to continue to eat, drink, talk, and participate in their own treatment decisions. (4) In addition, patients do not require sedation, airway defence mechanisms and swallowing functions are maintained, trauma to the trachea and larynx are avoided, and the risk of VAP is reduced. (9) Common complications associated with NPPV are damage to facial and nasal skin, higher incidence of gastric distension with aspiration risk, sleeping disorders, and conjunctivitis. (7) In addition, NPPV does not allow direct access to the airway to drain secretions and requires patients to cooperate, and due to potential discomfort, compliance and tolerance may be low. (4;7;9) Furthermore, there are various contraindications to NPPV: coma, shock, cardiorespiratory arrest, swallowing disorders, mental immaturity, face deformations, and an unstable respiratory centre. (7)

NPPV to Wean COPD Patients From IMV

In addition to treating ARF, NPPV can be used to wean patients from IMV. Approximately one third of the time patients spend on mechanical ventilation is spent weaning the patient from IMV through the gradual removal of ventilation support until the patient can breathe spontaneously. (10) Many patients are weaned without difficultly, but 5% to 30% have difficultly weaning, a problem which can be common in COPD patients. (10) Tapering levels of ventilatory support to wean patients from IMV can be achieved using IMV or NPPV. The use of NPPV helps to reduce the risk of VAP by shortening the time the patient is intubated.

NPPV to Prevent or Treat Recurrent ARF After Extubation From IMV

Following extubation from IMV, ARF may recur leading to extubation failure and the need for reintubation. Extubation failure has been associated with an increased risk of nosocomial pneumonia and mortality. (11) To avoid these complications, NPPV has been proposed to help prevent ARF recurrence and/or to treat respiratory failure when it recurs, thereby preventing the need for reintubation.

Evidence-Based Analysis

Research Questions

1. What is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of acute hypercapnic respiratory failure due to acute exacerbations of COPD compared with
   a. usual medical care, and
   b. invasive mechanical ventilation?
2. What is the effectiveness, cost-effectiveness, and safety of NPPV compared with IMV in COPD patients after IMV for the following purposes:
   a. weaning COPD patients from IMV,
   b. preventing ARF in COPD patients after extubation from IMV, and
   c. treating ARF in COPD patients after extubation from IMV?

Research Methods

Literature Search

Search Strategy

A literature search was performed on December 3, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), Wiley Cochrane, and the Centre for Reviews and Dissemination/International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2004 until December 3, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Since there were numerous studies that examined the effectiveness of NPPV for the treatment of ARF due to exacerbations of COPD published before 2004, pre-2004 trials which met the inclusion/exclusion criteria for this evidence-based review were identified by hand-searching reference lists of included studies and systematic reviews.

Inclusion Criteria

- English language full-reports;
- health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials (RCTs);
- studies performed exclusively in patients with a diagnosis of COPD or studies performed with patients with a mix of conditions if results are reported for COPD patients separately;
- patient population: (Question 1) patients with acute hypercapnic respiratory failure due to an exacerbation of COPD; (Question 2a) COPD patients being weaned from IMV; (Questions 2b and 2c) COPD patients who have been extubated from IMV.

Exclusion Criteria

- < 18 years of age
- animal studies
- duplicate publications
- grey literature
- studies examining noninvasive negative pressure ventilation
- studies comparing modes of ventilation
- studies comparing patient-ventilation interfaces
- studies examining outcomes not listed below such as physiologic effects including heart rate, arterial blood gases, and blood pressure

Outcomes of Interest

- mortality
- intubation rates
- length of stay (intensive care unit [ICU] and hospital)
- health-related quality of life (HRQOL)
- breathlessness
- duration of mechanical ventilation
- weaning failure
- complications
- NPPV tolerance and compliance

Statistical Analysis

When possible, results were pooled using Review Manager 5 Version 5.1 (12), otherwise, the results were summarized descriptively. Dichotomous data were pooled into relative risks using random effects models and continuous data were pooled using weighted mean differences with a random effects model. Analyses using data from RCTs were done using intention-to-treat protocols; *P* values < 0.05 were considered significant. Post hoc sample size calculations were performed using STATA 10.1.

A priori subgroup analyses were planned for the severity of respiratory failure, location of treatment (ICU or hospital ward), and mode of ventilation, with additional subgroups as needed based on the identified literature. For the severity of respiratory failure subgroups, the mean pH level was used to classify a study as mild ($pH \geq 7.35$), moderate ($7.30 \leq pH < 7.35$), severe ($7.25 \leq pH < 7.30$), and very severe ($pH < 7.25$) respiratory failure. For those studies that presented the mean pH for each study group separately, and the mean pH of the 2 arms fell into separate categories, the higher category was used.

Quality of Evidence

The quality of each included study was assessed taking into consideration the following 7 study design characteristics:

- adequate allocation concealment,
- randomization (study must include a description of the randomization procedure used and must be a proper method),
- power/sample size (adequate sample size based on a priori calculations; underpowered studies were identified, when possible, using post hoc sample size power calculations),
- blinding (if double blinding is not possible, a single blind study with unbiased assessment of outcomes was considered adequate for this criterion),
- < 20% withdrawals/dropouts,
- intention-to-treat analysis conducted and done properly (withdrawals/dropouts considered in analysis), and
- other criteria as appropriate for the particular research question and study design

To evaluate the quality of the weaning trials, several additional quality factors were identified based on the quality assessments conducted in previous systematic reviews on this topic by Burns et al (13;14):

- daily screening to identify patients capable of unassisted breathing,
- predefined criteria to identify weaning candidates,
- use of weaning protocols or guidelines (in both groups),
- predefined criteria for failure of a prerandomization spontaneous breathing trial,
- predefined criteria for discontinuation of mechanical ventilation (in both groups), and
- predefined criteria for reintubation after weaning failure.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (15) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding, and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High Further research is very unlikely to change confidence in the estimate of effect.

Moderate Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very Low Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

The database search yielded 2,585 citations published between January 1, 2004, and December 3, 2010 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded in the analysis.

Nineteen studies (11 systematic reviews and 8 RCTs) met the inclusion criteria. The references lists of the included studies and identified systematic reviews were hand searched to identify any additional potentially relevant studies, and 12 additional citations (3 systematic reviews and 9 RCTs) which were published *before the 2004 search* date were included for a total of 31 included citations.

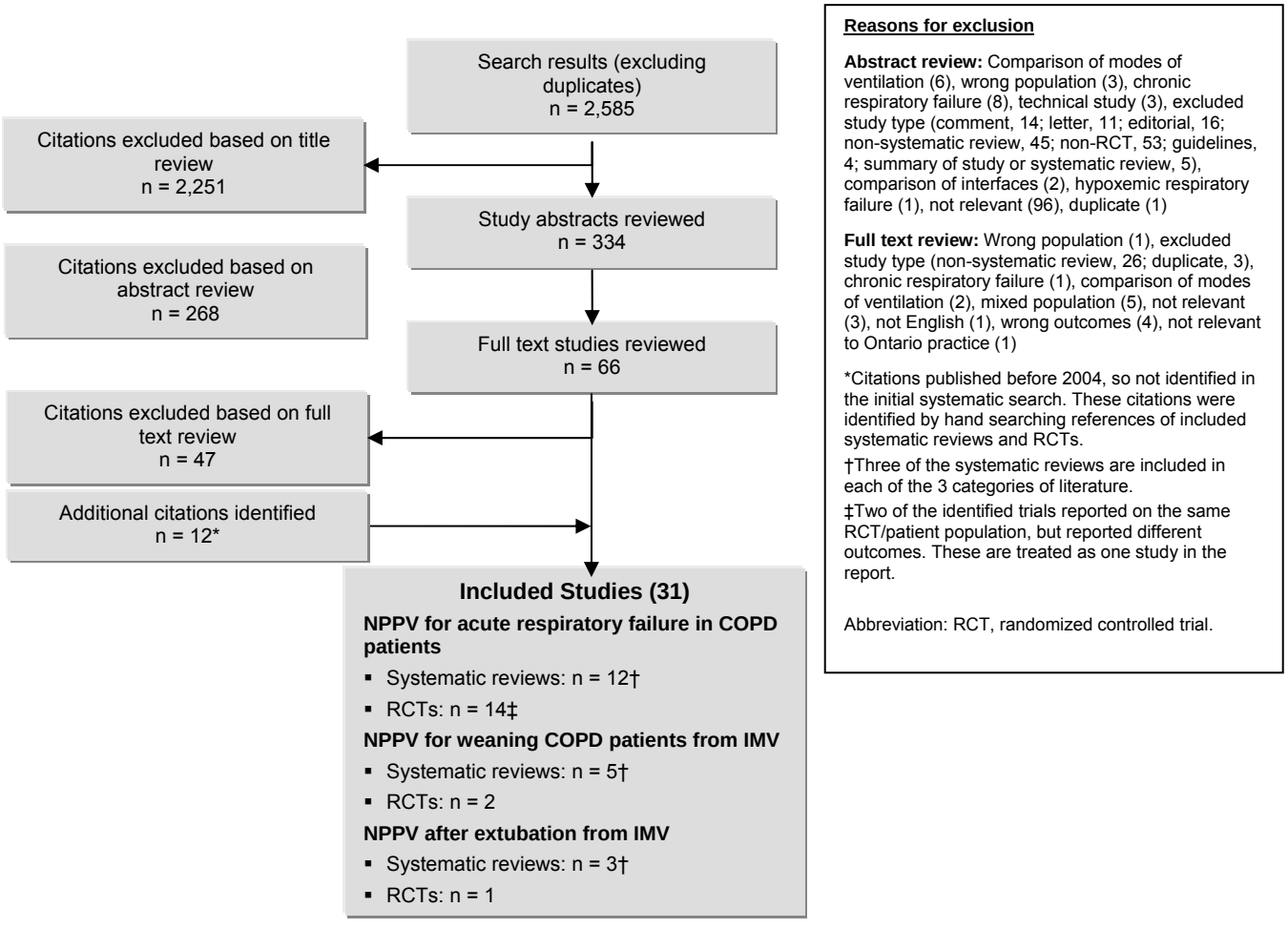


Figure 1: Citation Flow Chart

For each included study, the study design was identified and is summarized below in Table 1, which is a modified version of a hierarchy of study design by Goodman. (16)

Table 1: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	14
Large RCT†	5‡
Small RCT	12§
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	0
Non-RCT with contemporaneous controls	0
Systematic review of non-RCTs with historical controls	0
Non-RCT with historical controls	0
Database, registry, or cross-sectional study	0
Case series	0
Retrospective review, modelling	0
Studies presented at an international conference or other sources of grey literature	0
Expert opinion	n/a
Total	31

*Abbreviation: RCT, randomized controlled trial.
†Large RCT refers to a study with at least 100 patients.
‡Two of the large RCTs report different outcomes for the same patient population.
§One study had more than 100 patients, but fewer than 100 COPD patients.

The results of this evidence-based analysis are divided into 3 sections:

- NPPV for the treatment of ARF due to acute exacerbations of COPD,
- NPPV for weaning COPD patients from IMV, and
- NPPV after extubation from IMV in COPD patients.

Each section addresses 1 or 2 of the research questions.

NPPV for the Treatment of Acute Respiratory Failure due to Acute Exacerbations of COPD

This section of the evidence-based review addresses the first research question: what is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of acute hypercapnic respiratory failure due to acute exacerbations of COPD?

Systematic Reviews

Twelve systematic reviews were identified that examined the published literature on the use of NPPV for the treatment of ARF due to exacerbations of COPD. (2-4;8;17-24) Seven of the reviews provide a narrative review of the evidence and discuss only a few of the key studies in the area or the findings and conclusions from other reviews/meta-analyses. (2;3;8;19;21;23;24) The remaining 5 reviews are more detailed and include statistical analyses such as meta-analyses. A main difference across the systematic reviews is the number of included studies. Common reasons for the variation in the studies included in these reviews are differences in language restrictions, inclusion or exclusion of unpublished (abstract) data, and inclusion or exclusion of studies with mixed patient populations.

Full details about the systematic reviews including a comparison of the included studies, and the methods and main findings can be found in Appendix 2. Overall, the systematic reviews found that NPPV plus UMC compared with UMC alone resulted in reduced mortality, intubation rates, and ICU or hospital lengths of stay.

Randomized Controlled Trials

Thirteen[1] RCTs evaluating the effectiveness of NPPV for the treatment of ARF due to acute exacerbations of COPD were identified. The following comparisons were examined:

- NPPV plus UMC versus UMC alone (11 RCTs)
- NPPV versus IMV (2 RCTs)

NPPV Plus UMC Compared With UMC Alone

For the 11 studies comparing NPPV plus UMC and UMC alone, the general study characteristics including inclusion and exclusion criteria, length of follow-up, outcomes, details about the intervention and UMC, and details on the patient populations included in each study are shown in Tables A1, A2, and A3 in Appendix 2.

The majority of the studies were conducted in either the ICU or respiratory wards in hospitals, with patients in the NPPV plus UMC group receiving BiPAP ventilatory support. All studies specified a protocol or schedule for NPPV delivery, but this varied substantially across the studies (Table A9). For example, some studies restricted the amount of ventilation per day (e.g., 6 hours per day) and the number of days it was offered (e.g., maximum of 3 days); whereas other studies provided patients with ventilation for as long as they could tolerate it and recommended it for much longer periods of time (e.g., 7 to 10 days). These differences are an important source of clinical heterogeneity between the studies.

Usual medical care varied between studies, but common medications included supplemental oxygen, bronchodilators, corticosteroids, antibiotics, diuretics, and respiratory stimulators. Patients had very severe COPD and ARF of varying severities from mild (mean pH $\geq$ 7.35) to very severe (mean pH $\leq$ 7.25).

Duration of NPPV

Given the differences in the ventilation protocols, the actual duration of NPPV, defined as either the number of hours of NPPV per day or the total number of days on NPPV, varied widely across studies (Table 2).

[1] Fourteen papers were identified; however 2 of the trials reported results for 1, study but different outcomes. These 2 papers have been treated as 1 study.

Table 2: Duration of NPPV (NPPV Plus UMC Versus UMC Alone Comparison)*

Author, Year	Duration NPPV, Mean Days (SD)	Duration NPPV, Mean Hours per Day (SD)	Duration of MV After Intubation, Days	
			NPPV	UMC
Barbe et al, 1996 (25)	Total: 3†	6 †	NR	NR
Bott et al, 1993 (26)	6 (range, 2–9)‡	7.63 (range, 1–23) per day‡	NR	NR
Brochard et al, 1995 (27)	4 (4) §	NR	25 (17)	17 (21)
Carrera et al, 2009 (28)	Total: 3	NPPV group Day 1: 13 (4) Day 2: 12 (4) Day 3: 11 (4) Sham group Day1 : 14 (5) Day 2: 13 (5) Day 3: 14 (5)	NR	NR
Dhamija et al, 2005 (29)	Total duration: 3 †	6 †	NR	NR
Dikensoy et al, 2002 (5)	Range, 6–36 hours	Mean total duration: 11.2 (9.5) (range, 6–36)	NR	NR
Keenan et al, 2005 (30)	Range, 0-3	For those compliant with therapy (>1 hour on day) Day 1: 6.2 (3.1) (range, 1–9), n = 22; Day 2: 5.7 (1.1) (range, 3–7), n = 17; Day 3: 4.2 (0.3) (range, 4–5), n = 12	NR	NR
Khilnani et al, 2010 (31)	NR	≤ 16/day†	NR	NR
Kramer et al, 1995 (9)	Mean (NPPV + IMV): 6.4 (2.4)	NR‖	NR	Mean (NPPV + IMV): 7.6 (3.6)
Plant et al, 2000/2001 (32)	Median, 3 (range, 0–26)	Day 1: median, 8 Day 2: median, 7 Day 3: median, 5	NR	NR
Wang et al, 2005 (33)	10 (7)	11 (5)	NR	NR

*Abbreviations: d, day; hr, hour; IMV, invasive mechanical ventilation; MV, mechanical ventilation; NPPV, noninvasive positive pressure ventilation; NR, not reported; SD, standard deviation; UMC, usual medical care.

†Based on study protocol, actual days or duration per day were not reported.

‡Results for the 26 patients who were compliant with NPPV therapy only

§n = 32, excludes those patients who received intubation and IMV

‖In all patients, including those without COPD, average daily use for the first 2 days was 14.4 ± 2.2 hours (range, 0.33–22 hours) throughout the day and night. Most patients were weaned entirely off NPPV after 3 to 4 days.

Need for Endotracheal Intubation

All 11 studies reported the need for endotracheal intubation as an outcome. (5;9;25-34) In some studies, the patients who were judged to need intubation for the delivery of IMV were not all intubated. Instead of intubation in these studies, patients may have been offered alternative treatment options or refused intubation. For example, patients in the UMC alone group may have been given the option of a trial of NPPV, the patients in the UMC or NPPV group may have refused the option of IMV and may have continued receiving NPPV or medical therapy, and/or the type of ventilator, ventilator mode, or interface may have been changed for the NPPV group. For the purposes of this analysis, all patients who failed their treatment and were judged to require intubation are included as events regardless of whether or not they were actually intubated.

When the results of all studies were pooled (Figure 2), there was a 62% reduction in the risk of the need for endotracheal intubation in the NPPV plus UMC group compared with the UMC alone group, and this reduction was statistically significant (RR, 0.38; 95% CI, 0.28–0.50; $P < 0.001$).

	NPPV		UMC			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Barbe 1996	0	10	0	14		Not estimable	
Bott 1993	0	30	5	30	1.0%	0.09 [0.01, 1.57]	
Brochard 1995	11	43	31	42	27.9%	0.35 [0.20, 0.60]	
Carrera 2009	5	37	13	38	9.5%	0.40 [0.16, 1.00]	
Dhamija 2005	0	14	1	15	0.8%	0.36 [0.02, 8.07]	
Dikensoy 2002	2	17	7	17	4.0%	0.29 [0.07, 1.18]	
Keenan 2005	2	25	5	27	3.4%	0.43 [0.09, 2.03]	
Khilnani 2010	3	20	12	20	6.7%	0.25 [0.08, 0.75]	
Kramer 1995	1	11	8	12	2.2%	0.14 [0.02, 0.92]	
Plant 2000	18	118	32	118	30.4%	0.56 [0.34, 0.94]	
Wang 2005	8	171	26	171	14.0%	0.31 [0.14, 0.66]	
Total (95% CI)		**496**		**504**	**100.0%**	**0.38 [0.28, 0.50]**	
Total events	50		140				

Heterogeneity: Tau² = 0.00; Chi² = 5.49, df = 9 (P = 0.79); I² = 0%
Test for overall effect: Z = 6.68 (P < 0.00001)

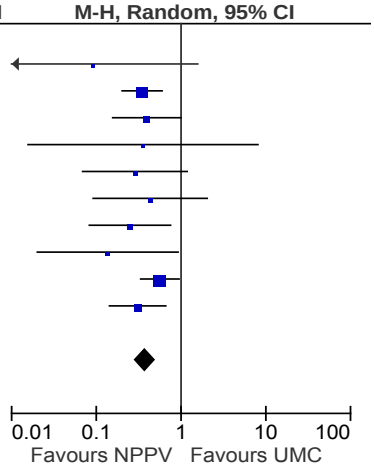


Figure 2: Pooled Results for the Need for Endotracheal Intubation (NPPV Plus UMC Versus UMC Alone)*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

When the results are subgrouped by severity of respiratory failure, the significant reduction is maintained in the mild, severe, and very severe groups, but the reduction in endotracheal intubation in the NPPV group with moderate respiratory failure is not statistically significant ($P = 0.21$) (Figure 3). Similarly, there is a significant reduction in the risk of the need for endotracheal intubation in the NPPV group for those patients treated in general or respiratory hospital wards ($P < 0.001$), patients treated in the ICU ($P < 0.00001$), studies which had a priori intubation criteria ($P < 0.001$), and studies which did not have a priori intubation criteria ($P = 0.02$) (Appendix 5).

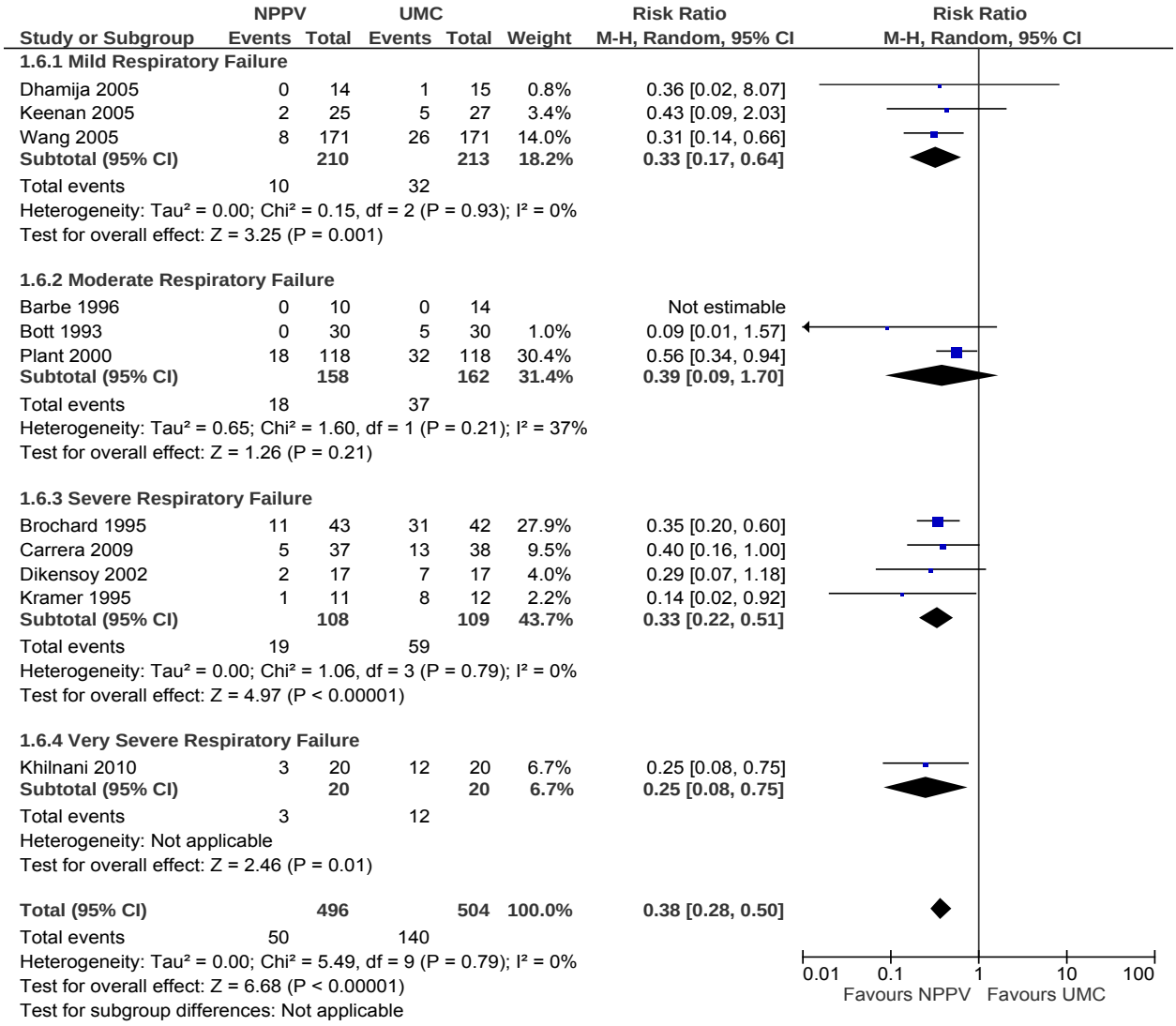


Figure 3: Pooled Results for the Need for Endotracheal Intubation Stratified by Severity of ARF (NPPV Plus UMC Versus UMC Alone Comparison)*

*Abbreviations: ARF, acute respiratory failure; CI, confidence interval; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

Mortality

All of the studies included mortality as an outcome. (5;9;25-34)[2] Inhospital mortality was most commonly reported, although Bott et al (26) reported 30-day mortality, and Plant et al (34) reported long-term survival (study follow-up ranged from 3 to 26 months).

Inhospital Mortality

When the results of all studies were pooled (Figure 4), there was a 47% reduction in the risk of death in the NPPV plus UMC group compared with the UMC alone group, and this reduction was statistically significant (RR, 0.53; 95% CI, 0.35–0.81, $P = 0.003$).

[2] The inhospital mortality results for Carrera et al (28) were obtained from the authors of the study.

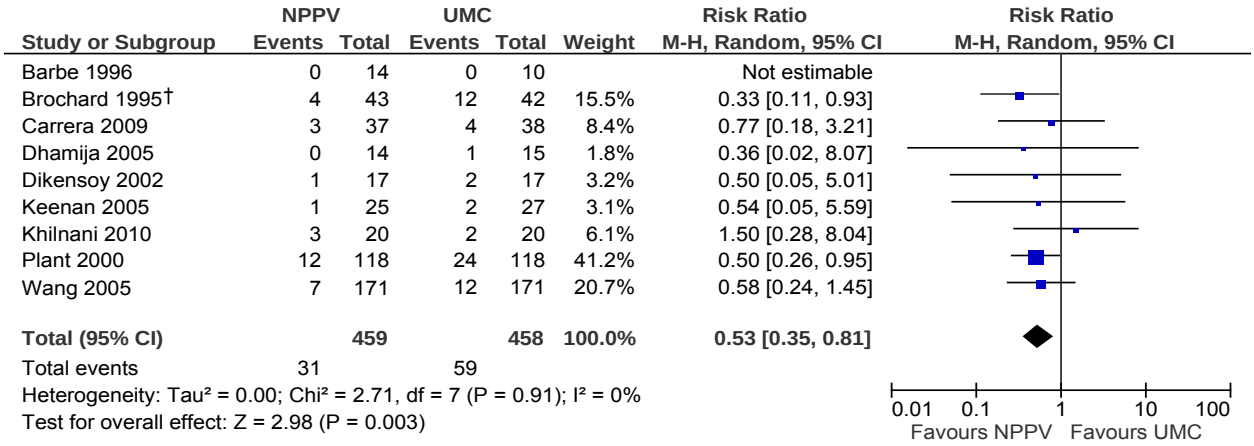


Figure 4: Pooled Results for Inhospital Mortality (NPPV Plus UMC Versus UMC Alone Comparison)*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

†While there was a significant difference in the inhospital mortality between the NPPV and UMC groups in Brochard et al (27), 3 of the 4 deaths in the NPPV group and 10 of the 12 deaths in the UMC alone group occurred in those patients who failed treatment and were intubated and mechanically ventilated. When the mortality rates were compared after adjustment for intubation, the difference was no longer significant. This indicates that the number of patients requiring intubation was the main factor influencing mortality. (27)

Note: the mortality data from Kramer et al (9) have been excluded from the pooled analysis because the results were for the entire study population and not presented separately for COPD patients only.

When the results are subgrouped by severity of respiratory failure, the significant reduction is maintained in the moderate and severe subgroups only. There is a nonsignificant reduction in the risk of death in the mild respiratory failure subgroup ($P = 0.16$). There is a nonsignificant increase in the risk of mortality in the NPPV group compared with the UMC alone group in the very severe respiratory failure subgroup, but this result is based on only 1 study with a small sample size ($P = 0.64$) (Figure 5).

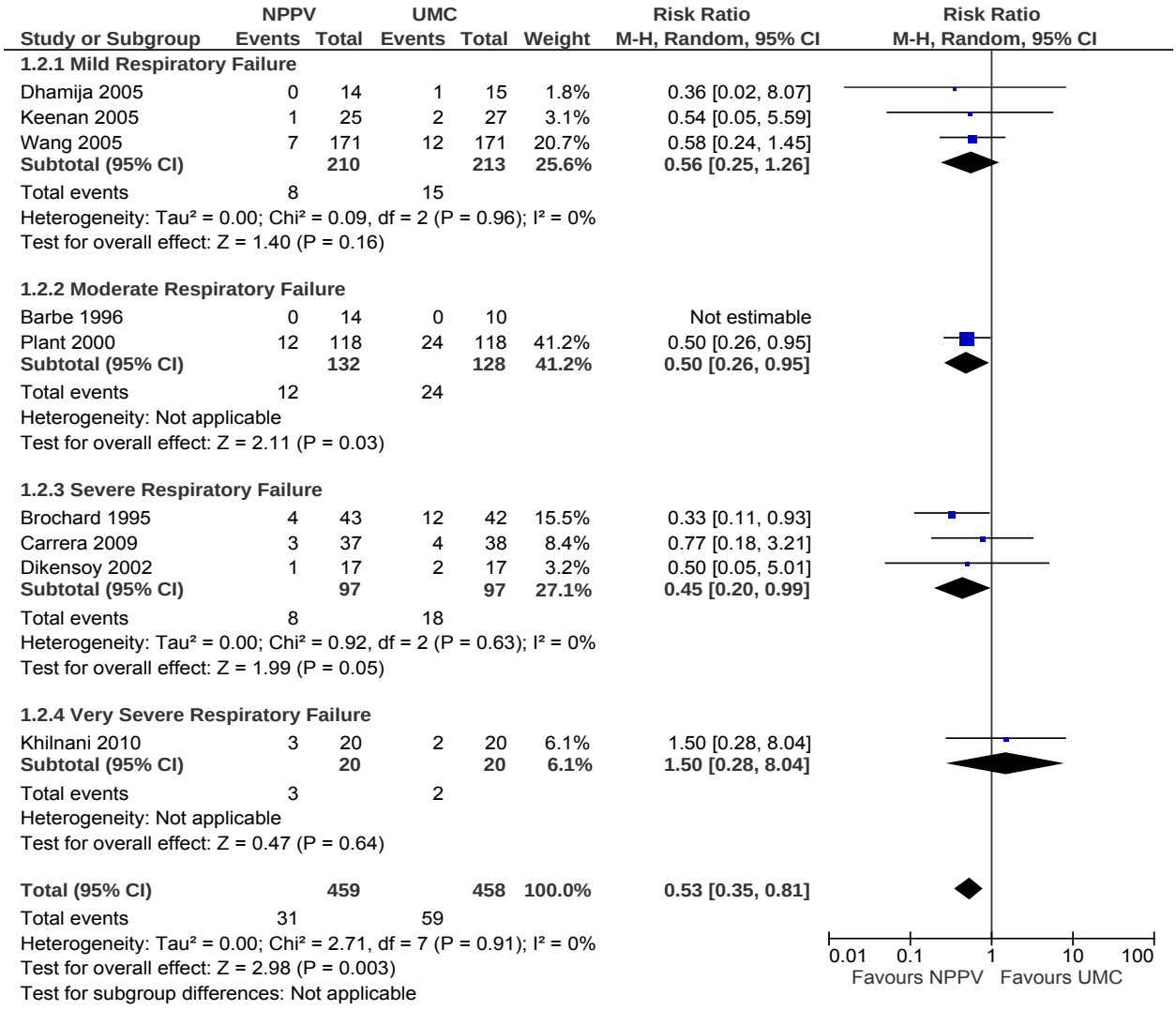


Figure 5: Pooled Results for Inhospital Mortality Stratified by Severity of ARF (NPPV Plus UMC Versus UMC Alone Comparison)*

*Abbreviations: ARF, acute respiratory failure; CI, confidence interval; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.
Note: the mortality data from Kramer et al (9) have been excluded from the pooled analysis because the results were for the entire study population and not presented separately for COPD patients only.

Thirty-Day Mortality

Bott et al (26) found a nonsignificant reduction in the risk of death in the NPPV plus UMC group compared with the UMC alone group at 30 days (3 deaths vs. 9 deaths, $P = 0.07$). However, there was a significant difference in survival between the 3 centres involved in this study: 0 deaths among those patients enrolled at centre C, 5 among those at centre B, and 7 among those at centre A (centre C vs. centre A and B: Fisher's exact test, $P = 0.005$). (26)

Long-Term Survival

The second publication from Plant et al (34) followed patients for 3 to 26 months after enrolment to assess long-term survival. There was no significant difference ($P = 0.12$) in the median survival between the NPPV plus UMC and the UMC alone groups (16.8 months vs. 13.4 months, respectively). The 1-year survival in the NPPV plus UMC group was 61.6% compared with 53.9% in the UMC alone group. (34)

Hospital Length of Stay

All 11 studies reported hospital length of stay (LOS) (Table 3). The mean hospital LOS was 2.68 days shorter in the NPPV plus UMC group compared with the UMC alone group (mean difference, −2.68; 95% CI, −4.41 to −0.94; *P* = 0.002) (Figure 6).

Table 3: Mean Hospital Length of Stay (NPPV Plus UMC Versus UMC Alone)*

	Hospital Length of Stay, Mean (SD), Days		
Author, Year	**NPPV + UMC**	**UMC**	***P* Value**
Barbe et al, 1996 (25)	10.6 (9)	11.3 (1.3)	> 0.05
Bott et al, 1993 (26)	9 (5.25)† Median, 9 (range, 1–22)	9 (9.5)† Median, 9 (range, 1–39)	NR
Brochard et al, 1995 (27)	23 (17)‡	35 ± 33‡	0.02
Carrera et al, 2009 (28)	10 (5)§ Median, 8.5 (IQ range, 6.75–11)	12 (6)§ Median, 10.5 (IQ range, 7–15)	0.06 Median, 0.65
Dhamija et al, 2005 (29)	9.77 (3.32)	10.20 (5.64)	> 0.05
Dikensoy et al, 2002 (5)	8 (2.1) (range, 5–15)	12.3 (3.3) (range, 5–21)	< 0.05
Keenan et al, 2005 (30)	6.5 (5.6) (range, 2–31)‖ Median, 5	9.1 (7.3) (range, 2–36) Median, 7	Mean, 0.18‖ Median, 0.07‖
Khilnani et al, 2010 (31)	9.4 (4.3)	17.8 (2.6)	0.001
Kramer et al, 1995 (9)	14.9 (3.3)	17.3 (3.0)	NR
Plant et al, 2000 (32;34)	10 (22.167)† Median, 10 (range, 4–137)	10 (19.5)† Median, 10 (range, 2–119)	Median, 0.27
Wang et al 2005 (33)	16 (9)	18 (11)	0.15

*Abbreviations: IQ, interquartile; LOS, length of stay; NPPV, noninvasive positive pressure ventilation; NR, not reported; SD, standard deviation; UMC, usual medical care.

†Mean calculated using the median and range based on methods from Hozo et al. (35)

‡In Brochard et al (27), the total LOS was not reported; however, 7 patients (18%) in the NPPV group stayed in hospital for more than 28 days compared with 13 (47%) in the UMC alone group (*P* = 0.004).

§Mean reported in abstract, median in results

‖One patient in the NPPV group was identified as an outlier as the patient's LOS was 374 days, while all other patients in both groups had a mean LOS of less than 37 days, and was excluded from the mean and range for the NPPV group and *P* value reported in the table. Including the outlier patient, the mean ± SD (range) for the NPPV group was: 21.2 ± 73.7 (2–374) and the *P* value comparing the mean LOS with that in the UMC alone group was 0.397 and comparing the median LOS was 0.136. (30)

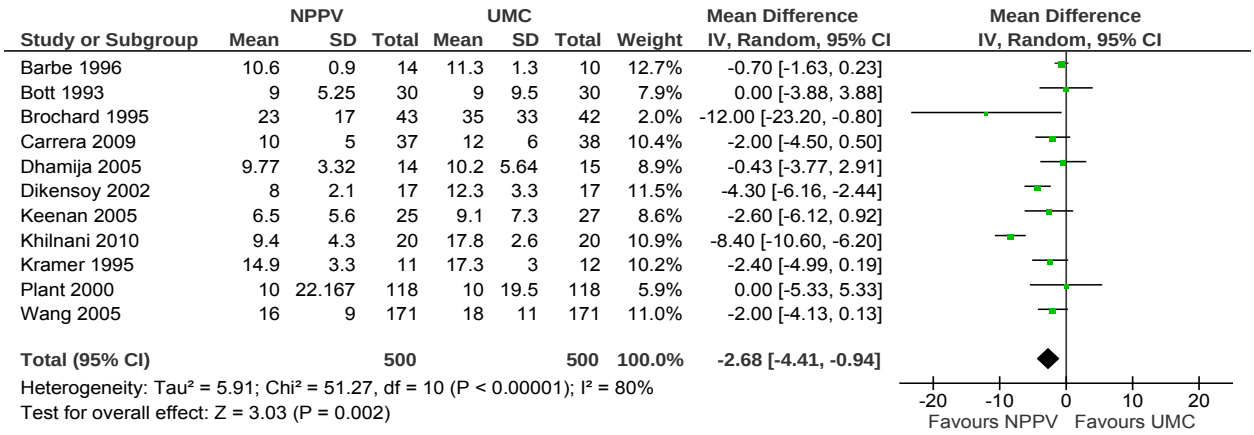


Figure 6: Pooled Results for Mean Hospital Length of Stay (NPPV Plus UMC Versus UMC Alone Comparison)[3]*

*Abbreviations: CI, confidence interval; NPPV, noninvasive positive pressure ventilation; SD, standard deviation; UMC, usual medical care.

Similarly, when the results are stratified by respiratory failure severity (Figure 7), the significant reduction in mean hospital LOS in the NPPV plus UMC group is maintained for the mild ($P = 0.03$), severe ($P < 0.001$), and very severe ($P < 0.001$) respiratory failure groups, with the benefit increasing as the disease severity increases.

[3] Bott et al (26) and Plant et al (32;34) reported median length of stay and range. These data were used to calculate approximate means and standard deviations for these 2 studies based on methods by Hozo et al (35). The resulting means and standard deviations were used to include these 2 studies in the pooled analysis.

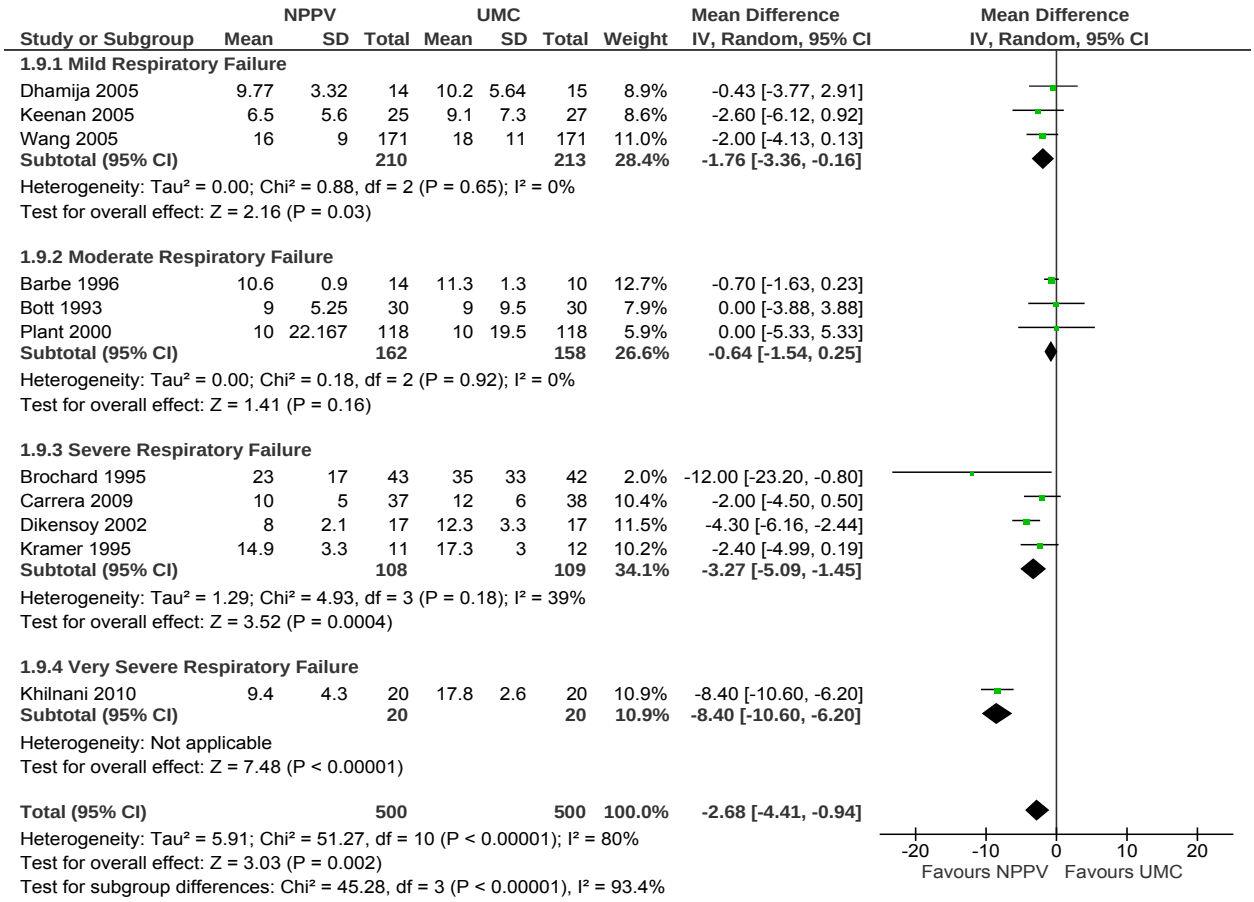


Figure 7: Pooled Mean Hospital Length of Stay Stratified by Severity of ARF (NPPV Plus UMC Versus UMC Alone)*

*Abbreviations: ARF, acute respiratory failure; CI, confidence interval; NPPV, noninvasive positive pressure ventilation; SD, standard deviation; UMC, usual medical care.

Dyspnea

Eight of the studies reported some measure of dyspnea as an outcome, but due to differences in reporting, the results could not be pooled. Individual study findings are listed in Table 4. The results are inconsistent: some studies reported a statistically significant decline in dyspnea in the NPPV plus UMC group compared with the UMC alone group, or a faster decline in dyspnea in the NPPV plus UMC group (results are shown in italics in Table 4), while other studies found no significant differences between the 2 groups.

Table 4: Dyspnea Results (NPPV Plus UMC Versus UMC Alone Comparison)*

Author, year	Breathlessness Measure	Results
Barbe et al, 1996 (25)	Borg Index	Significant decrease in dyspnea during hospitalization ($P < 0.001$) at 72 hours, 80 hours, and discharge in both NPPV plus UMC and UMC alone groups, but no significant difference between groups.
Bott et al, 1993 (26)	Visual analogue scale	*Over the first 3 days, there was a significantly lower score for dyspnea for the NPPV plus UMC group (median, 2.3 cm; range, 0.1–5.5 cm) than the UMC alone group (median, 4.5 cm; range, 0.9–8.8), P < 0.03.* This difference was no longer significant at 7 days and discharge.
Carrera et al, 2009 (28)	Borg scale	No significant change in dyspnea status during study period in either group. At discharge, there was no significant difference between the Borg scores (4 ± 2 in both groups).
Dhamija et al, 2005 (29)	Borg scale	Both groups reported a significant improvement in Borg scale within 1 hour of therapy.
Keenan et al, 2005 (30)	Borg scale	*Borg index at 1 hr and on day 2 were significantly better in NPPV plus UMC compared with the UMC alone group (P = 0.004 and P = 0.03, respectively).†*
Kramer et al, 1995 (9)	NR‡	n/a
Plant et al, 2000 (32)	5 point verbal rating score	*NPPV plus UMC group had a more rapid relief of breathlessness (P = 0.03).* Median time to relief of breathlessness was 4 days in the NPPV group compared with 7 days in UMC alone group.
Wang et al, 2005 (33)	Dyspnea score (4 point scale)	No significant reduction in dyspnea score between baseline and 24 hours in both groups. NPPV plus UMC: baseline, 3.6 ± 0.7; 24 hr, 3.3 ± 0.8 hr UMC alone: baseline, 3.6 ± 0.7; 24 hr, 3.3 ± 0.8 hr

*Abbreviations: hr, hour; n/a, not applicable; NPPV, noninvasive positive pressure ventilation; NR, not reported; SD, standard deviation; UMC, usual medical care.

†Borg scores were available for 80-90% of patients at each time point, but the number of patients with data for consecutive measurements fell off over time, with only 60% of patients having data out to day 3. Therefore the analysis was only done until day 3, so the repeated measures analysis was only done to day 3. (30)

‡Results were not reported for the COPD patients only. For the entire population including non-COPD patients, scores decreased in both groups and tended to be lower in the NPPV group compared with control throughout study. The decline from baseline was significantly greater among NPPV than control at 6 hours. (9)

Noninvasive Positive Pressure Ventilation Tolerance and Compliance

Patient tolerance or compliance with NPPV was reported in 8 studies (Table 5). In these studies, NPPV intolerance ranged from 5% to 29%. Factors that might contribute to this range include severity of respiratory failure, with more severe patients having increased tolerance compared with less severe patients, and the interface used to deliver NPPV.

Table 5: NPPV Tolerance (NPPV Plus UMC Versus UMC Alone Comparison)*

Author, Year	Number of Patients Who Could Not Tolerate NPPV (%)	Reason: n
Barbe et al, 1996 (25)	4 (29)	• Claustrophobia: 3 • Anxiety: 1
Bott et al, 1993 (26)	4 (13)	• Could not breathe through nose: 1 • Too confused to use NPPV: 2 • Withdrew from active treatment: 1
Dhamija et al, 2005 (29)	1 (7)	• Could not tolerate mask: 1
Dikensoy et al, 2002 (5)	2 (12)	• Discomfort: 2
Keenan et al, 2005 (30)	3† (12)	NR
Khilnani et al, 2010 (31)	1 (5)	• Could not tolerate mask: 1
Kramer et al, 1995 (9)	NR‡	–

*Abbreviations: n, number of patients; NPPV, noninvasive positive pressure ventilation; NR, not reported; UMC, usual medical care.

†Patients refused NPPV after its initial application, so they received less than 1 hour of NPPV. (30)

‡Data on tolerance/compliance were not reported for the COPD patients only. For the entire NPPV group including those without COPD, 4 patients did not tolerate NPPV. The reasons for the lack of tolerance in the 4 patients were not reported. (9)

Plant et al (32) and Keenan et al (30) reported compliance with NPPV. In Keenan et al (30), NPPV was provided to patients over 3 days. Out of 25 patients, 88% were compliant on day 1, 68% on day 2, and 48% on day 3. (30) Similarly, in Plant et al (32), 92.8% of patients were compliant on day 1, 76.4% on day 2, and 67.7% on day 3. In this study, patients who were not compliant with NPPV included those who could not tolerate NPPV, those who failed NPPV and were invasively ventilated, and those who self-weaned because they thought they no longer needed NPPV. (32) Both of these studies suggest that compliance decreases over time, even over short periods of time such as 3 days.

Plant et al (32) also reported mask comfort using a 5-point verbal rating score. The median comfort score during the first 3 days of NPPV was 2, which translates to mildly uncomfortable.

Complications

Five studies reported complications, although most reported complications associated with the NPPV procedure only. (5;27;30;31;33) While Kramer et al (9) also reported complications, they were not presented for the COPD group separately, so the study is not included in the results.

In Brochard et al (27), the proportion of patients with 1 or more complications was reported. Patients in the UMC alone group reported a significantly higher proportion of complications than patients in the NPPV plus UMC group (20 of 42 vs. 7 of 43; $P = 0.001$). In total, 232 complications were reported in the UMC alone group and 9 in the NPPV plus UMC group. The breakdown of the complications is shown in Table 6.

Table 6: Reported Complications by Study Group (NPPV Plus UMC Versus UMC Alone Comparison)*

Complication	Number of Complications	
	NPPV + UMC	UMC
Pneumonia	2	7
Sepsis	2	3
Gastrointestinal tract disorders	1	2
Myocardial infarction	1	2
Multiple pneumothoraxes	0	1
Difficult or complicated endotracheal intubation	0	4
Pulmomary embolism	0	1
Cerebral hemorrhage	1	0
Cardiac or respiratory problems when weaning	1	1
Cardiac arrest after weaning	0	2
Facial-skin necrosis	1	0

*Abbreviations: NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.
Source: Brochard et al, 1995. (27)

In Dikensoy et al (5) complications were reported in 7 patients in the NPPV plus UMC group: nasal bridge ulceration (n = 2), eye irritation (n = 3), conjunctivitis (n = 2), and gastric insufflation (n = 2). Only complications related to NPPV were reported. (5)

Keenan et al (30) reported no nosocomial complications in the NPPV plus UMC group. Two nosocomial complications were reported in the UMC alone group: 1 patient who failed medical treatment and was intubated and invasively ventilated developed ventilator-associated pneumonia, and 1 patient developed hospital-acquired pneumonia and a urinary tract infection (this patient was not intubated). (30)

In Khilnani et al (31) 4 patients in the NPPV plus UMC group and 10 patients in the UMC alone group developed complications. In the NPPV plus UMC group, complications were aspiration pneumonia (n = 1), abdominal bloating sensation and irritation in the eyes (n = 2), and upper gastrointestinal bleed (n = 1). Complications in the UMC alone group were nosocomial pneumonia (n = 4), upper gastrointestinal bleed (n = 3), pneumothorax (n = 2), and paroxysmal supraventricular tachycardia (n = 1). (31)

Finally, in Wang et al (33), the following complications associated with NPPV were reported: gastric insufflation (n = 40), local facial skin abrasion (n = 27), sinusitis (n = 3), and aspiration pneumonia (n = 2). As well, mask leaks causing insufficient ventilation occurred in 51 of 171 patients.

Of the 3 studies that reported complications in both groups, each study reported fewer complications in the NPPV plus UMC group compared with the UMC alone group. It was not appropriate to pool these data because each reported different information.

Other Results

Many of the studies also reported changes in arterial blood gases, pulmonary function, heart rate, blood pressure, and respiratory rate; these outcomes, however, were out of scope of this review and are not reported in this analysis.

Bott et al (26) was the only study to report some measure of health-related quality of life (HRQOL). A visual analogue score was used to assess quality of sleep and general well-being; no significant differences were found between the scores for the NPPV plus UMC and UMC alone groups. (26)

While most studies did not report information on the number of patients in the NPPV plus UMC group who were successfully weaned from NPPV after resolution of the respiratory failure, most of the study protocols called for NPPV for a set number of days, so it was unlikely that patients continued on NPPV after the study. In Bott et al (26), however, 1 patient continued on NPPV after discharge from the hospital.

Comments on the Studies

One of the challenges of pooling the data from the studies for any of the outcomes is that many of the studies had very different ventilation protocols, both in terms of the total duration of NPPV (e.g., some studies called for NPPV for 7 to 10 days or as long as clinically necessary, but others only allowed for NPPV for a maximum of 3 days) and the number of hours per day of NPPV (e.g., some studies encouraged NPPV for as long as the patient could tolerate and some capped NPPV at 6 hours per day). These differences limit the generalizability of the studies and may provide a reason for the high statistical heterogeneity (measured by the I^2) observed in some of the pooled analyses such as mean hospital LOS. Given the limited reporting on total duration of NPPV and hours per day in some studies, and the variability across each study, it was not possible to create clear subgroups based on NPPV protocol or actual duration of NNPV to further explore this clinical heterogeneity.

Due to differences in the severity of respiratory failure of the patients in the included studies, stratified analyses were conducted for mild ($pH \geq 7.35$), moderate ($7.30 \leq pH < 7.35$), severe ($7.25 \leq pH < 7.30$), and very severe ($pH < 7.25$) respiratory failure. Studies were classified based on the mean pH of the patients included in the study; however, this does not account for the fact that some studies may have included some patients with substantially different pH levels from that of the mean. For example, in Wang et al (33), a subgroup analysis within the study shows that 151 patients (44%) had a pH greater than or equal to 7.35, but 118 patients (35%) had a more moderate respiratory failure ($7.30 \leq pH < 7.35$) and 73 patients (21%) had severe respiratory failure ($pH < 7.30$). Similarly, while the mean pH of the NPPV plus UMC and UMC alone groups in Bott et al (26) classifies the study as moderate respiratory failure, the mean pH of patients enrolled at centre C was 7.369, which indicates the patients at this centre had mild respiratory failure.

Different ventilators, pressure settings, ventilation modes, and interfaces were used across the studies. These factors may play a role in the effectiveness of the NPPV due to their impact on achieving adequate ventilation and patient tolerance, so these differences may also contribute to some of the heterogeneity across the studies.

In the studies by Barbe et al (25), Keenan et al (30), and Wang et al (33), initiation of noninvasive ventilation in the NPPV plus UMC group was not immediate, but delayed between 12 and 48 hours after the patients presented to the emergency department. This delay may have reduced the effectiveness of NPPV and therefore bias the results against NPPV.

A common theme identified by many of the study authors was the need for patients on NPPV to be closely monitored by trained clinicians. In some studies, NPPV use was commonplace before the study, but in others (especially those conducted in hospital wards), NPPV was not used before the study was initiated. Skill level and familiarity or comfort with NPPV may impact the study results because

physicians who are less comfortable with NPPV may be more likely to switch patients to intubation and IMV, especially in those studies which did not have a priori objective intubation criteria.

Quality of Evidence

The analysis was based on RCT evidence, but the majority of the trials had serious methodological issues based on the information available in the published papers[4]. Common methodological problems included lack of allocation concealment, unclear methods used for randomization, lack of blinding without adequate objective outcome assessment, and inadequate sample sizes to eliminate type II error (based on post hoc sample size calculations when possible) (summarized in Table A17 in Appendix 4).

The GRADE system was used to evaluate the quality of the overall body of evidence for NPPV plus UMC compared with UMC alone for the treatment of ARF due to acute exacerbations of COPD. The GRADE ranged from moderate to low. Detailed information on the GRADE by outcome is available in Table A18 in Appendix 4.

Summary of Findings

Based on moderate quality of evidence:

- Compared with the UMC alone group, there is a significant reduction in the risk of the need for endotracheal intubation and IMV in the NPPV plus UMC group.
- Compared with the UMC alone group, there is a significant reduction in the risk of inhospital mortality in the NPPV plus UMC group.
- Compared with the UMC alone group, there is a significant reduction in the mean length of hospital stay in the NPPV plus UMC group.

Based on low quality of evidence, complications are lower in the NPPV plus UMC group compared with the UMC alone group.

Due to limited and inconsistent data, conclusions on the effectiveness of NPPV plus UMC in reducing dyspnea compared with UMC alone could not be made.

NPPV Compared with Invasive Mechanical Ventilation

The remaining 2 studies that examined the use of NPPV for the treatment of ARF due to acute exacerbations of COPD compared the use of NPPV and IMV. (7;36) For these studies, the general study characteristics and details on the patient populations included in each study are shown in Tables A11, A12, and A13 in Appendix 3.

The Conti et al (36) trial enrolled patients who had failed usual medical treatment and required ventilatory support, but failed medical treatment was not a requirement for enrolment in Jurjevic et al (7) (based on the availability of information in the published paper). Therefore, it is uncertain whether the 2 studies have enrolled similar patient populations. For this reason, the results of the 2 studies were not pooled.

Mortality

Overall, there were no statistically significant differences between the NPPV and IMV groups in terms of ICU mortality, inhospital mortality, and 1-year mortality (Table 7). The results of ICU mortality are inconsistent between the 2 studies: Conti et al (36) observed a nonsignificant increase in mortality in the NPPV group; Jurjevic et al (7) observed a nonsignificant decrease in mortality in the NPPV group.

[4] It is possible that some of the methodological flaws which were identified in these studies were not actual flaws but the result of incomplete reporting in the published methods.

Table 7: Summary of Results (NPPV Versus IMV Comparison)*

Author, Year	NPPV	IMV	*P* value
ICU Mortality	**n/N (%)**	**n/N (%)**	
Conti et al, 2002 (36)	5/23 (21.7)	3/26 (11.5)	NR
Jurjevic et al, 2009 (7)	4/78 (5.1)	5/78 (6.4)	0.93
Inhospital Mortality	**n/N (%)**	**n/N (%)**	
Conti et al, 2002 (36)	6/23 (26.1)	4/26 (15.4)	NR
Jurjevic et al, 2009 (7)	NR	NR	n/a
1-year Mortality	**n/N (%)**	**n/N (%)**	
Conti et al, 2002 (36)	6/23 (26.1)	12/26 (46.1)	0.24
Jurjevic et al, 2009 (7)	NR	NR	n/a
Successful Treatment	**n/N (%)**	**n/N (%)**	
Conti et al, 2002 (36)	NR	NR	n/a
Jurjevic et al, 2009 (7)	48/78 (61)	38/78 (49)	0.32
ICU LOS	**LOS, Mean (SD), Days**	**LOS, Mean (SD), Days**	
Conti et al, 2002 (36)	22 (19)	21 (20)	NR
Jurjevic et al, 2009 (7)	5 (1.35)* Median: 5	9.29 (3)* Median: 9.29	Mean: NR Median: < 0.001
Duration of MV	**Mean (SD), Days**	**Mean (SD), Days**	
Conti et al, 2002 (36)	16 (19)	15 (21)	0.21
Jurjevic et al, 2009 (7)	3.92 (1.08) Median: 3.92†	7.17 (2.22) Median: 7.17†	Mean: NR Median: < 0.001

*Abbreviations: d, days; ICU, intensive care unit; IMV, invasive mechanical ventilation; MV, mechanical ventilation; N, sample size of group; n, number; n/a, not applicable; NPPV, noninvasive positive pressure ventilation; NR, not reported; LOS, length of stay; SD, standard deviation.

†The published reports provided only the median LOS and duration of mechanical ventilation. The median and range information provided in the report were used to calculate the mean and standard deviation according to the methods by Hozo et al. (35)

Intensive Care Unit Length of Stay

The ICU LOS results (Table 7) are inconsistent between the 2 studies. The mean LOS was slightly longer in the NPPV group compared with the IMV group in Conti et al, (36) although this difference was not significant. In Jurjevic et al (7) however, the mean LOS[5] was significantly shorter in the NPPV group compared with the IMV group. Furthermore, the mean LOS in the ICU was substantially longer in both groups (21 to 22 days) in the Conti et al (36) study compared with the Jurjevic et al (7) study (5 to 10 days).

Successful Treatment

Jurjevic et al (7) reported mechanical ventilation treatment success for both groups, which was defined as patients who remained in spontaneous respiration for at least 48 hours after the withdrawal of ventilation. Based on this definition, 48 patients (61%) in the NPPV group and 38 patients (49%) in the IMV group were treated successfully with mechanical ventilation during their stay in the ICU (Table 7). (7)

[5] The published results by Jurjevic et al only report the median ICU length of stay. The median length of stay and range were converted into the mean length of stay and standard deviation using the methods outlined by Hozo et al. (35) Median LOS (range): NPPV, 5 days (3.6–11.7 days); invasive mechanical ventilation: 9.29 days (6–24 days). (7)

Duration of Mechanical Ventilation

The results of duration of mechanical ventilation (including both noninvasive and invasive ventilation) are also inconsistent between the 2 studies (Table 7). The mean duration of mechanical ventilation was slightly longer (but this was not significant) in the NPPV group compared with the IMV group in Conti et al (36); however, the mean duration of mechanical ventilation[6] was significantly shorter in the NPPV group compared with the IMV group in the Jurjevic et al study. (7) In addition, the mean duration of mechanical ventilation was substantially longer in both groups (15 to 16 days) in the Conti et al (36) study compared with the Jurjevic et al (7) study (4 to 7 days).

Tolerance

Tolerance was only reported in 1 study. Conti et al (36) reported that 3 patients in the NPPV group required intubation and mechanical ventilation due to mask intolerance.

Complications

In Conti et al (36), the proportion of patients who developed at least 1 complication was not significantly different between the NPPV and IMV groups (6 patients vs. 11 patients, $P = 0.37$). The breakdown of complications were: septic shock (5 vs. 4, $P = 0.41$), sepsis or severe sepsis (1 vs. 9, $P = 0.009$), ventilator-associated pneumonia (3 vs. 9, $P = 0.07$), tracheotomy (3 vs. 6, $P = 0.29$), acute renal failure (1 vs. 0, $P = 0.46$), pneumothorax (1 vs. 0, $P = 0.46$), urinary tract infection (0 vs. 2, $P = 0.27$), gastrointestinal bleeding (0 vs. 1, $P = 0.58$), and other (1 vs. 2, $P = 0.54$). All of the complications in the NPPV group occurred in patients who failed NPPV and were intubated and mechanically ventilated. (36)

Both studies reported a reduction in the number of cases of VAP and tracheotomies in the NPPV groups compared with the IMV groups, although these reductions were only significant in the Jurjevic et al (7) study ($P < 0.001$) (Table 8).

Table 8: Complications (NPPV Versus IMV Comparison)*

Author, Year	NPPV	IMV	*P* value
Ventilator-associated Pneumonia	**n/N (%)**	**n/N (%)**	
Conti et al, 2002 (36)	3/23 (13.0)	9/26 (34.6)	0.07
Jurjevic et al, 2009 (7)	5/78 (6.4)	29/78 (37.2)	< 0.001
Tracheotomies	**n/N (%)**	**n/N (%)**	
Conti et al, 2002 (36)	3/23 (13.0)	6/26 (23.1)	0.29
Jurjevic et al, 2009 (7)	5/78 (6.4)	27/78 (34.6)	< 0.001

*Abbreviations: IMV, invasive mechanical ventilation; N, sample size of group; n, number; NPPV, noninvasive positive pressure ventilation.

Other Outcomes

Conti et al (36) also measured a variety of additional outcomes during the 12 months of follow-up. Over the 12-month follow-up, there were no significant differences between the NPPV and IMV groups in terms of number of hospital readmissions (18 vs. 22; $P = 0.8$), ICU readmissions (3 vs. 2; *P* not reported), or patients with open tracheostomy (2 vs. 6; $P = 0.16$). In the NPPV group, however, significantly fewer patients required de novo permanent oxygen supplementation at home compared with the IMV group (0 vs. 5; $P = 0.01$). (36) In addition, patients in the IMV group had a significant increase in functional

[6] The published results by Jurjevic et al (7) only report the median duration of mechanical ventilation. The median duration of mechanical ventilation and range were converted into the mean and standard deviation using the methods outlined by Hozo et al. (35) Median duration of mechanical ventilation (range): NPPV, 3.92 days (2.91–8.79 days); invasive mechanical ventilation: 7.17 days (4.38–17.71 days). (7)

limitations due to COPD (visual analogue scale changed from 4.3 ± 1.4 to 5.3 ± 0.8, $P = 0.02$), but this change was not observed in the NPPV group. (36)

Quality of Evidence

The analysis was based on RCT evidence, but both had some serious methodological issues based on the information available in the published papers[7], including lack of allocation concealment, unclear methods used for randomization, lack of blinding without adequate objective outcome assessment, and inadequate sample sizes to eliminate type II error (based on post hoc sample size calculations when possible) (summarized in Table A17 in Appendix 4).

The GRADE system was used to evaluate the quality of the overall body of evidence on the use of NPPV compared with IMV for the treatment of ARF secondary to acute exacerbations of COPD after failing UMC. The GRADE level ranged from low to very low (Table A19 in Appendix 4). Due to the uncertainty associated with low and very low quality of evidence, further research is likely to have an impact on the confidence in the estimate of effect and is likely to change the estimate.

Summary of Findings

The 2 RCTs comparing NPPV and IMV for the treatment of ARF due to acute exacerbations of COPD in patients who have failed UMC alone were not pooled due to potential differences in the study populations. Due to the inconsistent and low quality of evidence, it is not possible to draw conclusions at this time.

NPPV for Weaning COPD Patients From IMV

This section of the evidence-based analysis addresses research question 2a: what is the effectiveness, cost-effectiveness, and safety of NPPV compared with IMV for weaning COPD patients from invasive mechanical ventilation?

Systematic Reviews

Five systematic reviews were identified that examined the published literature on the use of NPPV to wean people with COPD from IMV. (13;14;17;19;21)[8] Full details on the systematic reviews can be found in Appendix 2.

Randomized Controlled Trials

Two RCTs on the use of NPPV for weaning patients from IMV were identified. The trials by Nava et al (37) and Prasad et al (38) compared the use of NPPV and IMV for COPD patients being invasively ventilated who failed a T-piece weaning trial. The general study characteristics of these studies, including inclusion and exclusion criteria, length of follow-up, outcomes, and details about the NPPV and IMV protocols, as well as details on the patient populations included in each study are shown in Tables A14, A15, and A16 in Appendix 3.

A total of 80 participants were included in the 2 RCTs; the sample sizes of the studies were 30 and 50 patients, respectively. (37;38) The mean age of the participants ranged from 58 to 69 years of age. Based on either the Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD stage criteria or the mean percent predicted forced expiratory volume in 1 second (FEV_1), both studies included patients with very severe COPD. Both studies also included patients with very severe respiratory failure (mean pH of the study populations was less than 7.23). Chronic obstructive pulmonary disease patients receiving IMV

[7] It is possible that some of the methodological flaws which were identified in these studies were not actual flaws but the result of incomplete reporting in the published methods.

[8] Keenan et al (17), Caples et al 2005 (21), and Hess et al 2004 (19) are the same systematic reviews that were included in the systematic reviews on noninvasive ventilation for ARF section.

were enrolled in the study if they failed a T-piece weaning trial (spontaneous breathing test), so they could not be directly extubated from IMV. (37;38)

Both studies were conducted in the ICU. Patients in the NPPV group received weaning using either BiPAP or pressure support ventilation NPPV through a face mask, and patients in the IMV weaning group received pressure support ventilation. In both cases, weaning was achieved by tapering the ventilation level. (37;38)

Of note, the patient populations in the two studies had some significant differences. Independent 2 sample t-tests found that the FEV_1, mean age, and mean pH were significantly substantially different in the Nava et al (37) and Prasad et al (38) studies.

Mortality

Intensive care unit mortality and 30-day mortality rates were not significantly different between the NPPV and IMV groups in Prasad et al (38) (ICU mortality: 3 vs. 5 deaths; $P > 0.05$; 30-day mortality: 5 vs. 9 deaths; $P > 0.05$). In contrast, Nava et al (37) reported a significant reduction in mortality in the NPPV group compared with the IMV group at 60 days (2 vs. 7 deaths, $P = 0.009$). When the 30- and 60-day mortality results are pooled, a 53% reduction in the risk of death is observed in the NPPV group (RR, 0.47; 95% CI, 0.23–0.97; $P = 0.04$), which is statistically significant (Figure 8).

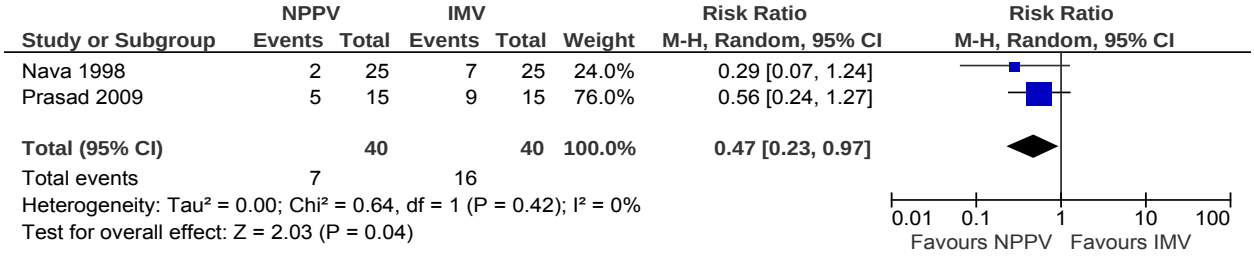


Figure 8: Pooled Mortality Results (NPPV Versus IMV for Weaning Comparison)*

*Abbreviations: CI, confidence interval; IMV, invasive mechanical ventilation; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation.

Intensive Care Unit (ICU) Length of Stay

Both Nava et al (37) and Prasad et al (38) reported a reduced ICU LOS in the NPPV group compared with the IMV group, but this reduction was only significant in the Nava et al (37) study. When the results are pooled, a nonsignificant reduction of 5.21 days (95% CI, −11.60 to 1.18; $P = 0.11$) in the ICU was found in the NPPV group compared with the IMV group (Figure 9).

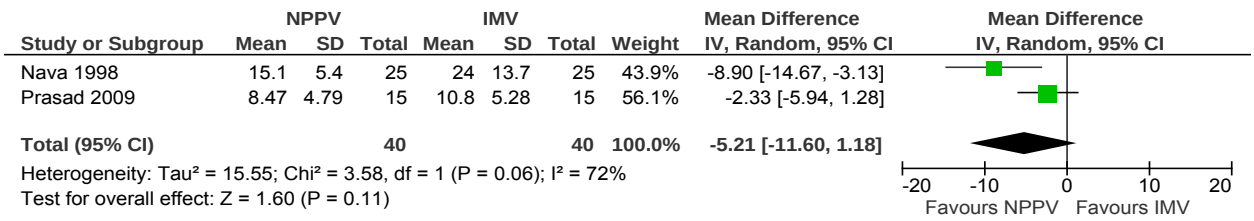


Figure 9: Pooled ICU Length of Stay Results (NPPV Versus IMV for Weaning Comparison)*

*Abbreviations: CI, confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; NPPV, noninvasive positive pressure ventilation; SD, standard deviation.

Duration of Mechanical Ventilation

Both studies showed a reduction in the duration of mechanical ventilation (including both invasive and noninvasive ventilation) in the NPPV group compared with the IMV group, but the difference was only significant in the Nava et al (37) study. (37;38) When the results are pooled, a nonsignificant reduction of 3.55 days (95% CI, −8.55 to 1.44 days; $P = 0.16$) of ventilation was found in the NPPV group compared with the IMV group (Figure 10).

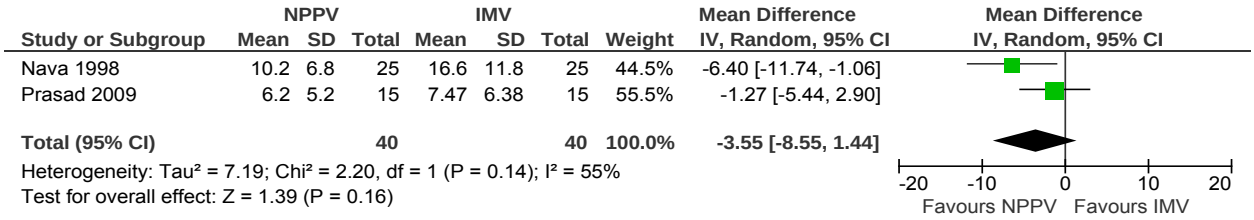


Figure 10: Pooled Duration of Mechanical Ventilation (NPPV Versus IMV for Weaning Comparison)*

*Abbreviations: CI, confidence interval; IMV, invasive mechanical ventilation; NPPV, noninvasive positive pressure ventilation; SD, standard deviation.

Complications

Both studies reported a lower incidence of nosocomial pneumonia in the NPPV group compared with the IMV group. When the results are pooled (Figure 11), an 84% reduction in the risk of nosocomial pneumonia was observed in the NPPV group (RR, 0.14; 95% CI, 0.03–0.71; $P = 0.02$). (37;38)

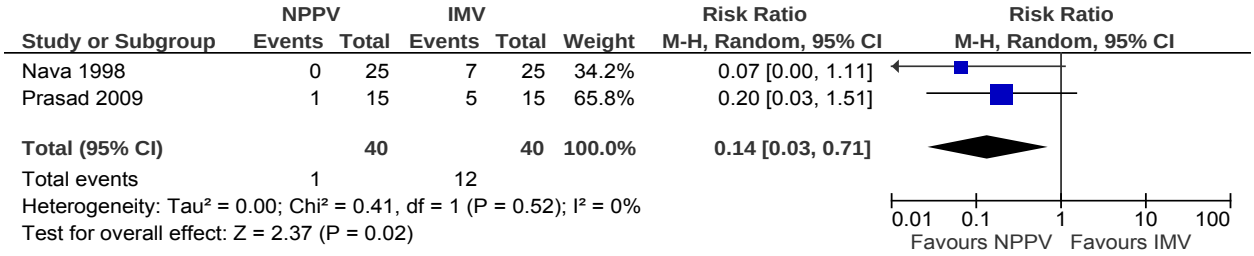


Figure 11: Pooled Incidence of Nosocomial Pneumonia (NPPV Versus IMV for Weaning Comparison)*

*Abbreviations: CI, confidence interval; IMV, invasive mechanical ventilation; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation.

Prasad et al (38) also reported the following complications related to NPPV: claustrophobia (n = 2), skin abrasions (n = 2), and gastric distension (n = 1). Similarly, Nava et al (37) reported cutaneous irritation of the nose (n = 20), nose abrasions (n = 14), and gastric distension (n = 2) in the NPPV group.

Other Outcomes

Weaning Failure

Nava et al (37) reported a significant reduction ($P = 0.02$) in the rate of weaning failure (defined as patients who could not be weaned because of death associated with mechanical ventilation, patients who were reintubated within 72 hours, and patients who could not be weaned within 60 days) in the NPPV group compared with the IMV group. The absolute rates of weaning failure were not reported in the published paper.

In the NPPV group, 1 patient could not be weaned after 60 days and was discharged with a prescription for nasal ventilation for 14 to 18 hours per day. In the IMV group, 2 patients could not be weaned after 60

days and were discharged with a prescription for at-home mechanical ventilation through a tracheostomy. (37)

Duration of Weaning
Prasad et al (38) observed a nonsignificant reduction in the duration of weaning in the NPPV group compared with the IMV group (35.17 ± 16.98 days vs. 47.05 ± 20.98 days; $P > 0.05$).

Health-Related Quality of Life
Nava et al (37) reported that most patients in the NPPV group experienced poor sleep quality, especially during the first few days of NPPV. No other measures of HRQOL were reported in either study.

Quality of Evidence
The quality of the overall body of evidence on the use of NPPV to wean COPD patients from IMV based on the GRADE criteria ranged from moderate to low (Table A20 in Appendix 4). The evidence was downgraded due to serious methodological limitations in the study design (Table A21 in Appendix 4.)

Summary of Findings
Moderate quality of evidence shows that weaning COPD patients who failed T-piece weaning trials using NPPV leads to significant reductions in mortality, nosocomial pneumonia, and weaning failure, compared with weaning patients using invasive pressure support ventilation.

NPPV After Extubation From IMV in COPD Patients

This section of the evidence-based review addresses the research questions 2b and 2c:

- What is the effectiveness, cost-effectiveness, and safety of NPPV for the prevention of ARF in COPD patients after extubation from IMV?
- What is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of ARF in COPD patients after extubation from IMV?

Systematic Reviews

Three systematic reviews were identified that examined the published literature on the use of NPPV after extubation from IMV to prevent or treat respiratory failure during the postextubation time period. (17;19;21)[9] The full details about the systematic reviews can be found in Appendix 2.

Early Application of NPPV to Prevent ARF After Extubation From IMV

Keenan et al (17) identified 4 studies which examined the use of NPPV after extubation to prevent deterioration and reintubation. Of those studies, 2 included patients with acute exacerbations of COPD. The results for the COPD patients are not presented separately in the review; the results for all patient groups combined showed statistically significantly reduced rates of reintubation (RR, 0.42; 95% CI, 0.25–0.70), ICU mortality (RR, 0.35, 95% CI, 0.16–0.78), and a nonsignificant reduction in the risk of hospital mortality (RR, 0.66; 95% CI, 0.42–1.04). (17)

The reviews by Caples et al (21) and Hess et al (19) did not address the use of NPPV for the prevention of ARF after extubation.

[9] Keenan et al 2011 (17), Hess et al 2004 (19), and Caples et al 2005 (21) are the same systematic reviews that were identified in the 2 previous sections.

Treatment of ARF After Extubation From IMV

The pooled analysis from Keenan et al (17) showed no significant difference between NPPV plus UMC versus UMC alone for the treatment of ARF after extubation from IMV (RR, 1.03; 95% CI, 0.84–1.25). The larger of the 2 trials showed a significant increase in the mortality rate in the NPPV group (28 of 114 patients vs. 15 of 107 patients, $P = 0.048$). Keenan et al (17) noted that both studies included very few COPD patients, so the overall conclusion was that "no recommendation (could be made) about the use of noninvasive positive pressure ventilation in patients who have COPD and postextubation failure, because of insufficient evidence."

Both Caples et al (21) and Hess et al (19) provided only a brief description of the included studies and did not conduct any pooled analyses. Caples et al (21) concluded that there is evidence from uncontrolled studies to support the use of NPPV after failed extubation from mechanical ventilation in patients with COPD. Furthermore, as the RCT evidence which showed no benefit from NPPV in this patient population included so few patients with COPD, it was not possible to generalize the higher quality evidence to the COPD patient population. (21) Hess et al (19) concluded that "the role of NPPV in the [periextubation] period remains to be determined."

Randomized Controlled Trials

Early Application of NPPV to Prevent ARF After Extubation From IMV

There were no RCTs identified that examined the early use of NPPV after patients have been extubated from IMV for the prevention of reintubation, which enrolled only COPD patients. Of the RCTs that were identified which enrolled mixed populations including some patients with COPD, the trials did not meet the inclusion criteria of this review because the results for the COPD patients were not presented separately. (39;40)

Treatment of ARF After Extubation From IMV

One RCT was identified that met the inclusion criteria of this analysis. Esteban et al (41) evaluated the use of NPPV plus UMC compared with UMC alone for the treatment of respiratory failure developed within 48 hours of extubation from IMV. Patients were enrolled in the study if they had received mechanical ventilation for at least 48 hours, were successfully extubated after a trial of spontaneous breathing, and then developed respiratory failure within 48 hours. Included patients had received mechanical ventilation for ARF due to pneumonia, postoperative respiratory failure, sepsis, trauma, cardiac failure, acute respiratory distress syndrome, and other causes, or acute-on-chronic respiratory failure due to COPD or asthma. (41)

Patients in the NPPV group received pressure support ventilation through a full facial mask continuously for 4-hour periods until the attending physician determined it was no longer necessary or the patient met the reintubation criteria. Patients in the UMC group received supplemental oxygen, respiratory physiotherapy, bronchodilators, and any other therapies that were needed. Patients were followed for the duration of their time in the ICU. (41)

Of the 221 patients included in the study, only 23 had COPD (14 in the NPPV group and 9 in the UMC group). The rate of reintubation was the only outcome that was reported for COPD patients separately. This post hoc analysis found a nonsignificant reduction in the rate of reintubation in the NPPV group compared with the UMC group (7 of 14 patients vs. 6 of 9 patients, $P = 0.67$). (41) The study was stopped early due a significant increase in mortality for the NPPV group compared with the UMC group (25% vs. 14%; RR, 1.78; 95% CI, 1.03–3.20; $P = 0.02$). It was noted that previous literature has shown NPPV to be more effective in the treatment of respiratory failure due to COPD compared to other etiologies, so there may also be a benefit in the postextubation period for COPD patients that could not be assessed in this study due to the small number of COPD patients enrolled. (41)

Quality of Evidence

While the Esteban et al (41) trial meets most of the methodological quality criteria (Table A22 in Appendix 4), the post hoc analysis with COPD patients is underpowered and the subgroup analysis breaks the study randomization. The overall quality of evidence evaluated using the GRADE criteria is low (Table A23 in Appendix 4).

Summary of Findings

At this time, there is inadequate evidence to reach conclusions on the comparative effectiveness of NPPV plus UMC and UMC alone for the prevention of recurrent respiratory failure in COPD patients after extubation from IMV or the treatment of recurrent respiratory failure in COPD patients following extubation from IMV.

Economic Analysis

The results of the economic analysis are summarized in issue 12 of the COPD series entitled *Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model*. This report can be accessed at: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Economic_March.pdf.

Conclusions

The conclusions are summarized in Table 9.

Table 9: Summary of Findings by Research Question*

Intervention	Comparator	Study Population	No. Studies (N)	Summary of Findings	GRADE Quality of Evidence
Research Question 1: What is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of acute hypercapnic respiratory failure due to acute exacerbations of COPD compared with UMC or IMV?					
NPPV + UMC	UMC	COPD patients with ARF due to acute exacerbations of COPD	11 (1000)	NPPV significantly reduces the risk of endotracheal intubation and IMV, inhospital mortality, and mean length of hospital stay compared with UMC.	Moderate
				NPPV results in fewer complications compared with UMC.	Low
NPPV	IMV	COPD patients with ARF†	2 (205)	At this time, no conclusions can be drawn regarding the comparative effectiveness of NPPV and IMV for this patient population.	Low
Research Question 2a: What is the effectiveness, cost-effectiveness and safety of NPPV compared with IMV for weaning COPD patients from IMV?					
NPPV	Pressure support IMV	COPD patients being invasively ventilated who fail T-piece weaning trials	2 (80)	NPPV leads to significant reductions in mortality, nosocomial pneumonia, and weaning failure compared with pressure support IMV.	Moderate
Research Question 2b: What is the effectiveness, cost-effectiveness, and safety of NPPV compared with UMC for the prevention of ARF in COPD patients after they have been extubated from IMV?					
NPPV	UMC	COPD patients after they have been extubated from IMV	0 (0)	No evidence was identified to evaluate the use of NPPV after extubation of COPD patients from IMV.	n/a
Research Question 2c: What is the effectiveness, cost-effectiveness, and safety of NPPV compared with UMC for the treatment of ARF in COPD patients after they have been extubated from IMV?					
NPPV	UMC	COPD patients who develop respiratory failure within 48 hours of extubation from IMV	1 (23)	At this time, there is inadequate evidence to reach conclusions on the comparative effectiveness of NPPV and UMC for the treatment of COPD patients who have developed ARF following extubation from IMV.	n/a

*Abbreviations: ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IMV, invasive mechanical ventilation N, sample size; n/a, not applicable; No., number; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

†The patient populations for these 2 studies are not clear: 1 study specifies that patients who were enrolled must have failed medical treatment, but 1 study does not specify this and may include patients who have not been treated first with UMC.

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity (FVC)	The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.

Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.
Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[1]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.
Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.

[1] The mild-to-moderate classification was created for the purposes of the report.

Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.
Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Medical Information Officer

Kellee Kaulback

Editorial Staff

Jan Collins
Irina Alecu

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

Appendices

Appendix 1: Literature Search Strategies

Search date: December 3, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database(s): Ovid MEDLINE(R) 1950 to November Week 3 2010

Search Strategy:

#	Searches	Results
1	exp Pulmonary Disease, Chronic Obstructive/	15011
2	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab.	21909
3	(copd or coad).ti,ab.	16795
4	chronic airflow obstruction.ti,ab.	493
5	exp Emphysema/	7051
6	((chronic adj2 bronchitis) or emphysema).ti,ab.	22960
7	or/1-6	54680
8	exp Respiration, Artificial/	51221
9	((artificial or non-invasive or noninvasive or invasive or nasal or mechanical or volume-controlled or pressure controlled or positive) adj2 (ventilat* or respiration)).ti,ab.	29829
10	(NIV or NPPV or NIPPV or NIAV or continous positive airway pressure or CPAP or bi-level positive pressure or ventilation support or BiPAP or endotracheal intubation or ventilat* failure).ti,ab.	10735
11	exp Ventilator Weaning/	2368
12	limit 11 to "all adult (19 plus years)"	1062
13	or/8-10	68682
14	7 and 13	3314
15	12 or 14	4228
16	limit 15 to (english language and humans and yr="2004 -Current")	1206

Database(s): EMBASE 1980 to 2010 Week 47
Search Strategy:

#	Searches	Results
1	exp chronic obstructive lung disease/	48840
2	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab.	26482
3	(copd or coad).ti,ab.	21755
4	chronic airflow obstruction.ti,ab.	551
5	exp emphysema/	25753
6	exp chronic bronchitis/	6600

7	((chronic adj2 bronchitis) or emphysema).ti,ab.	25596
8	or/1-7	89245
9	exp artificial ventilation/	86836
10	((artificial or non-invasive or noninvasive or invasive or nasal or mechanical or volume-controlled or pressure controlled or positive) adj2 (ventilat* or respiration)).ti,ab.	36697
11	(NIV or NPPV or NIPPV or NIAV or continous positive airway pressure or CPAP or bi-level positive pressure or ventilation support or BiPAP or endotracheal intubation or ventilat* failure).ti,ab.	13569
12	(ventilat* adj2 wean*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	971
13	limit 12 to (adult <18 to 64 years> or aged <65+ years>)	357
14	or/9-11	102073
15	8 and 14	6573
16	13 or 15	6871
17	limit 16 to (human and english language and yr="2004 -Current")	2094

CINAHL

#	Query	Results
S14	(S11 or S12) Limiters - Published Date from: 20040101-20101231; English Language	416
S13	(S11 or S12)	794
S12	s6 and s10	585
S11	(MH "Ventilator Weaning") Limiters - Age Groups: Aged: 65+ years	235
S10	S7 or S8 or S9	12790
S9	NIV or NPPV or NIPPV or NIAV or continous positive airway pressure or CPAP or bi-level positive pressure or ventilation support or BiPAP or endotracheal intubation or ventilat* failure	1689
S8	artificial N2 ventil* or non-invasive N2 ventil* or noninvasive N2 ventil* or invasive N2 ventil* or nasal N2 ventil* or mechanical N2 ventil* or volume-controlled N2 ventil*or pressure controlled N2 ventil*or positive N2 ventil* or artificial N2 respirat* or non-invasive N2 respirat* or noninvasive N2 respirat* or invasive N2 respirat* or nasal N2 respirat* or mechanical N2 respirat* or volume-controlled N2 respirat*or pressure controlled N2 respirat*or positive N2 respirat*	9597
S7	(MH "Respiration, Artificial+")	10081
S6	S1 or S2 or S3 or S4 or S5	7579
S5	chronic bronchitis or emphysema	1606
S4	(MH "Emphysema+")	982
S3	copd or coad	4153

S2	(chronic obstructive and (lung* or pulmonary or airway* or airflow or respiratory) and (disease* or disorder*))	5747
S1	(MH "Pulmonary Disease, Chronic Obstructive+")	4462

Appendix 2: Details About Included Systematic Reviews

NPPV for the Treatment of Acute Respiratory Failure due to Acute Exacerbations of COPD: Systematic Reviews

Although 12 systematic reviews were identified on this topic, only 8 of the reviews are summarized in the following tables. These 8 reviews were chosen because they are the 5 reviews that include statistical analyses and 3 of the less detailed reviews that provide a summary table of the included studies in addition to the narrative review.

Table A1: Comparison of Systematic Reviews Published Since 2000 and MAS Evidence-Based Reviews*

Component RCTs: Author, Year	Author, Year of Literature Search Inclusion for Identified Systematic Reviews								MAS Review	
	Keenan et al, 2009 (17)	Keenan et al, 2006† (2)	Quon et al, 2006 (18)	Caples et al, 2005 (21)	Hess et al, 2003 (19)	Keenan et al, 2002 (20)	Ram et al, 2003 (4)	Peter et al, 2000 (22)	Study Included	Reasons for Exclusion
Angus et al, 1996 (42)	‡	✓	✓		✓	✓		✓	X	NPPV versus Doxapram (drug not used in Ontario)
Avdeev et al, 1998 (43)	✓	✓			✓	✓	✓	✓	X	Not English
Barbe et al, 1996 (25)	✓	✓	✓		✓	✓	✓	✓	✓	
Bardi et al, 2000 (44)					✓			✓	X	Not randomized
Bott et al, 1993 (26)	†	✓	✓	✓	✓	✓	✓	✓	✓	
Brochard et al, 1995 (27)	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Carrera et al, 2009 (28)									✓	
Celikel et al, 1998 (45)	✓	✓	✓	✓	✓	✓	✓	✓	X	Mixed population§
Confalonieri et al, 1999 (46)		✓		✓		✓		✓	X	Patients with CAP and COPD‖
Conti et al, 2002 (36)	✓			✓			✓		✓	
Daskalopoulou et al, 1993 (47)			✓			✓		✓	X	Abstract

Component RCTs: Author, Year	Author, Year of Literature Search Inclusion for Identified Systematic Reviews								MAS Review	
	Keenan et al, 2009 (17)	Keenan et al, 2006† (2)	Quon et al, 2006 (18)	Caples et al, 2005 (21)	Hess et al, 2003 (19)	Keenan et al, 2002 (20)	Ram et al, 2003 (4)	Peter et al, 2000 (22)	Study Included	Reasons for Exclusion
Del Castillo et al, 2003 (48)	✓	✓					✓		X	Not English
Dhamija et al, 2005 (29)	✓	✓	✓						✓	
Dikensoy et al, 2002 (5)		✓	✓		✓	✓	✓		✓	
Honrubia et al, 2005 (49)	✓								X	Mixed population¶
Jurjevic et al, 2009 (7)									✓	
Keenan et al, 2005 (30)	✓	✓	✓						✓	
Khilnani et al, 2002 (50)						✓	✓		X	Abstract
Khilnani et al, 2010 (31)									✓	
Kramer et al, 1995 (9)	✓	✓	✓	✓		✓	✓	✓	✓	
Lapinsky et al, 1999 (51)								✓	X	Abstract
Liao et al, 2004 (52)	✓	✓							X	Not English
Martin et al, 2000 (53)			✓	✓		✓		✓	X	Mixed population#
Marvisi et al, 2004 (54)	✓								X	Outcomes
Matic et al, 2007 (55)	✓								X	Duplicate publication**
Matuska et al, 2006 (56)	✓	✓							X	Not English
Pastaka et al, 2007 (57)	✓								X	Patients have chronic respiratory failure
Plant et al, 2000 (32)	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Component RCTs: Author, Year	Author, Year of Literature Search Inclusion for Identified Systematic Reviews								MAS Review	
	Keenan et al, 2009 (17)	Keenan et al, 2006† (2)	Quon et al, 2006 (18)	Caples et al, 2005 (21)	Hess et al, 2003 (19)	Keenan et al, 2002 (20)	Ram et al, 2003 (4)	Peter et al, 2000 (22)	Study Included	Reasons for Exclusion
Servillo et al, 1994 (58)			✓			✓	✓		X	Abstract
Thys et al, 2002 (59)							✓		X	Mixed population††
Wang et al, 2005 (33)	✓	✓	✓						✓	
Wood et al, 1998 (60)				✓				✓	X	Mixed population‡‡
Zhou et al, 2001 (61)	✓	✓					✓		X	Not English

*Abbreviations: ARF, acute respiratory failure; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; MAS, Medical Advisory Secretariat; NPPV, noninvasive positive pressure ventilation; RCTs, randomized controlled trials.

† It is not clear from the methods section of the published paper, which years were included in the systematic search of the literature. The most recent included study was published in 2006, so that has been estimated as the year until which the literature was searched. (2)

‡The studies by Bott et al (26) and Angus et al (42) were identified by the reviews, but they were not included in the results because the patients who developed respiratory failure were not offered endotracheal intubation. (17)

§Celikel et al (45) enrolled COPD patients with respiratory failure caused by several etiologies including pneumonia, COPD exacerbations, and heart failure. Since the results for these groups were not presented separately, and the mechanism for ARF due to heart failure is different (Expert Opinion), this study is excluded from the MAS evidence-based review.

‖The primary diagnosis of patients in this study was respiratory failure due to community-acquired pneumonia rather than acute exacerbations of COPD. (46)

¶Includes patients with respiratory failure due to multiple etiologies, as well as both hypoxemic and hypercapnic respiratory failure. While some results are presented separately for the COPD group, the results are not stratified by hypoxemic and hypercapnic respiratory failure, so it was not possible to identify if the patients in the COPD group had hypercapnic and/or hypoxemic respiratory failure. (49)

#Martin et al (53) enrolled patients with ARF due to a variety of etiologies. Since the COPD patient group includes patients with both hypercapnic and hypoxemic respiratory failure and the results are not presented separately for the hypercapnic patients, this study has been excluded from the MAS evidence-based analysis.

**Matic et al (55) appears to be a duplicate publication that is updated in the Jurjevic et al (7) paper, so it was excluded. The authors of the paper have been contacted to confirm that the papers include some of the same patients, but no response has been received to date.

††Thys et al (59) enrolled patients with ARF due to a variety of etiologies. The results for the COPD patients are only presented separately for the arterial blood gas outcomes, outcomes which were out of scope of this analysis, so this study has been excluded from the MAS evidence-based analysis.

‡‡Wood et al (60) enrolled patients with ARF due to a variety of etiologies. The results for the COPD patients are not presented separately, so this study was excluded from the MAS evidence-based analysis.

Table A2: Summary of the Systematic Reviews' Methods*

Author, Year	Date Literature Current to	Databases Searched	Population Included	Included Study Designs	Total N (No. Studies)	Statistical Methods	Outcomes
Caples et al, 2005 (21)	2005†	MEDLINE, CINAHL, EMBASE, Web of Science	Use of NPPV in ICU settings for any etiology	RCTs, cohort, & observational studies‡	2068 (28)§	• Descriptive narrative of results	ETI or failure criteria, mortality, improvement in physiology, complications
Hess et al, 2004 (19)	2003†	PubMed	Adult patients with ARF Excluded: long-term NPPV for stable patients with pulmonary or neuromuscular disease	RCTs‡	NR (8)	• Relative risks were calculated • Pooled analyses were conducted using random effects models • Results for NPPV for COPD patients are based on results from other meta-analyses. The authors did not conduct their own analysis on this topic.	Not specified in methods. Outcomes included in the COPD section include treatment failure, mortality, intubation, and complications
Keenan et al, 2011 (17)	June 2009	MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effectiveness, Cochrane Database of Systematic Reviews, ACP Journal Club Database, MetaRegister of Controlled Trials, clinicaltrials.gov website, and Journals@OVID database	Hospitalized adult patients who had or who were at risk for ARF including both acute and acute-on-chronic respiratory failure. Included studies with predominately COPD patients. Excluded: studies of chronic respiratory failure in an outpatient setting	Parallel-design RCTs (abstracts excluded)	NR (16)‖	• Relative risks and weighted mean differences were calculated • Pooled analyses were conducted using random effects models • Subgroups included severe versus mild exacerbations and patients with acute exacerbations of COPD in the setting of severe CAP	Physiologic outcomes including arterial blood gases and vital signs; clinical outcomes including endotracheal intubation and hospital mortality In the section on NPPV vs. UMC, the following outcomes were reported: hospital mortality and ETI In the section on NPPV vs. conventional mechanical ventilation, the following outcomes were reported: hospital mortality, ICU mortality, and ETI avoidance
Keenan et al, 2009 (2)	2006†¶	PubMed, MEDLINE, EMBASE, Cochrane Database	Patients with ARF of any etiology Excluded: trials with mixed populations in which the data were not presented separately by etiology	RCTs (abstracts excluded)	1216 (17)	• Descriptive narrative of results • Results subgrouped by severity of COPD exacerbation	Failure rate, intubation rate, hospital mortality

Author, Year	Date Literature Current to	Databases Searched	Population Included	Included Study Designs	Total N (No. Studies)	Statistical Methods	Outcomes
Kennan et al, 2003 (20)	December 2002	MEDLINE, EMBASE, Cochrane Library (including Controlled Trial Registry), Database of Abstracts of Reviews of Effectiveness, Cochrane Database of Systematic Reviews, Methodology Database, abstracts of meetings from American Thoracic Society, American College of Chest Physicians, Society of Critical Care Medicine, European Society of Critical Care Medicine, European Respiratory Society, written request to authors for additional studies	Adults with an acute exacerbation of COPD who were hospitalized	RCTs (abstracts included)	628# (15)	• Summary risk differences and weighted mean differences were calculated • Pooled analyses were conducted using random effects models • Subgroup analyses included: severity of COPD exacerbation; full length published trials vs. abstracts; different NPPV failure definitions; different predefined intubation criteria	Endotracheal intubation, hospital LOS, inhospital mortality rate
Peter et al, 2002 (22)	2002†	MEDLINE, manual search of abstracts from American Journal of Respiratory and Critical Care Medicine, Chest, Critical Care Medicine, European Respiratory Journal, Intensive Care Medicine, Thorax, contacted industry for additional studies	Adult patients presenting with ARF Exclusions: studies on cardiogenic pulmonary edema, use of NIV in weaning and postintubation, postoperative NIV, studies comparing NIV with mechanical ventilation, and studies of NIV in specialized subgroups (e.g. cancer)	RCTs (abstracts included)	793 (15)	• Risk differences, weighted mean differences, and meta-analytic regression were calculated • Pooled analyses were conducted using fixed or random effects models depending on the amount of heterogeneity • Subgroups included: baseline risk, COPD vs. mixed patients, published vs. unpublished (abstracts)	Mortality, intubation, hospital LOS

Author, Year	Date Literature Current to	Databases Searched	Population Included	Included Study Designs	Total N (No. Studies)	Statistical Methods	Outcomes
Quon et al, 2008 (18)	November 2006	MEDLINE, EMBASE, Cochrane Database of Systematic Reviews	Adult patients experiencing an acute COPD exacerbation Excluded: patients with an alternative primary diagnosis	RCTs with Jadad score ≥ 2 (abstracts included)	979 (14)	• Relative risks and weighted mean differences were calculated • Pooled analyses were conducted using fixed effects or random effects models depending on amount of heterogeneity	Intubation, inhospital mortality, hospital LOS
Ram et al, 2004 (4)	September 2003	Cochrane Airways Group RCT register (includes MEDLINE, CINAHL, EMBASE, UK Research Register, abstracts from meetings of American Thoracic Society, British Thoracic Society, European Respiratory Society)	Adult patients with ARF and admitted to hospital due to an acute exacerbation of COPD with baseline admission $PaCO_2$ > 6 kPa Excluded: patients with primary diagnosis of pneumonia, weaning studies, patients with underlying pathologies, studies where CPAP or ETI preceded enrolment of patients into trial	RCTs (abstracts included)	758 (14)	• Relative risks and weighted mean differences or standardized mean differences were calculated • Pooled analyses were conducted using fixed effects or random effects models depending on amount of heterogeneity • Subgroups included: pH, location (ICU vs. ward), study quality, NPPV duration, type of mask, type of NPPV	Treatment failure (mortality, intubation, and intolerance to allocated treatment), inhospital mortality, ETI hospital LOS, ICU LOS, symptom scores (breathlessness scores), complications, arterial blood gas tensions 1-hour post intervention (pH, $PaCO_2$, PaO_2)

*Abbreviations: ARF, acute respiratory failure; CAP, community acquired pneumonia; CINAHL, the Cumulative Index to Nursing and Allied Health Literature; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; ETI, endotracheal intubation; ICU, intensive care unit; kPa, kilopascals; LOS, length of stay; N, sample size; NIV, noninvasive ventilation; no., number; NPPV, noninvasive positive pressure ventilation; NR, not reported; O_2, oxygen; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PaO_2, partial pressure of oxygen in the arterial blood; RCTs, randomized controlled trials; UMC, usual medical care.

†Month was not specified in published results. (19;21;22)

‡Unclear from published methods whether abstracts were included.

§Includes studies with patients with respiratory failure due to any etiology, not just COPD patients.

‖16 RCTs that compared NPPV versus standard therapy and 2 RCTs that compared NPPV versus conventional mechanical ventilation were identified. The results from 2 of the trials on NPPV vs. standard medical therapy were excluded as they did not offer patients who developed respiratory failure endotracheal intubation and mechanical ventilation.

¶The systematic review was published in 2009. It is not clear from the methods which years were included in the systematic search of the literature. The most recent included study was published in 2006, so that has been estimated as the year until which the literature was searched.

#The sample size excludes non-COPD patients from those trials with mixed populations. (20)

Table A3: Summary of the Systematic Reviews' Results*

Author, Year	Findings
Caples et al, 2005 (21)	Pooled results were not reported.† Summary: "From these study results, treatment of hypercapnic patients with acute exacerbations of COPD can generally be expected to reduce intubation rates, mortality, and ICU or hospital LOS."
Hess et al, 2004 (19)	Pooled results were not reported. Summary: "Studies report benefit for (the COPD patient) population with the exception of patients suffering mild exacerbations. The use of NPPV for COPD-exacerbation patients is now considered a standard of care, the evidence for which is established in 2 meta-analyses".‡
Keenan et al, 2011 (17)	NPPV vs. standard medical therapy Intubation: RR, 0.39 (95% CI, 0.28–0.54)§ Hospital mortality: RR, 0.52 (95% CI, 0.36–0.76)‖ NPPV vs. conventional mechanical ventilation ICU mortality: RR, 1.24 (95% CI, 0.45–3.41) Recommendations: "We recommend the use of NPPV in addition to usual care in patients who have a severe exacerbation (pH < 7.35 and relative hypercarbia) of COPD (GRADE 1A). … We make no recommendation about the use of NPPV in patients who have a severe exacerbation of COPD that requires ventilatory support due to insufficient evidence."¶
Keenan et al, 2009 (2)	Pooled results were not reported. Summary: "9 of 16 studies found a lower failure rate with NIV than with standard therapy, and only 3 of the trials reported lower hospital mortality… NIV appears to offer the greatest absolute reduction in failure rate, intubation rate, and hospital mortality in patients with more severe COPD exacerbations. There is also benefit for patients with milder COPD exacerbations, although the evidence is not as strong and is of a lesser degree (lower absolute risk difference). … We recommend that NIV be considered first-line therapy for patients who present with respiratory distress and respiratory acidosis." #
Kennan et al, 2003 (20)	Mortality: risk reduction, 10% (95% CI, 5%–15%)** Intubation: risk reduction, 28% (95% CI, 15%–40%)**†† Hospital LOS: absolute reduction, 4.75 days (95% CI, 2.30–6.83 days)**††
Peter et al, 2002 (22)	Mortality (COPD subgroup): risk difference, −0.13 (95% CI, −0.21 to −0.06) Intubation (COPD subgroup): risk difference, −0.18 (95% CI, −0.33 to −0.03) Hospital LOS (COPD subgroup): −5.66 (95% CI, −10.10 to −1.23) Complications (all studies): risk difference, −15% (95% CI, −31.6% to1%), *P* = 0.07 Dropout due to mask intolerance: 14% (6 studies, all studies)
Quon et al, 2008 (18)	Intubation: RR, 0.35 (95% CI, 0.26–0.47)‡‡ Inhospital Mortality: RR, 0.45 (95% CI, 0.30–0.66) LOS: WMD, −1.94 (95% CI, −3.87 to −0.01)§§

Author, Year	Findings
Ram et al, 2004 (4)	Treatment failure: RR, 0.48 (95% CI, 0.37–0.63), $P < 0.001$‖‖ Mortality: RR, 0.52 (95% CI, 0.35–0.76), $P < 0.001$¶¶; NNT, 10 (95% CI: 7–20) Intubation: RR, 0.42 (95% CI, 0.33–0.53), $P < 0.001$; NNT, 4 (95% CI: 4–5) Hospital LOS: WMD, -3.24 (95% CI, −4.42 to −2.06), $P < 0.001$*** ICU LOS: −4.71 (95% CI, −9.59 to 0.16), $P = 0.06$*** *Symptom scores* Borg score: WMD, −0.31 (95% CI, −1.42 to 0.80), $P = 0.59$ Visual analogue scale: WMD, −2.11 (95% CI, −3.32 to −0.90), $P < 0.001$ Complications of treatment: RR, 0.38 (95% CI, 0.24–0.60), $P < 0.001$

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; LOS, length of stay; NNT, number needed to treat; NPPV, noninvasive positive pressure ventilation; NIV, noninvasive ventilation; RR, risk ratio; WMD, weighted mean difference.

†Caples et al (21) did not conduct a meta-analysis of the data, but instead presented a descriptive summary of the results of some key studies in the area. While studies on the topic were identified, results were only presented in terms of improved, declined, or stayed the same.

‡Hess et al (19) did not conduct a new meta-analysis of the data, but instead presented the pooled results for treatment failure, mortality, intubation, and complications from Lightowler et al (62) and provided a brief commentary on the overall evidence on this topic.

§For the subgroup of patients with milder exacerbations, the risk ratio was not significant (RR, 0.71; 95% CI, 0.16–3.08), but the reduction in endotracheal intubation in the subgroup of patients with community-acquired pneumonia was significant ($P = 0.005$). (17)

‖For the subgroup of patients with milder exacerbations, the risk ratio was not significant (RR, 1.05; 95% CI, 0.07–6.36) (17)

¶Very little data were provided in the published report, so the guideline recommendation has been summarized as well. (17)

#Only a descriptive narrative of the results were provided in the published report. (2)

**Greater reduction in subgroup of patients with severe COPD exacerbations (pH < 7.30 or hospital mortality rate > 10% in control group): inhospital mortality rate: risk reduction, 12% (95% CI, 6%–18%); rate of intubation: risk reduction, 34% (95% CI, 22%–46%); hospital LOS: absolute reduction, 5.59 days (95% CI, 3.66–7.52). Trials with mild COPD exacerbations did not find a benefit in hospital survival (risk reduction, 2%; 95% CI, −8% to 12%), intubation (risk reduction, 0%; 95% CI, −11% to 11%) or hospital LOS (absolute reduction, 0.82 days; 95% CI, −0.12 to 1.77). (20)

††Results were heterogeneous across studies ($P < 0.001$).

‡‡The benefits were modified by the average pH; the beneficial effects increased as the baseline pH decreased ($P = 0.047$). (18)

§§There was significant heterogeneity in these results. (18)

‖‖When the results are subgrouped by location, the benefit is larger for patients being treated in the ICU (RR, 0.29; 95% CI, 0.18–0.47) than patients being treated in wards (RR, 0.61; 0.44–0.86). (4)

¶¶When the results are subgrouped by location, the risk ratio is not significant (RR, 0.61; 95 %CI, 0.32–1.18) for patients being treated in the ICU but remains significant for patients being treated in wards (RR, 0.43; 95% CI, 0.26–0.71). (4)

##When the results are subgrouped by admission pH, the pooled risk ratio is not significant (RR, −0.89; 95% CI, −2.92 to 1.14) for the group with an admission pH between 7.35 and 7.30, but remains significant for the group with an admission pH below 7.30 (RR, −4.43; −5.88 to −2.98). (4)

***When the results are subgrouped by admission pH, the pooled risk ratio is not significant (WMD, −4.71; 95% CI, −9.59 to 0.16) for the group with an admission pH below 7.30. (4)

NPPV for Weaning COPD Patients From Invasive Mechanical Ventilation: Systematic Reviews

Although 5 systematic reviews were identified on this topic, only 4 of the reviews are summarized in the following tables. One systematic review is excluded from the tables because although its topic is NPPV for weaning, no results or conclusions on this topic were reported.

Table A4: Comparison of Systematic Reviews Published Since 2000 (NPPV for Weaning)*

Component RCTs: Author, Year	Author, Year of Literature Search Inclusion of Identified Systematic Reviews				MAS Review	
	Keenan et al, 2009 (17)	Burns et al, 2008 (14)	Hess et al, 2003 (19)	Burns et al, 2003 (13)	Study Included	Reasons for Exclusion
Chen et al, 2001 (63)	✓	✓		✓	X	Not English
Ferrer et al, 2003 (64)	✓	✓	✓	✓	X	Mixed population
Girault et al, 1999 (65)	✓	✓	✓	✓	X	Mixed population
Hill et al, 2000 (66)		✓		✓	X	Abstract
Nava et al, 1998 (37)	✓	✓	✓	✓	✓	
Prasad et al, 2008		✓			X	Unpublished thesis
Prasad et al, 2009 (38)					✓	
Rabie et al, 2004 (67)		✓			X	Abstract
Trevisan et al, 2008 (10)	✓	✓			X	Mixed population
Wang et al, 2004 (68)	✓	✓			X	Not English
Collaborating Research Group†, 2005 (6)	✓	✓			X	Not relevant to Ontario practice‡
Zheng et al, 2005 (69)	✓	✓			X	Not English
Zou et al, 2005 (70)	✓	✓			X	Not English

*Abbreviations: MAS, Medical Advisory Secretariat; NPPV, noninvasive positive pressure ventilation; RCTs, randomized controlled trials.

†Collaborating Research Group for Noninvasive Mechanical Ventilation of Chinese Respiratory Society

‡Expert opinion

Table A5: Summary of the Systematic Reviews' Methods (NPPV for Weaning)*

Author, Year	Date Literature Current to	Databases Searched	Population Included	Included Study Designs	Total N (No. Studies)	Statistical Methods	Outcomes
Burns et al, 2010 (14)	April 2008	Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and conference proceedings from the American Journal of Respiratory and Critical Care Medicine, Intensive Care Medicine, Critical Care Medicine, and Chest	Ventilated adults with ARF of any etiology weaned using either a strategy of early extubation followed by immediate NPPV or continued IPPV weaning. Excluded: RCTs not weaning, immediate postoperative setting or following unplanned extubation, and the application of NPPV with supplemental O_2 compared with unassisted O_2 following elective or unplanned extubation	RCTs, quasi-randomized trials (abstracts included)	530 (12†)	• Relative risks and weighted mean differences were calculated • Pooled analyses were conducted using random effects models • Subgroup analyses compared results for COPD patients and mixed patient populations	All-cause mortality, weaning failure, VAP, ICU LOS, hospital LOS, total duration of MV, duration of mechanical support related to weaning, duration of ETMV, adverse events, QOL
Burns et al, 2006 (13)	July 2003	MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, abstracts published in conference proceedings of the American Journal of Respiratory and Critical Care Medicine, Intensive Care Medicine, Critical Care Medicine, and Chest	Adults invasively ventilated for at least 24 hr with ARF. Included study populations were predominately people with COPD. Excluded: NPPV and IPPV in immediate postoperative setting and application of NPPV and supplement O_2 to unassisted O_2 following elective or unplanned extubation	RCTs, quasi-randomized trials (abstracts included)	171 (5‡)	• Relative risks and weighted mean differences were calculated • Pooled analyses were conducted using random effects models • Subgroup analyses compared results for COPD patients and mixed patient populations	Mortality, incidence of VAP, weaning failure, ICU LOS, hospital LOS, total duration of MV, duration of MV related to weaning, duration of ETMV
Hess et al, 2004 (19)	2003‡	PubMed	Adult patients with ARF. Excluded: long-term NPPV for stable patients with pulmonary or neuromuscular disease	RCTs§	NR (2)	• Relative risks were calculated • Pooled analyses were conducted using random effects models • Results for NPPV for COPD patients are based on results from other meta-analyses. The authors did not conduct their own analysis on this topic.	Not specified in methods. Outcomes included in the COPD section on weaning success, duration of mechanical ventilation, survival, ICU LOS, hospital LOS

Author, Year	Date Literature Current to	Databases Searched	Population Included	Included Study Designs	Total N (No. Studies)	Statistical Methods	Outcomes
Keenan et al, 2011 (17)	June 2009	MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effectiveness, Cochrane Database of Systematic Reviews, ACP Journal Club Database, MetaRegister of Controlled Trials, clinicaltrials.gov website, and Journals@OVID database	Hospitalized adult patients who had or who were at risk for ARF including both acute and acute-on-chronic respiratory failure. Included studies with predominately COPD patients. Excluded: studies of chronic respiratory failure in an outpatient setting.	Parallel-design RCTs (abstracts excluded)	NR (9‖)	• Relative risks and weighted mean differences were calculated • Pooled analyses were conducted using random effects models	Physiologic outcomes including arterial blood gases and vital signs; clinical outcomes including endotracheal intubation and hospital mortality In the section on weaning, the following outcome was reported: hospital mortality

*Abbreviations: ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; ETMV, endotracheal mechanical ventilation; Hr, hour; ICU, intensive care unit; IPPV, invasive positive pressure ventilation; LOS, length of stay; MV, mechanical ventilation; N, sample size; no. number; NPPV, noninvasive positive pressure ventilation; NR, not reported; O_2, oxygen; QOL, quality of life; RCTs, randomized controlled trials; VAP, ventilator-associated pneumonia.

†Includes 1 quasi-randomized trial (patients randomized based on order), 2 abstracts, and 1 unpublished doctoral dissertation

‡4 RCTs and 1 quasi-randomized trial

§Unclear from published results whether abstracts were included in the analysis.

‖Studies included in the section on weaning

Table A6: Summary of the Systematic Reviews' Results (NPPV for Weaning)*

Author, Year	Findings
Burns et al, 2010 (14)	Mortality: RR, 0.42 (95% CI, 0.25–0.69), *P* < 0.001† Weaning failure: RR, 0.50 (95% CI, 0.22–1.12), *P* = 0.09† Nosocomial pneumonia: RR, 0.29 (95% CI, 0.19–0.45), *P* < 0.001 ICU LOS: WMD, −6.27 (−8.77 to −3.78), *P* ≤ 0.001 Hospital LOS: WMD, −7.19 (95% CI, −10.80 to −3.58), *P* < 0.001 Average total duration of MV support: WMD, −5.64 (95% CI, −9.50 to −1.77), *P* = 0.004 Average duration of MV related to weaning: WMD, −0.94 (95% CI, −3.24 to 1.36), *P* = 0.42 Duration of ETMV: WMD, −7.81 (95% CI, −11.31 to −4.31), *P* < 0.001 <u>Adverse events</u> Reintubation: RR, 0.73 (95% CI, 0.40–1.34), *P* = 0.31 Tracheostomy: RR, 0.16 (95% CI, 0.04–0.75), *P* = 0.02 Arrhythmia: RR, 1.05 (95% CI, 0.17–6.67), *P* = 0.96
Burns et al, 2006 (13)	Mortality: RR, 0.25 (95% CI, 0.07–0.91), *P* = 0.04† Incidence of VAP: RR, 0.28 (95% CI, 0.09–0.85), *P* = 0.03 Weaning failure: RR, 0.38 (95% CI, 0.11–1.25), *P* = 0.11† ICU LOS: WMD, −6.88 (95% CI, −12.60 to −1.15), *P* = 0.02 Hospital LOS: WMD, −7.33 (95% CI, −14.05 to −0.61), *P* = 0.03 Total duration of MV: WMD, −7.33 (95% CI, −11.45 to −3.22), *P* < 0.001 Duration of MV related to weaning: WMD, −2.72 (95% CI, −15.58 to 10.14), *P* = 0.68 Duration of ETMV: WMD, −6.32 (−12.12 to −0.52), *P* = 0.03
Hess et al, 2004 (19)	Hess et al (19) did not report pooled analyses or a specific summary of the results of the 2 included trials on weaning.
Keenan et al, 2011 (17)	Recommendation: "We suggest that NPPV be used to facilitate early liberation from mechanical ventilation in patients who have COPD but only in centers that have expertise in NPPV (GRADE 2B)." (17)‡

*Abbreviations: CI, confidence intervals; COPD, chronic obstructive pulmonary disease; ETMV, endotracheal mechanical ventilation; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; N, sample size; no. number; NPPV, noninvasive positive pressure ventilation; RCT, randomized controlled trials; RR, relative risk; VAP, ventilator-associated pneumonia; WMD, weighted mean difference.

†Results are for the subgroup of patients with COPD only and exclude the results from the trials with mixed populations.

‡Only the results for the 3 trials including mixed population on hospital mortality were presented in the published report. Since inadequate data were presented, the guideline recommendation has been summarized instead.

NPPV for Acute Respiratory Failure After Extubation From Invasive Mechanical Ventilation: Systematic Reviews

Table A7: Comparison of Systematic Reviews Published Since 2000 (NPPV Postextubation from IMV)*

Component RCTs: Author, Year	Author, Year of Literature Search Inclusion of Identified Systematic Reviews			MAS Review	
	Keenan et al, 2009 (17)	Caples et al, 2006 (21)	Hess et al, 2003 (19)	Study Included	Reasons for Exclusion
Esteban et al, 2004 (41)†	✓	✓		✓‡	
Esteban et al, 2003 (71)†			✓	X	Abstract
Ferrer et al, 2006 (39)§	✓			X	Mixed population
Ferrer et al, 2009 (40)§‡	✓			X	Mixed population
Jiang et al, 1999 (11)§‡	✓	✓	✓	X	Mixed population
Keenan et al, 2002 (72)‡	✓	✓	✓	X	Mixed population
Luo et al, 2001 (73)§	✓			X	Not English
Nava et al, 2005 (74)§	✓			X	Mixed population

*Abbreviations: ARF, acute respiratory failure; IMV, invasive mechanical ventilation; MAS, Medical Advisory Secretariat; NPPV, noninvasive positive pressure ventilation; RCTs, randomized controlled trials.
†Studies examined the use of NPPV to treat respiratory failure that developed in patients after they were extubated from invasive mechanical ventilation.
‡One outcome (need for reintubation) was presented for the COPD group alone (post hoc analysis). (41)
§Studies examined the early application of NPPV after extubation to prevent the development of ARF after extubation from IMV.
Note: As these systematic reviews were also identified in other sections of this evidence-based analysis, for details on the methods of these reviews, refer to the tables above.

Appendix 3: Detailed Study Descriptions

NPPV for the Treatment of ARF due to Acute Exacerbations of COPD: NPPV Plus UMC Versus UMC Alone

Table A8: General Study Characteristics (NPPV Plus UMC Versus UMC Alone)*

Author, Year	Country, Number of Sites	Sample Size	Location†	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
NPPV + UMC vs. UMC Alone							
Barbe et al, 1996 (25)	Spain, 1	24‡	Respiratory ward	Patients with ARF with severe COPD	NR	Duration of hospital stay	Pulmonary function, breathlessness, hospital mortality, intubation, NPPV tolerance, hospital LOS, respiratory muscle function, arterial blood gases
Bott et al, 1993 (26)	England, 3	60	Ward	Patients admitted for an acute exacerbation of chronic obstructive airway disease, aged ≤ 80 years, arterial PaO_2 < 7.5 kPa, arterial $PaCO_2$ > 6 kPa	Severe disease not attributable to COPD, severe psychiatric disease, used NPPV at home	At least 30 days	Hospital LOS, arterial blood gases, breathlessness, quality of sleep, general well-being, nursing care, survival
Brochard et al, 1995 (27)	France, Italy, Spain, 5	85	ICU	Adult patients hospitalized for acute exacerbations of COPD with known disease or a high probability of disease (based on clinical history, physical exam, and chest film) with respiratory acidosis and an elevated bicarbonate level. Patients must have an exacerbation of dyspnea lasting less than 2 weeks and at least 2 of the following: respiratory rate > 30 breaths/minute, a PaO_2 < 45 mm Hg, and an arterial pH below 7.35 after patient had been breathing room air for at least 10 minutes.	Respiratory rate < 12 breaths/ minute, need for immediate intubation, a tracheotomy or endotracheal intubation performed before admission, administration of sedative drugs within previous 12 hours, CNS disorder related to hypercapnic encephalopathy or hypoxemia, cardiac arrest (within previous 5 days), cardiogenic pulmonary edema, kyphoscoliosis, upper airway obstruction or asthma, clear cause of decompensation requiring specific treatment, facial deformity, or enrolment in other investigative protocols, patients refusing intubation	Until discharge from hospital, 3 months for some outcomes	Need for endotracheal intubation, hospital LOS, complications, duration of ventilatory assistance, hospital mortality rate, pulmonary function, arterial blood gases, respiratory rate, encephalopathy score

Author, Year	Country, Number of Sites	Sample Size	Location†	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
Dhamija et al, 2005 (29)	Turkey, 1	29	Respiratory ward	Patients with COPD exacerbation complicated by mild to moderate respiratory failure (acute or chronic) not requiring invasive mechanical ventilatory support and stable enough to be admitted to the general respiratory ward. Patients with pulmonary function tests suggesting COPD, chest radiograph showing no evidence of acute infection or any other pulmonary disease, and presence of any of the following: pH more than 7.25, arterial $PaCO_2$ > 45 mmHg on room air	Respiratory rate > 35 breaths/minute, pH < 7.25, $PaCO_2$ > 70 mmHg, need for urgent intubation, medically unstable, unable to protect airways, excessive secretions, pulmonary tuberculosis (past or present), history of recent MI or abdominal surgery, any other respiratory disorder	Duration of hospital stay	Arterial blood gases, need for intubation, heart rate, breathlessness, hospital LOS, respiratory rate
Dikensoy et al, 2002 (5)	Turkey, 1	34‡	General ward	Patients with an acute exacerbation of COPD, arterial pH < 7.35, and arterial $PaCO_2$ > 45 mmHg	Urgent need for intubation, haemodynamic instability (systolic blood pressure < 90 mmHg, heart rate > 140 beats/minute), excessive secretions, lack of patient compliance with the study protocol or refusal to participate in the study	Duration of hospital stay	Respiratory rate, arterial blood gases, heart rate, blood pressure, need for intubation due to treatment failure, mortality, hospital LOS, compliance, complications
Keenan et al, 2005 (30)	Canada, 1	52	Respiratory ward	Patients with COPD (documented in prior admission to hospital or received diagnosis from GP and being treated with medication), presented with recent onset of shortness of breath, pH > 7.30	Respiratory arrest, decreased level of consciousness, hemodynamic instability, excess secretions, inability to communicate with patient, use of CPAP at home, associated pneumonia demonstrated on chest radiograph, patient judged to be in respiratory extremis by the admitting physician	Duration of hospital stay	Breathlessness, need for intubation, duration of further mechanical ventilation (if necessary), inhospital LOS, ICU LOS, hospital mortality, pulmonary function, arterial blood gases

Author, Year	Country, Number of Sites	Sample Size	Location†	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
Khilnani et al, 2010 (31)	India, 1	40	ICU	Patients with an acute exacerbation of COPD (diagnosis based on findings from history and clinical examination with typical radiograph abnormalities) leading to hypoxemia and respiratory acidosis with pH < 7.35 and $PaCO_2$ > 45 mmHg admitted to the ICU	Respiratory arrest, hemodynamic instability, altered sensorium, copious secretions, uncooperative patients	Duration of hospital stay	Need for intubation (primary outcome), hospital mortality, hospital LOS, clinical and blood gas parameters, complications
Kramer et al, 1995 (9)	United States, 2	23§	ICU or step down unit	Patients with ARF upon admission or during hospitalization who are otherwise stable. Selection criteria: respiratory distress evidenced by moderate to severe dyspnea, accessory muscle use, or abdominal paradox and ARF as evidenced by pH < 7.35, $PaCO_2$ > 45 mmHg, and respiratory rate > 24 breaths/minute	Respiratory arrest or need for immediate intubation, hypotension (systolic BP < 90 mmHg), uncontrolled arrhythmias, upper airway obstruction or facial trauma, inability to clear secretions, inability to cooperate or fit mask	Duration of hospital stay	Need for intubation (primary outcome), arterial blood gases, heart and respiratory rate, breathlessness, pulmonary function, nursing and respiratory therapy time, difficulty of caring for patients, hospital LOS, morality, charges for total hospital stay and respiratory services, and complications
Plant et al, 2000/2001 (32;34)‖	United Kingdom, 14¶	236	General medical and respiratory wards	Adult patients admitted with an acute exacerbation of COPD (on basis of clinical history, physical examination and chest radiograph), who were tachypnoeic with a respiratory rate > 23 breaths/minute and pH 7.25 – 7.35 and $PaCO_2$ > 6 kPa on arrival to general respiratory ward (after initial treatment in ED and within a maximum of 12 hours of admission)	Glasgow coma score < 8, pneumothorax, active treatment deemed inappropriate	Until hospital discharge and long-term survival (up to 26 months maximum)	Need for intubation (primary outcome), respiratory rate, arterial blood gases, mobility, nutritional status, mask comfort and tolerance, breathlessness, nursing workload In a second publication (34), long-term survival and factors associated with failure of treatment were reported
Wang et al, 2005 (33)	China, 19	342	General ward	Patients with definite or probable COPD (based on clinical history, examination, chest radiography, spirometry, and arterial blood gas findings), acute exacerbation of COPD (characterized by an exacerbation of dyspnea, cough	Refused to receive NPPV, pH < 7.25, Glasgow Coma Score < 8, airway or facial deformity, pneumothorax or pneumomediastinum, unable to spontaneously clear secretions from their airway, systolic BP < 80 mmHg, uncontrolled cardiac	Duration of hospital stay	Need for intubation (primary outcome), hospital mortality, hospital LOS, respiratory rate, heart rate, blood pressure, arterial blood gases, breathlessness, accessory muscle use, adverse effects of NPPV

Author, Year	Country, Number of Sites	Sample Size	Location†	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
				and increase of sputum production and changes in chest radiograph), age < 85 years, pH > 7.25, $PaCO_2$ > 45 mmHg on arrival to the general ward	arrhythmias, unable to cooperate with the application of NPPV, severe organ dysfunction, severe abdominal distension, or NPPV duration < 3 days		
NPPV + UMC vs. Sham + UMC							
Carrera et al, 2009 (28)	Spain, 7	75‡	Respiratory ward	Patients with an acute exacerbation of COPD (increase in dyspnea, cough and/or sputum production of recent onset – last 2 weeks – in absence of another diagnosis) requiring hospitalization, arterial pH between 7.25 and 7.35, $PaCO_2$ > 50 mmHg 30–60 minutes after intensive medical management had been started in the ED, recruitment into study within 24 hours of admission	Respiratory rate < 12 breaths/minute or need for immediate intubation for resuscitation, Glasgow coma score < 8, administration of sedatives within previous 12 hours, neuromuscular disorders, thoracoplasty, kyphoscoliosis, known cause of decompensation requiring specific treatment, history of sleep apnea, asthma, or severe systemic disease, BMI > 40 kg/m^2, facial deformities, history of acute episodes requiring NPPV in the past or chronic NPPV treatment, history of alcohol or drug abuse, and/or refusal to participate	Until discharge from hospital	Need for intubation (primary outcome), arterial blood gases, hospital LOS

*Abbreviations: ARF, acute respiratory failure; BMI, body mass index; BP, blood pressure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; ED, emergency department; GP, general practitioner; ICU, intensive care unit; kg/m^2, kilogram per square meter; kPa, kilopascals; LOS, length of stay; MI, myocardial infarction; mmHg, millimeters of mercury; NPPV, noninvasive positive pressure ventilation; NR, not reported; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PaO_2, partial pressure of oxygen in the arterial blood; UMC, usual medical care.

†ICU, general or respiratory hospital ward, or emergency department

†Consecutive patients

§31 patients were enrolled in the study, but only 23 patients had respiratory failure due to acute exacerbations of COPD. Since this is the patient population of interest in this analysis, only the results for this patient population are presented when possible. (31)

‖Two papers by Plant et al (32;34) were identified. Both report on the same study and patient population; however, the second publication provides results on some additional outcomes not reported in the first paper.

¶14 hospitals participated from which 22 wards were used as sites for NPPV. (32)

Table A9: General Study Characteristics – Intervention and Control Group Details (NPPV Plus UMC Versus UMC Alone)*

Author, Year	Ventilation Mode	Interface	Pressures	Ventilator Schedule	Usual Medical Care	A Priori Intubation Criteria	Severity of Respiratory Failure Categorization†
NPPV + UMC vs. UMC Alone							
Barbe et al, 1996 (25)	BiPAP	Nasal mask	*Expiratory pressure:* set at 5 cm H_2O *Inspiratory pressure:* set to maximum tolerated value in each patient (mean ± SEM, 14.8 ± 0.5 cm H_2O) Ventilatory regimen was not modified during the 3 days of support.	6 hours per day (3 hours in the morning, 3 in the afternoon) during first 3 days in hospital	Aerosolized salbutamol, intravenous prednisolone, and controlled oxygen therapy	No	Moderate
Bott et al, 1993 (26)	Volume cycled	Nasal mask	NR	Encouraged to use NPPV for up to 16 hours per day including all night, with ventilation discontinued for eating, drinking, and moving around. As patients improved, NPPV duration was reduced first during the day and then at night.	Oxygen, inhaled bronchodilators, and all or a combination of antibiotics, diuretics, respiratory stimulants, intravenous or oral corticosteroids, and bronchodilators. Patients who required it were treated by a physiotherapist.	No	Moderate
Brochard et al, 1995 (27)	Pressure support ventilation	Face mask	*Expiratory pressure:* atmospheric *Inspiratory pressure:* 20 cm H_2O and lower levels used in the case of leaks	Ventilation for at least 6 hours each day; time could be lengthened based on clinical tolerance. Overall duration determined on basis of clinical criteria and arterial blood gas levels. 2 hours each day, patients allowed to breathe spontaneously with oxygen but without assistance	Oxygen, subcutaneous heparin, antibiotic agents, bronchodilators (subcutaneous terbutaline, aerosolized and intravenous albuterol, corticosteroids or intravenous aminophylline or both) with correction of electrolyte abnormalities	Yes	Severe
Dhamija et al, 2005 (29)	BiPaP	Face or nasal mask	NR	6 hours per day in 2 sittings of 3 hours each for 3 days (patients were admitted for a minimum of 3 days)	Controlled oxygen, nebulised salbutamol, nebulised ipratropium bromide, oral prednisolone, antibiotics, aminophylline, and diuretics	Yes	Mild

Author, Year	Ventilation Mode	Interface	Pressures	Ventilator Schedule	Usual Medical Care	A Priori Intubation Criteria	Severity of Respiratory Failure Categorization†
Dikensoy et al, 2002 (5)	BiPAP	Full face mask	*Inspiratory pressure:* 9 cm H_2O increasing to highest tolerable level by 1 cm H_2O increments (mean, 15.3 ± 4.3 cm H_2O) *Expiratory pressure:* 3 cm H_2O	Continued until respiratory rate < 25 breaths/minute, pH > 7.35, and sPO_2 > 88% (during oxygen inhalation)	Oxygen therapy, salbutamol, nebulised ipratropium bromide, prednisolone, aminophylline infusion, enoxaparin sodium, and antibiotics	No	Severe
Keenan et al, 2005 (30)	BiPAP	Full face mask or nasal mask‡	*Expiratory pressure:* 4 cm H_2O (mean, 4.7 ± 0.6 cm H_2O) *Inspiratory pressure:* 9 cm H_2O (mean, 9.8 ± 0.6 cm H_2O) Spontaneous mode was used and pressures were titrated as necessary for patient comfort	Initiated within 24 hours of arrival at ED; 8 hours on first day, 6 hours on second day, and 4 hours on third day and then stopped	Supplemental oxygen, pharmacotherapy with inhaled beta-agonists and inhaled ipratropium bromide as clinically indicated, systemic steroids, and antibiotics for infectious exacerbations not due to pneumonia	Yes	Mild
Khilnani et al, 2010 (31)	BiPAP	Nasal mask	*Expiratory pressure:* 4 cm H_2O *Inspiratory pressure:* 8 cm H_2O Adjustments were made according to need of patient and results of blood gas analysis (each inspiration triggered by patient's spontaneous breath)	Encouraged to use NPPV up to 16 hours per day including day and night, discontinued for eating and drinking	Oxygen, bronchodilators, (inhaled salbutamol, ipratropium bromide, subcutaneous terbutaline, and steroids [IV hydrocortisone]), intravenous antibiotics	Yes	Very severe
Kramer et al, 1995 (9)	BiPAP	Nasal mask or oronasal face mask§	*Expiratory pressure:* lowest possible setting (about 2 cm H_2O) *Inspiratory pressure:* 8 cm H_2O increased by 1 cm H_2O every 15 to 30 minutes or as tolerated during initial trial	Encouraged to use NPPV for as long as tolerated aiming for at least 8 hours per day. Mask could be removed for meals, conversation, comfort, and respiratory treatments as needed	Supplemental oxygen, corticosteroids, frequent respiratory treatments, antibiotics	Yes	Severe

Author, Year	Ventilation Mode	Interface	Pressures	Ventilator Schedule	Usual Medical Care	A Priori Intubation Criteria	Severity of Respiratory Failure Categorization†
Plant et al, 2000/2001 (32;34)	BiPAP	Face or nasal mask	*Expiratory pressure :* 4 cm H_2O *Inspiratory pressure :* initially set at 10 cm H_2O and increased in increments of 5 cm H_2O to 20 cm H_2O, or the maximum tolerated over 1 hour	Encouraged to use NPPV as much as possible on day 1, 16 hours on day 2, 12 hours on day 3. NPPV was routinely discontinued on day 4 but was continued if clinically indicated.	Oxygen, nebulised salbutamol or terbutaline, nebulised ipratropium bromide, corticosteroids (prednisolone), and an antibiotic. Aminophylline and doxapram could also be used.	Yes	Moderate
Wang et al, 2005 (33)	BiPAP	Oronasal mask	*Expiratory pressure:* 2–4 cm H_2O and increased to 4–6 cm H_2O gradually (mean, 4.3 ± 1.2 cm H_2O) *Inspiratory pressure:* 6–8 cm H_2O which was adjusted in increments of 2 cm H_2O to obtain satisfactory spontaneous breathing pattern in every 5 to 6 minutes or to the maximum tolerated value (mean, 12.9 ± 3.7 cm H_2O)	At least 12 hours for the first 3 days, and 8 hours for days 4 and 5. At least 5 days of continuous ventilatory support should be given for all patients and 7 to 10 days was recommended	Oxygen, steroids, beta-agonists, theophylline, mucolytics, respiratory stimulants, and antibiotics	Yes	Mild
NPPV + UMC vs. Sham + UMC							
Carrera et al, 2009 (28)	BiPAP	Facial masks	*Expiratory pressure:* set at 4 cm H_2O *Inspiratory pressure:* adjusted individually to maximum tolerated in assisted/controlled mode	During the first 3 days of hospitalization for as much time as possible between 3:00 pm and 8:00 am (started in respiratory ward). Routinely discounted on 4th day of hospitalization	Supplementary oxygen, bronchodilators, steroids, and antibiotics when indicated	Yes	Severe

*Abbreviations: BiPAP, bilevel positive airway pressure; cm, centimeters; COPD, chronic obstructive pulmonary disease; ED, emergency department; H_2O, water; NPPV, noninvasive positive pressure ventilation; NR, not reported; SEM, standard error of the mean; sPO_2, saturation of peripheral oxygen, UMC, usual medical care.

†As outlined in the methods section, severity of respiratory failure was defined based on the mean pH of the study population into the following categories: mild (pH ≥ 7.35), moderate (7.30 ≤ pH < 7.35), severe (7.25 ≤ pH < 7.30), and very severe (pH < 7.25) respiratory failure.

‡Patients who could not tolerate the full face mask could be switched to the nasal mask. (30)

§Patients who could not tolerate the nasal mask or there was excessive air leakage through the mouth were switched to oronasal face masks. (9)

Table A10: Characteristics of the Patients in the Included Studies (NPPV Plus UMC Versus UMC Alone)*

Author, Year	N		FEV_1 % Predicted		Age, Mean (SD), (Years)		Percent Male		pH, Mean (SD)		$PaCO_2$, Mean (SD), mmHg		PaO_2, Mean (SD), mmHg	
	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC
NPPV + UMC vs. UMC Alone														
Barbe et al, 1996 (25)	14†	10	36 (4)	30 (3)	70 (2)	65 (3)	100	100	7.33 (0.01)		7.9 (0.3)‡		6.0 (0.2)‡	
Bott et al, 1993 (26)	30	30	NR	NR	NR	NR	NR	NR	7.34 (0.07)‡	7.33 (0.07)‡	8.6 (1.4)‡§	8.6 (1.67)‡§	5.28 (1.0)‡§	5.2 (1.07)‡§
Brochard et al, 1995 (27)	43	42	NR	NR	71 (9)	69 (10)	NR	NR	7.27 (0.10)	7.28 (0.11)	70 (12)	67 (16)	41 (10)	39 (12)
Dhamija et al, 2005 (29)	14	15	NR	NR	NR	NR	NR	NR	7.37 (0.06)	7.38 (0.06)	62.6 (5.2)	58.2 (5.6)	43.3 (6.4)	50.6 (9.8)
Dikensoy et al, 2002 (5)	17	17	37.9 (14.3)	42.2 (11.7)	65 (6)	64 (8)	47	71	7.28 (0.8)‖	7.29 (0.5)‖	78.4 (9.7)	64.3 (8.4)	56 (13)	50.7 (14)
Keenan et al, 2005 (30)	25	27	36 (12)	31 (15)	69 (9)	71 (8)	40	52	7.40 (0.04)	7.40 (0.05)	50 (15)	51 (17)	NR	NR
Khilnani et al, 2010 (31)	20	20	NR	NR	55 (10)	60 (11)	75	80	7.23 (0.07)	7.23 (0.07)	85.4 (14.9)	81.1 (11.7)	61.2 (14.7)	61.5 (15.1)
Kramer et al, 1995 (9) §	11	12	NR	NR	67 (2)¶	70 (2)¶	56	60	7.27 (0.02)¶#	7.29 (0.02)¶#	80.9 (5.9)¶#	80.6 (9.3)¶#	61.0 (4.4)¶#	56.8 (5.6)¶#
Plant et al, 2000 (32)	118	118	NR	NR	69 (7)	69 (8)	46	53	7.32 (range, 7.25–7.35)**	7.31 (range, 7.26–7.35)**	8.820 (1.15)‡	8.65 (1.70)‡	6.88 (range, 4.50–13.8)‡**	7.00 (range, 4.71–12.31)‡**
Wang et al, 2005 (33)	171	171	FEV_1: 0.6 (0.5) L	FEV_1: 0.6 (0.4) L	69 (10)	70 (8)	66	58	7.34 (0.06)	7.35 (0.06)	66 (13)	65 (12)	PaO_2/FiO_2: 254 (68)	PaO_2/FiO_2: 255 (75)

Author, Year	N		FEV_1 % Predicted		Age, Mean (SD), (Years)		Percent Male		pH, Mean (SD)		$PaCO_2$, Mean (SD), mmHg		PaO_2, Mean (SD), mmHg	
	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC
NPPV + UMC vs. Sham NPPV + UMC														
Carrera et al, 2009 (28)	37	38	39 (11)††	37 (11)††	72 (10)	69 (7)	NR	NR	7.31 (0.02)	7.31 (0.05)	69 (14)	69 (13)	43 (9)‡‡	48 (9)‡‡

*Abbreviations: ARF, acute respiratory failure; FEV_1, forced expiratory volume in 1 second; FiO_2, fraction of inspired oxygen; mmHg, millimeters of mercury; N, sample size; NPPV, noninvasive positive pressure ventilation; NR, not reported; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PaO_2,partial pressure of oxygen in the arterial blood; SD, standard deviation; UMC, usual medical care.

†The published results state that half of the patients were randomized to NPPV, which would be 12 patients; however, the abstract and discussion both state that 14 patients were randomized to NPPV. (25)

‡kPa

§Data were obtained from the Ram et al (4) systematic review as the results by NPPV versus UMC were presented stratified by centre in the published results; however, Ram et al (4) obtained data from the authors.

‖ $P < 0.05$ (5)

¶Mean ± standard error

#Patients with ARF due to various etiologies were enrolled in the study. Patient population characteristics are listed for only the COPD patient group where possible and are indicated by this symbol. (9)

**Ranges in parentheses are median data with 5th and 95th percentiles.

††FEV_1 at discharge

‡‡$P = 0.05$

NPPV for the Treatment of Acute Respiratory Failure due to Acute Exacerbations of COPD: NPPV Versus IMV

Table A11: General Study Characteristics (NPPV Versus IMV)*

Author, Year	Country, Number of Sites	Sample Size	Location	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
Conti et al, 2002 (36)	Italy, 1	49	ICU	Patients with ARF due to COPD who failed a course of medical treatment. Patients with ARF defined as respiratory acidosis with pH lower than 7.32, bicarbonate levels higher than 30 mEq/l, hypoxemia with PaO_2 < 45 mmHg while breathing room air, respiratory rate > 30 breaths/minute, history of worsening dyspnea < 2 weeks duration. Of these patients, those who required ventilatory support in ICU deteriorated despite medical treatment and met at least 1 of the following criteria: pH less than 7.20, arterial oxygen saturation > 90% with a fraction of inspired oxygen of 0.35 or higher, respiratory rate < 35 breaths/minute, or severe deterioration in mental status with Kelly score ≥ 4 were included	Presence of tracheostomy or endotracheal intubation performed before ICU admission, facial deformities, upper airway obstruction, recent surgery, trauma, CNS alterations unrelated to hypercapnic encephalopathy, presence of cardiogenic pulmonary edema, pneumothorax, pulmonary thromboembolism, hemoptysis, neoplasms, septic shock, need for urgent intubation	12 months	ICU LOS, arterial blood gases, duration on mechanical ventilation, complications, ICU mortality, inhospital mortality, 1-year survival, need for intubation, hospital readmissions, requirement for de novo oxygen supplementation
Jurjevic et al, 2009 (7)	Croatia, 1	156	ICU	Patients with COPD	Expected mechanical ventilation duration < 24 hours, use of mechanical ventilation on admission to ICU, patients in coma, patients in shock, patients who had cardio-respiratory arrest within 5 days, patients scheduled for organ donation, patients admitted to ICU because of ARF due to COPD within 3 months	Duration of ICU stay	Total duration ventilation, ICU LOS, success of mechanical ventilation, need for tracheotomy, incidence of VAP, ICU mortality, need for intubation in NPPV group

*Abbreviations: ARF, acute respiratory failure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; mEq/l, milliequivalents per litre; mmHg, millimeters of mercury; NPPV, noninvasive positive pressure ventilation; VAP, ventilator-associated pneumonia.

Table A12: General Study Characteristics – Intervention and Control Group Details (NPPV Versus IMV)*

	Noninvasive Positive Pressure Ventilation				Invasive Mechanical Ventilation
Author, Year	**Ventilation Mode**	**Interface**	**Pressures**	**Ventilator Schedule**	**Pressure Settings and Weaning**
Conti et al, 2002 (36)	BiPAP	Full face mask	Initial level of pressure support (16 ± 2 cm H_2O) adjusted to obtain tidal volume 8–10 ml/kg and respiratory rate of 25 breaths/minute. CPAP pressure of 5 cm H_2O. Settings were adjusted on the basis of continuous oximetry and measurements of arterial blood gases. Weaning Pressure support was decreased progressively with degree of clinical improvement by 3 cm H_2O steps (twice a day) and discontinued when patient maintained respiratory rate < 30 breaths/minute with pH higher than 7.35 and SaO_2 higher than 90% with a FiO_2 of 0.28 in presence of normal mental and hemodynamic status.	During first 12 hours, NPPV was administered continuously and then interrupted for short periods of oxygen supplementation alone (FiO_2 28%) to allow drinking and expectorating.	Initial ventilator setting was assist-control with a delivered tidal volume of 8–10 ml/kg and a respiratory rate of 10–14 breaths/minute and FiO_2 of 0.35. PEEP was set at 5 cm H_2O and trigger at −1 cm H_2O. IV propofol at 2 mg/kg was given for sedation at time of intubation. When spontaneous breathing reappeared, ventilator settings were changed to pressure support ventilation (14–20 cm H_2O) titrated to achieve a spontaneous tidal volume of 8–10 ml/kg, respiratory rate < 25 breaths/minute, and disappearance of accessory muscle activity. After 24 hours, pressure support ventilation was progressively reduced by 3 cm H_2O steps (twice daily). Weaning Patients who tolerated a pressure support level of 8 cm H_2O underwent a 2-hour T-piece trial at FiO_2 0.28. If patients maintained a respiratory rate < 30 breaths/minute, SaO_2 > 90%, pH higher than 7.35, and normal mental and hemodynamic status, then they were extubated. If after 12 days, patients were still intubated, and receiving mechanical ventilation, a tracheostomy was performed. If patients were still ventilator-dependant after 60 days, physicians had the option of discharging patients on home-care ventilation.
Jurjevic et al, 2009 (7)	BiPAP	Nasal or face mask	Ventilator parameters were set to: CPAP to 0 cm H_2O, PSV 10 cm H_2O, and FiO_2 adjusted to reach $SatO_2$ > 90%. Then, set to CPAP 3-5 cm H_2O, PSV 10-25 cm H_2O to reach tidal volume > 5 ml/kg and respiratory rate < 30 breaths/minute. According to patient's development, ventilatory support level was reduced until ventilation could be discontinued.	NR	Patients received the lowest respiratory support level that secured SaO_2 > 90% with FiO_2 ≤ 0.6, $PaCO_2$ ≤ 45 mmHg, and stable hemodynamic patient condition. Weaning Weaning process was conducted using pressure support ventilation. Initial pressure support was 18 cm H_2O which was then reduced by 2–4 cm H_2O depending on clinical status, pulmonary mechanics, biochemistry, and circulation. Patients were extubated at pressure support of 5 cm H_2O.

*Abbreviations: BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; FiO_2,fraction of inspired oxygen; H_2O, water; IV, intravenous; kg, kilograms; ml, milliliters; mmHg, millimeters of mercury; NPPV, noninvasive positive pressure ventilation; NR, not reported; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation; SaO_2,oxygen saturation of arterial blood

Table A13: Characteristics of the Patients in the Included Studies (NPPV Versus IMV)*

Author, Year	Sample Size		FEV_1 % Predicted		Age, Mean (SD), Years		Percent Male		pH, Mean (SD)		$PaCO_2$, Mean (SD), mmHg		PaO_2, Mean (SD), mmHg	
	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV
Conti et al, 2002 (36)	23	26	28 (5)	33 (10)	73 (8)	71 (8)	NR	NR	7.2 (0.05)	7.2 (0.05)	85 (16)	87 (14)	PaO_2:FiO_2 ratio: 168 (38)	PaO_2:FiO_2 ratio: 171 (38)
Jurjevic et al, 2009 (7)	78	78	NR	NR	Median, 58 (range, 35–82)	Median, 54 (range, 38–78)	68	64	7.21 (0.09)	7.22 (0.07)	84 (18)	83 (16)	66 (15)	66 (12)

*Abbreviations: FEV_1, forced expiratory volume in 1 second; FiO_2, fraction of inspired oxygen in a gas mixture; IMV, invasive mechanical ventilation; mmHg, millimeters of mercury; NPPV, noninvasive positive pressure ventilation; NR, not reported; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; SD, standard deviation.

NPPV for Weaning COPD Patients from Invasive Mechanical Ventilation

Table A14: General Study Characteristics (NPPV Versus IMV for Weaning)*

Author, Year	Country, Number of Sites	Sample Size	Patient Population	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
Nava et al, 1998 (37)	Italy, 3	50	Patients with acute exacerbations of COPD who required IMV and failed a T-piece weaning test	Patients with known COPD admitted for an acute relapse defined as respiratory acidosis (pH ≤ 7.33 while breathing room air), elevated bicarbonate levels, hypoxemia ($PaCO_2$ ≤ 45 mmHg while breathing room air), and severe dyspnea in the absence of an objectively documented cause such as pneumonia, who needed intubation, were eligible for the study. Those patients who had satisfactory neurologic status, body temperature of 37°C or less, were hemodynamically stable, and had SaO_2 ≥ 88% for an FiO_2 of 40% during a brief discontinuation of mechanical ventilation were given a T-piece trial. Those patients who failed the T-piece trial (had any of the following: respiratory rate > 35 breaths/minute, PaO_2 < 50 mmHg for an FiO_2 of 40%, heart rate more than 145 beats/minute or sustained increase or decrease in heart rate of more than 20%, severe arrhythmia, systolic BP > 180 mmHg or < 70 mmHg, agitation, anxiety, or diaphoresis) were eligible for inclusion in the trial.	Concomitant severe diseases, cardiac arrest, cardiogenic pulmonary edema, cardiogenic shock, aortic aneurysm, acute MI, gastrointestinal perforation, obstruction or bleeding, sepsis, trauma, metabolic coma, diabetic ketoacidosis, drug overdose, coagulopathy, other hematologic diseases, postoperative patients, and patients who have a successful T-piece trial	ICU stay (up to 60 days)	Arterial blood gases, pulmonary function, complications, duration of mechanical ventilation, ICU LOS, % patients who could not be weaned (due to death, reintubation within 72 hours, and failure to be weaned at 60 days), mortality
Prasad et al, 2009 (38)	India, 1	30	Patients admitted to ICU with acute exacerbation of COPD and needing IMV	Patients with acute hypercapnic respiratory failure in COPD defined as severe dyspnea in the absence of objectively documented causes such as pneumonia and with the following arterial blood gases: pH < 7.33	Patients who died immediately during intubation, patients with successful T-piece trials, patients with concomitant neurological disease (other than hypercapnic encephalopathy), cardiac arrest, cardiogenic pulmonary edema,	ICU stay (up to 30 days)	Duration of mechanical ventilation, duration of ICU stay, duration of weaning, nosocomial pneumonia, mortality at discharge from ICU and 30-day discharge

Author, Year	Country, Number of Sites	Sample Size	Patient Population	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
			who failed a T-piece weaning test	(breathing at room air), PaO_2 < 50 mmHg, $PaCO_2$ > 50 mmHg who were intubated. T-piece weaning trial was given to the patients when they were judged to have reached satisfactory neurological status, clinical and biochemical parameters with an SaO_2 of ≥ 88% for a FiO_2 of 40% after a minimum of 24 hours of ventilation. T-piece weaning failure was characterized by any of the following: PaO_2 < 50 mm for a FiO_2 of 40%, pH < 7.35, respiratory rate > 35 breathes/minute, heart rate > 145 beats/minute, systolic BP > 180 mmHg or < 70 mmHg, significant arrhythmia, or agitation, anxiety or diaphoresis. Those patients that failed the T-piece trial were enrolled in the study.	cardiogenic shock, acute MI, gastrointestinal perforation/obstruction, metabolic coma, coagulopathy, postoperative respiratory failure		

*Abbreviations: BP, blood pressure; COPD, chronic obstructive pulmonary disease; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; MI, myocardial infarction; mmHg, millimeters of mercury; NPPV, noninvasive positive pressure ventilation; PaO_2, partial pressure of oxygen in the arterial blood; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; SaO_2, saturation of oxygen of arterial blood.

Table A15: General Study Characteristics – Intervention and Control Group Details (NPPV Versus IMV for Weaning)*

Author, Year	Initial IMV Settings and Protocol	NPPV Weaning Protocol				IMV Weaning Protocol
		Ventilation Mode	Interface	Pressures	Ventilator Schedule	Pressure Settings and Protocol
Nava et al, 1998 (37)	Patients ventilated in controlled mode during the first 12 hours (sedated and curarized and airway secretions suctioned frequently during first 6–8 hours) with the following settings: tidal volume: 8–10 mL/kg, respiratory rate: 12–16 breaths/minute, FiO_2 as required to obtain SaO_2 of 95%. Then, patients were given pressure support ventilation (21 ± 2 cm H_2O) for an additional 24–36 hours. Extrinsic positive end-expiratory pressure was added when intrinsic positive end-expiratory pressure was clinically suspected. Then, a T-piece weaning trial was given to those patients who were judged to have satisfactory neurological status, body temperature of 37°C or less, hemodynamically stable, SaO_2 of 88% or more for an FiO_2 of 40% during a brief discontinuation of mechanical ventilation. After failure of T-piece weaning trial, patients were reconnected to the ventilator in pressure support ventilation mode until the previous $PaCO_2$ and pH values were reached (30–60 minutes) and the respiratory rate under ventilation was ≤ 30 breaths/minute.	Pressure support ventilation	Face mask	Patients received ventilation with level of pressure support (19 ± 2 cm H_2O) that was adjusted to achieve satisfactory blood gases and respiratory rate < 25 breaths/minute.	During the first 48 hours, NPPV was delivered until it was well tolerated (20–22 hours/day) spaced by periods of spontaneous inhalation of oxygen during meals and to expectorate. The level of pressure support was decreased by 2 or 4 cm H_2O per day in patients with good tolerance and patients were allowed to breathe spontaneously. At least 2 trials of spontaneous breathing of gradually increased duration were attempted each day.	The pressure was titrated to achieve a breathing frequency of ≤ 25 breaths/minute. Pressure support ventilation was initially set at 17.6 ± 2.1 cm H_2O and then the level was gradually decreased and intermittent trials of spontaneous breathing were performed 2 times/day by using a T-tube circuit or a continuous-flow circuit with a continuous positive airway pressure < 5 cm H_2O.
Prasad et al, 2009 (38)	Patients were ventilated with control/assist mode in a step-wise manner (considering their level of consciousness, sedation, and improvement in arterial blood gases). Muscle relaxants and sedation were used as required. The following ventilator settings were	BiPAP	Full face mask	Level of IPAP and EPAP support was used to achieve satisfactory blood gases and a respiratory rate < 25 breaths/minute. Once that was	Patients received NPPV continuously except for meals and expectoration.	Patients received pressure support ventilation with a particular level of pressure support that achieved satisfactory blood gases and a respiratory rate < 25 breaths/minute. Once that was achieved, pressure support was decreased by 2 cm H_2O every 4 hours with a good tolerance. As soon as the pressure support and PEEP reached 10 and 5 cm H_2O, respectively, with a pH ≥ 7.35, SaO_2 ≥ 90%, FiO_2 ≤ 40%, and respiratory rate <

Author, Year	Initial IMV Settings and Protocol	NPPV Weaning Protocol				IMV Weaning Protocol
		Ventilation Mode	Interface	Pressures	Ventilator Schedule	Pressure Settings and Protocol
	used: respiratory rate of 12 breaths/minute, tidal volume 8–10 mL/kg, FiO_2 to obtain SaO_2 of 90% with PEEP of 5 cm H_2O and an I:E ratio of 1:2.5–3.0. T-piece weaning trials were given to patients that were judged to have satisfactory neurological status, clinical and biochemical parameters with an $SaO_2 \geq 88\%$ for a FiO_2 of 40% after a minimum of 24 hours of ventilation. After failure of T-piece weaning trial, patients were put back on control/assist ventilation mode until previous $PaCo_2$ and pH values were reached with a respiratory rate ≤ 30 breaths/minute.			achieved, pressure support was decreased by 2 cm H_2O every 4 hours with a good tolerance. As soon as the IPAP and EPAP levels were reduced to 8 and 4 cm H_2O, respectively, with a satisfactory pH ≥ 7.35, $SaO_2 \geq 90\%$, $FiO_2 \leq 40\%$, and respiratory rate < 30 breaths/minute, patients were allowed to breathe spontaneously.		30 breaths/minute, patients were extubated and allowed to breathe spontaneously.

*Abbreviations: BiPAP, bilevel positive airway pressure; cm H_2O, centimeters of water; E, expiratory; EPAP, expiratory positive airway pressure; FiO_2, fraction of inspired oxygen; I, inspiratory; IMV, invasive mechanical ventilation; IPAP, inspiratory positive airway pressure; NPPV, noninvasive positive pressure ventilation; NR, not reported; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PEEP, positive end-expiratory pressure; SaO_2, oxygen saturation of arterial blood; SIMV, synchronous intermittent mechanical ventilation.

Table A16: Characteristics of the Patients in the Included Studies (NPPV Versus IMV for Weaning)*

Author, Year	Sample Size		FEV_1 % Predicted		Age, Mean (SD), Years		Percent Male		pH, Mean (SD)		$PaC0_2$, Mean (SD), mmHg		PaO_2, Mean (SD), mmHg	
	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV
Nava et al, 1998 (37)	25	25	16.9 (10)	17.4 (9)	68.7 (8.5)	67.0 (9.2)	NR	NR	7.22 (0.07)	7.22 (0.08)	96.3 (19.6)	91.9 (13.8)	PaO_2: FiO_2 ratio: 1.48 (0.3)	PaO_2:FiO_2 ratio: 1.42 (0.4)
Prasad et al, 2009 (38)	15	15	29.77 (6.98)	29.33 (5.61)	57.7 (11.2)	61.1 (8.1)	80	60	7.13 (0.06)	7.13 (0.07)	95.98 (21.28)	102.54 (28.36)	NR	NR

*Abbreviations: FEV_1, forced expiratory volume in 1 second; FiO_2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; mmHg, millimeters of mercury; NPPV, noninvasive positive pressure ventilation; NR, not reported; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PaO_2, partial pressure of oxygen in the arterial blood; SD, standard deviation.

Appendix 4: Summary Tables of Study Methodological Quality and GRADE Quality of Evidence

NPPV for the Treatment of ARF due to Acute Exacerbations of COPD: NPPV for ARF

Table A17: Summary of Study Methodological Characteristics That Impact Study Quality (NPPV Plus UMC Versus UMC Alone or IMV)*

Author, Year	Sample Size	Adequate Randomization Methods	Adequate Allocation Concealment	Blinding	Power	Loss to Follow-Up	Intention-to-Treat
NPPV + UMC vs. UMC Alone							
Barbe et al, 1996 (25)	24	Unclear†	Unclear	X‡	X§	NR	X‖
Bott et al, 1993 (26)	60	Unclear†	Unclear	X‡	X§	NR	Some outcomes¶
Brochard et al, 1995 (27)	85	Unclear†	Unclear	n/a#	✓**	NR	✓
Carrera et al, 2009 (28)	75	✓	✓	✓††	X§	0%	✓
Dhamija et al, 2005 (29)	29	✓	Unclear	n/a#	X§	NR	X‡‡
Dikensoy et al, 2002 (5)	34	X§§	Unclear	X‡	Some outcomes‖ ‖	NR	X¶¶
Keenan et al, 2005 (30)	52	✓	✓	X‡	X##	NR	✓
Khilnani et al, 2010 (31)	40	✓	Unclear	X‡	Some outcomes***	NR	✓
Kramer et al, 1995 (9)	23	Unclear†	Unclear	n/a#	X †††	NR	✓
Plant et al, 2000 (32)	236	✓	✓	n/a#	Some outcomes‡‡‡	0%	✓
Wang et al, 2005 (33)	342	Unclear§§§	Unclear	n/a#	Some outcomes‖ ‖ ‖	NR	✓
NPPV vs. IMV							
Conti et al, 2002 (36)	156	Unclear¶¶¶	Unclear¶¶¶	n/a#	X§	0%	✓
Jurjevic et al, 2009 (7)	49	Unclear###	✓	n/a#	Some outcomes****	NR	✓

*Abbreviations: BiPAP, bilevel positive airway pressure; IMV, invasive mechanical ventilation; n/a, not applicable; LOS, length of stay; NPPV, noninvasive positive pressure ventilation; NR, not reported; UMC, usual medical care.

†The study is identified as randomized, but the methods of randomization are not reported.

‡The study was not blinded. Some of the outcomes could have been influenced by lack of blinding (e.g., if there were no a priori intubation criteria, if patients were discharged by a physician who was not blinded, and/or if the study used subjective outcome measurements).

§The study did not report an a priori sample size calculation, and post hoc power calculations show that the study was underpowered.

‖The 4 patients who could not tolerate NPPV were excluded from the published analysis. (25)

¶The survival analysis is performed using intention-to-treat; however, the symptom assessments were not, as patients with missing data were excluded. (26)

#While the study was not blinded, most outcomes were objective and so the impact of the lack of blinding was minimized.

**The study did not report an a priori sample size calculation. Post hoc power calculations show that the study was adequately powered for some outcomes (complication rate and intubation rate). While the post hoc power calculations show the other outcomes were underpowered, the results were statistically significant, so type II error is unlikely. (27)

††Sham BiPAP machine was used and those physicians making treatment decisions were blinded to treatment group. (28)

‡‡One patient who could not tolerate the mask in the NPPV group was excluded from the analysis.

§§The randomization method is reported as direct enumeration which does not provide adequate information to assess the method of randomization. Patients who did not comply with the study treatment were excluded from the study and then randomization continued with the next patient. (5)

‖‖While the study did not report an a priori sample size calculation, and post hoc power calculations showed that it was underpowered for most outcomes, the study was adequately powered for hospital LOS. In addition, the results for the need for intubation were statistically significant, which suggests type II error is not an issue for this outcome.

¶¶The 2 patients who were not compliant to NPPV were excluded from the analysis.

##While an a priori sample size calculation is provided, due to changes in funding at the hospital in which the study was conducted, the study did not enrol adequate patients to reach their sample size target to achieve 80% power. (30)

***While the study did not report an a priori sample size calculation and post hoc power calculations showed that some outcomes were underpowered, some outcomes were adequately powered.

†††While the study did not report an a priori sample size calculation and post hoc power calculations showed that the outcomes were underpowered, one outcome did show a significant result which suggests type II error is not an issue for this outcome.

‡‡‡A priori sample size calculation was reported for the primary outcome (need for intubation); however, post hoc power calculations show that the study was underpowered to assess mortality.

§§§A centralized, interactive voice system was used to randomize patients. Inadequate information on this method of randomization was provided to determine if this is an appropriate and adequate method of randomization.

‖‖‖While no a priori sample size calculation was reported, post hoc power calculations show that the study was adequately powered to assess the primary outcome (need for intubation), but not mortality or hospital LOS.

¶¶¶Random assignment was made with sealed envelopes, however, this is not enough information to determine if the methods of randomization are adequate, and since the envelopes were not specified as opaque, it was not possible to assess adequacy of allocation concealment either. (36)

###Patients were randomized using closed, non-transparent envelopes; however, this is not enough information to determine if the methods of randomization are adequate. (7)

****The study reported an a priori sample size calculation, but the paper did not report what outcome this sample size calculation referred to. Post hoc power calculations show that some outcomes are underpowered (mortality and success of treatment) while others (incidence of ventilator-associated pneumonia and tracheotomy) are adequately powered.

Table A18: GRADE Quality of Evidence (NPPV Plus UMC Versus UMC Alone)*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: need for endotracheal intubation							
11	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: inhospital mortality							
9	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: 30-day mortality							
1	RCT	Serious limitations†	n/a	No serious limitations	No serious limitations	n/a	Low
Outcome: long-term survival							
1	RCT	Serious limitations†	n/a	No serious limitations	No serious limitations	n/a	Moderate
Outcome: hospital length of stay							
11	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: dyspnea							
8	RCT	Serious limitations†	Serious limitations‡	No serious limitations	No serious limitations	n/a	Low
Outcome: complications							
5	RCT	Serious limitations†	Serious limitations§	No serious limitations	No serious limitations	n/a	Low

*Abbreviations: n/a, not applicable; NPPV, noninvasive positive pressure ventilation; RCT, randomized controlled trial; UMC, usual medical care.

†Study quality was downgraded due to the serious limitations shown in Table A17 above.

‡Downgraded due to lack of consistency in the results, with some studies showing significantly faster improvements in dyspnea in the NPPV plus UMC group compared with the UMC group, and other studies showing no significant difference between the 2 groups.

§Brochard et al (27) reported 232 complications in the UMC group, whereas the other studies which reported complications in the UMC group reported 10 or fewer complications.

Table A19: GRADE Quality of Evidence (NPPV Versus IMV)*

No. of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: ICU mortality							
2	RCT	Serious limitations†	Serious limitations‡	Serious limitations§	Serious limitations	n/a	Very low
Outcome: inhospital mortality							
1	RCT	Serious limitations†	n/a	No serious limitations	Serious limitations‖	n/a	Low
Outcome: 1-year mortality							
1	RCT	Serious limitations†	n/a	No serious limitations	Serious limitations‖	n/a	Low
Outcome: successful treatment							
1	RCT	Serious limitations†	n/a	No serious limitations	Serious limitations‖	n/a	Low
Outcome: ICU length of stay							
2	RCT	Serious limitations†	Serious limitations‡	Serious limitations§	Serious limitations	n/a	Very low
Outcome: duration of mechanical ventilation							
2	RCT	Serious limitations†	Serious limitations‡	Serious limitations§	No serious limitations	n/a	Very low
Outcome: ventilator-associated pneumonia							
2	RCT	Serious limitations†	Serious limitations‡	Serious limitations§	No serious limitations	n/a	Very low
Outcome: tracheotomy							
2	RCT	Serious limitations†	No serious limitations‡	Serious limitations§	No serious limitations	n/a	Very low

*Abbreviations: ICU, intensive care unit; IMV, invasive mechanical ventilation; n/a, not applicable; No., number; NPPV, noninvasive positive pressure ventilation; RCT, randomized controlled trial.

†Downgraded due to serious limitations in individual study quality which are outlined in Table A17.

‡Downgraded due to inconsistency between the results of the 2 studies. One study showed significant benefits in the NPPV group and the other showed no significant differences between the 2 groups.

§Downgraded because the generalizability of the Jurjevic et al (7) is unknown due to the lack of clear inclusion criteria in the study.

‖Downgraded due to imprecision.

NPPV for Weaning COPD Patients from IMV: NPPV Versus IMV

Table A20: GRADE Quality of Evidence (NPPV Versus IMV for Weaning)*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: mortality							
2	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: ICU length of stay							
2	RCT	Serious limitations†	No serious limitations	No serious limitations	Serious limitations‡	n/a	Low
Outcome: duration of mechanical ventilation							
2	RCT	Serious limitations†	No serious limitations	No serious limitations	Serious limitations‡	n/a	Low
Outcome: nosocomial pneumonia							
2	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: other complications							
2	RCT	Serious limitations†	Serious limitations§	No serious limitations	No serious limitations	n/a	Low
Outcome: weaning failure							
1	RCT	Serious limitations†	n/a	No serious limitations	No serious limitations	n/a	Moderate

*Abbreviations: ICU, intensive care unit; IMV, invasive mechanical ventilation; NPPV, noninvasive positive pressure ventilation; n/a, not applicable; RCT, randomized controlled trial.

†Individual study quality was downgraded due to serious limitations in study methodology shown in Table A21.

‡Downgraded due to imprecision in the pooled summary estimates.

§Downgraded due to inconsistency in the number of complications, with one study having a much higher incidence of complications than the other.

Table A21: Summary of Study Methodological Characteristics That Impact Study Quality (NPPV Versus IMV for Weaning)*

Author, Year	Sample Size	Adequate Randomization Methods	Adequate Allocation Concealment	Blinding	Power	Loss to FUP	ITT	Weaning Criteria (refer to methods section for more details on these criteria)					
								Daily Screening	Criteria to Identify Weaning Candidates	Weaning Protocols / Guidelines	Criteria for Failed SBT	Criteria for Discontinued MV	Criteria for Reintubation
NPPV vs. IMV to wean patients from IMV													
Nava et al, 1998 (37)	50	Unclear†	✓	Some outcomes‡	Some outcomes§	NR	✓	X	✓	✓	✓	✓‖	✓
Prasad et al, 2009 (38)	30	✓	Unclear	Some outcomes‡	X¶	NR	✓	X	✓	✓	✓	✓	✓

*Abbreviations: FUP, follow-up; IMV, invasive mechanical ventilation; ICU, intensive care unit; ITT, intention-to-treat; MV, mechanical ventilation; NPPV, noninvasive positive pressure ventilation; NR, not reported; SBT, spontaneous breathing trial.

†Methods of randomization are not provided in the published report.

‡The study was not blinded; however, some of the outcomes are objective and should be less impacted by lack of blinding. Some outcomes such as length of stay may be more likely to be affected.

§No a priori sample size is reported. Based on post hoc power calculations, the study is adequately powered to assess ICU length of stay. The study was underpowered for mortality and duration of mechanical ventilation, these outcomes were significant, and so type II error is unlikely. Finally, the study was underpowered to assess ventilator-associated pneumonia based on post hoc power calculations.

‖MV was discontinued after a successful spontaneous breathing test of at least 3 hours. (37)

¶No a priori sample size calculation is reported, and based on post hoc power calculations, the study was underpowered.

NPPV for ARF After Extubation From IMV: NPPV Plus UMC Versus UMC Alone

Table A22: Summary of Study Methodological Characteristics That Impact Study Quality (NPPV Versus UMC After Extubation)*

Author, Year	Sample Size	Adequate Randomization Methods	Adequate Allocation Concealment	Blinding	Power	Loss to Follow-Up	Intention-to-Treat
Esteban et al, 2004 (41)	23	✓	✓	✓†	X‡	NR	✓

*Abbreviations: COPD, chronic obstructive pulmonary disease; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

†While the study was not blinded, need for reintubation was based on a priori criteria which were based primarily on objective measurements.

‡While the study reported an a priori sample size calculation for the COPD patients separately, the study was underpowered based on a post hoc power analysis.

Table A23: GRADE Quality of Evidence (NPPV Versus UMC After Extubation)*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: reintubation							
1	RCT	Serious limitations†	n/a	No serious limitations	Serious limitations‡	n/a	Low

*Abbreviations: n/a, not applicable; NPPV, noninvasive positive pressure ventilation; RCT, randomized controlled trial; UMC, usual medical care.

†Post hoc analysis from an RCT, which breaks the study randomization

‡One study with a very small sample size (n = 23)

Appendix 5: Subgroup Analyses

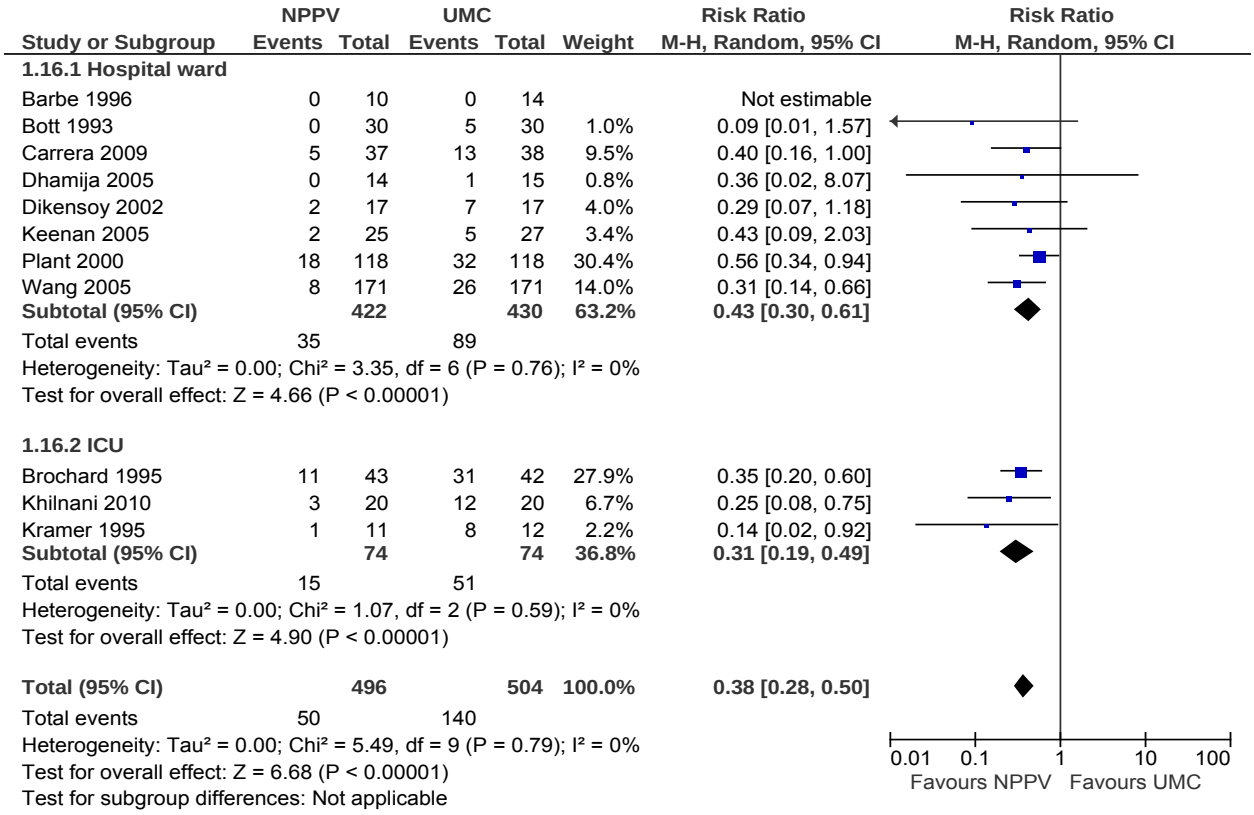


Figure A1: Pooled Results for the Need for Endotracheal Intubation by Hospital Ward or ICU (NPPV Plus UMC Versus UMC Alone)*

*Abbreviations: CI, confidence interval; ICU, intensive care unit; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

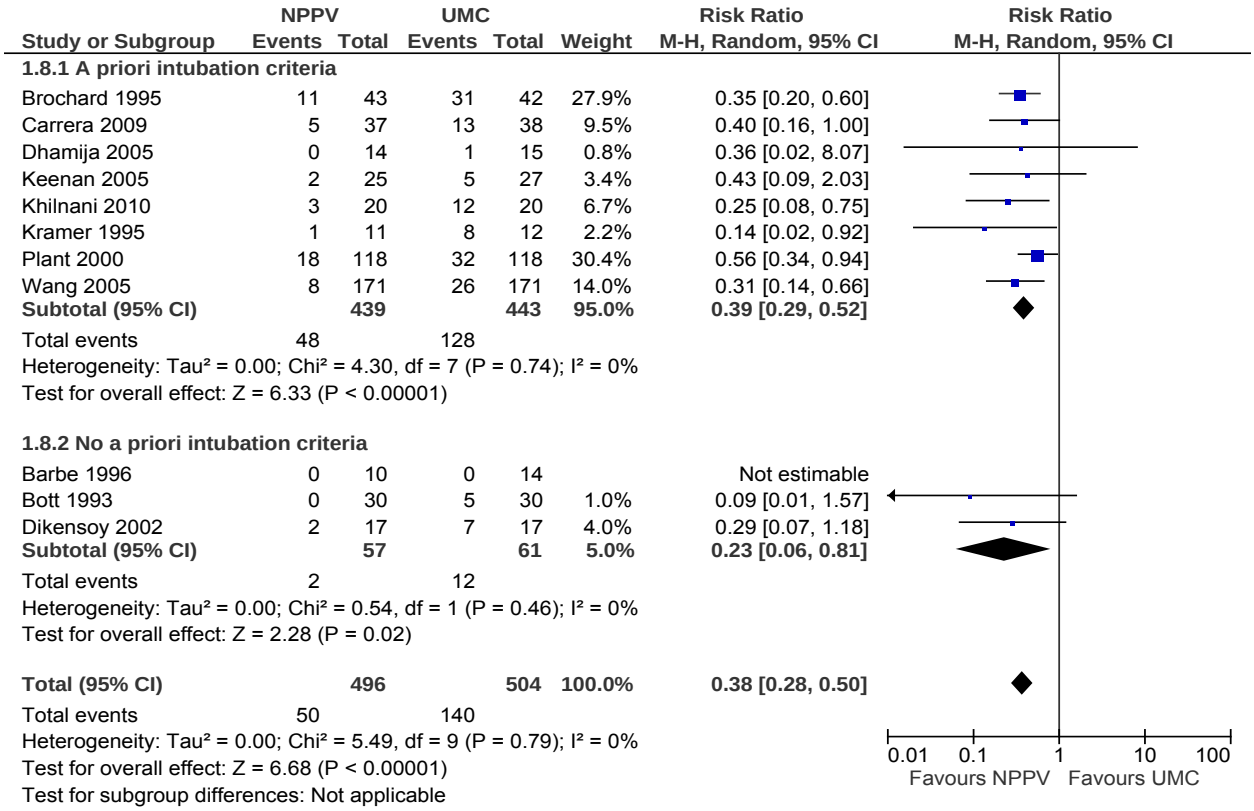


Figure A2: Pooled Results for the Need for Endotracheal Intubation by Presence of A Priori Intubation Criteria (NPPV Plus UMC Versus UMC Alone)*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

References

(1) Kaynar AM, Sharma S. Respiratory Failure [Internet]. [updated 2010 Sep 28; cited 2011 May 6]. Available from: http://emedicine.medscape.com/article/167981-overview

(2) Keenan SP, Mehta S. Noninvasive ventilation for patients presenting with acute respiratory failure: the randomized controlled trials. Respir Care. 2009;54(1):116-26.

(3) Ward NS, Dushay KM. Clinical concise review: Mechanical ventilation of patients with chronic obstructive pulmonary disease. Crit Care Med. 2008 May;36(5):1614-9.

(4) Ram FSF, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. Cochrane Database Sys Rev. 2004, Issue 3. Art. No.:D004104.DOI: 10.1002/14651858.CD004104.pub3.

(5) Dikensoy O, Ikidag B, Filiz A, Bayram N. Comparison of non-invasive ventilation and standard medical therapy in acute hypercapnic respiratory failure: a randomised controlled study at a tertiary health centre in SE Turkey. Int J Clin Pract. 2002 Mar;56(2):85-8.

(6) Collaborating Research Group for Noninvasive Mechanical Ventilation of Chinese Respiratory Society. Pulmonary infection control window in treatment of severe respiratory failure of chronic obstructive pulmonary diseases: a prospective, randomized controlled, multi-centred study. Chin Med J (Engl). 2005 Oct 5;118(19):1589-94.

(7) Jurjevic M, Matic I, Sakic-Zdravcevic K, Sakic S, Danic D, Bukovic D. Mechanical ventilation in chronic obstructive pulmonary disease patients, noninvasive vs. invasive method (randomized prospective study). Coll Antropol. 2009 Sep;33(3):791-7.

(8) Bolton R, Bleetman A. Non-invasive ventilation and continuous positive pressure ventilation in emergency departments: Where are we now? Emerg Med J. 2008;25(4):190-4.

(9) Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med. 1995 Jun;151(6):1799-806.

(10) Trevisan CE, Vieira SR, Research Group. Noninvasive mechanical ventilation may be useful in treating patients who fail weaning from invasive mechanical ventilation: a randomized clinical trial. Crit Care. 2008;12(2):R51.

(11) Jiang JS, Kao SJ, Wang SN. Effect of early application of biphasic positive airway pressure on the outcome of extubation in ventilator weaning. Respirology. 1999 Jun;4(2):161-5.

(12) Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

(13) Burns KE, Adhikari NK, Meade MO. A meta-analysis of noninvasive weaning to facilitate liberation from mechanical ventilation. Can J Anaesth. 2006 Mar;53(3):305-15.

(14) Burns KEA, Adhikari NKJ, Keenan SP, Meade MO. Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. Cochrane Database Syst Rev. 2010, Issue 8. Art. No.:CD004127.DOI:10.1002/14651858.CD004127.pub2.

(15) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490.

(16) Goodman, C. Literature searching and evidence interpretation for assessing health care practices. Stockholm, Sweden: Swedish Council on Technology Assessment in Health Care; 1996 81 p. SBU Report No. 119E.

(17) Keenan SP, Sinuff T, Burns KE, Muscedere J, Kutsogiannis J, Mehta S, et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ. 2011 Feb 14;183(3):E195-E214.

(18) Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. Chest. 2008 Mar;133(3):756-66.

(19) Hess DR. The evidence for noninvasive positive-pressure ventilation in the care of patients in acute respiratory failure: a systematic review of the literature. Respir Care. 2004 Jul;49(7):810-29.

(20) Keenan SP, Sinuff T, Cook DJ, Hill NS. Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. Ann Intern Med. 2003 Jun 3;138(11):861-70.

(21) Caples SM, Gay PC. Noninvasive positive pressure ventilation in the intensive care unit: a concise review. Crit Care Med. 2005 Nov;33(11):2651-8.

(22) Peter JV, Moran JL, Phillips-Hughes J, Warn D. Noninvasive ventilation in acute respiratory failure--a meta-analysis update. Crit Care Med. 2002 Mar;30(3):555-62.

(23) Jarvis H. Exploring the evidence base of the use of non-invasive ventilation. Br J Nurs. 2006 Jul 27;15(14):756-9.

(24) Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007 Sep 15;176(6):532-55.

(25) Barbe F, Togores B, Rubi M, Pons S, Maimo A, Agusti AG. Noninvasive ventilatory support does not facilitate recovery from acute respiratory failure in chronic obstructive pulmonary disease. Eur Respir J. 1996 Jun;9(6):1240-5.

(26) Bott J, Carroll MP, Conway JH, Keilty SE, Ward EM, Brown AM, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet. 1993 Jun 19;341(8860):1555-7.

(27) Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995 Sep 28;333(13):817-22.

(28) Carrera M, Martin J, Anton A, Chiner E, Alonso ML, Masa JF, et al. A controlled trial of noninvasive ventilation for chronic obstructive pulmonary disease exacerbations. J Crit Care. 2009 Sep;24(3):473.e7-14.

(29) Dhamija A, Tyagi P, Caroli R, Ur RM, Vijayan VK. Noninvasive ventilation in mild to moderate cases of respiratory failure due to acute exacerbation of chronic obstructive pulmonary disease. Saudi Med J. 2005 May;26(5):887-90.

(30) Keenan SP, Powers CE, McCormack DG. Noninvasive positive-pressure ventilation in patients with milder chronic obstructive pulmonary disease exacerbations: a randomized controlled trial. Respir Care. 2005 May;50(5):610-6.

(31) Khilnani GC, Saikia N, Banga A, Sharma SK. Non-invasive ventilation for acute exacerbation of COPD with very high PaCO(2): A randomized controlled trial. Lung India. 2010 Jul;27(3):125-30.

(32) Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet. 2000 Jun 3;355(9219):1931-5.

(33) Wang C. Early use of non-invasive positive pressure ventilation for acute exacerbations of chronic obstructive pulmonary disease: A multicentre randomized controlled trial. Chin Med J (Engl). 2005;118(24):2034-40.

(34) Plant PK, Owen JL, Elliott MW. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. Thorax. 2001 Sep;56(9):708-12.

(35) Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5(13):[10 p.].

(36) Conti G, Antonelli M, Navalesi P, Rocco M, Bufi M, Spadetta G, et al. Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. Intensive Care Med. 2002 Dec;28(12):1701-7.

(37) Nava S, Ambrosino N, Clini E, Prato M, Orlando G, Vitacca M, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. Ann Intern Med. 1998 May 1;128(9):721-8.

(38) Prasad SBN, Chaudhry D, Khanna R. Role of noninvasive ventilation in weaning from mechanical ventilation in patients of chronic obstructive pulmonary disease: An Indian experience. Indian J Crit Care Med. 2009;13(4):207-12.

(39) Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006 Jan 15;173(2):164-70.

(40) Ferrer M, Sellares J, Valencia M, Carrillo A, Gonzalez G, Badia JR, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. Lancet. 2009 Sep 26;374(9695):1082-8.

(41) Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apeztequia C, Lez M, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004 Jun 10;350(24):2452-60.

(42) Angus RM, Ahmed AA, Fenwick LJ, Peacock AJ. Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chronic obstructive pulmonary disease. Thorax. 1996 Oct;51(10):1048-50.

(43) Avdeev SN, Tret'iakov AV, Grigor'iants RA, Kutsenko MA, Chuchalin AG. [Study of the use of noninvasive ventilation of the lungs in acute respiratory insufficiency due exacerbation of chronic obstructive pulmonary disease]. Anesteziol Reanimatol. 1998 May;(3):45-51.

(44) Bardi G, Pierotello R, Desideri M, Valdisserri L, Bottai M, Palla A. Nasal ventilation in COPD exacerbations: early and late results of a prospective, controlled study. Eur Respir J. 2000 Jan;15(1):98-104.

(45) Celikel T, Sungur M, Ceyhan B, Karakurt S. Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. Chest. 1998 Dec;114(6):1636-42.

(46) Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA, Umberto MG. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med. 1999 Nov;160(5 Pt 1):1585-91.

(47) Daskalopoulou E, Teara V, Fekete K, et al. Treatment of acute respiratory failure in COPD patients with positive airway pressure via nasal mask. Chest. 1993;103:271S.

(48) del Castillo D, Barrot E, Laserna E, Otero R, Cayuela A, Castillo GJ. [Noninvasive positive pressure ventilation for acute respiratory failure in chronic obstructive pulmonary disease in a general respiratory ward]. Med Clin (Barc). 2003 May 10;120(17):647-51.

(49) Honrubia T, Garcia Lopez FJ, Franco N, Mas M, Guevara M, Daguerre M, et al. Noninvasive vs conventional mechanical ventilation in acute respiratory failure: a multicenter, randomized controlled trial. Chest. 2005 Dec;128(6):3916-24.

(50) Khilnani GC, Saikia N, Sharma S. Efficacy of non-invasive positive pressure ventilation (NPPV) for management of COPD with acute or acute on chronic respiratory failure: A randomized controlled trial [abstract]. Am J Respir Crit Care Med. 2002;165(8).

(51) Lapinsky SE, Aubin M. Randomized trial of noninvasive ventilation in acute respiratory failure - factors affecting mortality. Am J Respir Crit Care Med. 1999;160:1585-91.

(52) Liao X, Li Q, Lin K, Zhang Q, Wang C, Qian G. Non-invasive positive pressure ventilation for early treatment of respiratory failure due to exacerbation of chronic obstructive pulmonary disease: a random controlled trial. Di 3 Jun Yi Da Xue Xue Bao. 2004;26:739-41.

(53) Martin TJ, Hovis JD, Costantino JP, Bierman MI, Donahoe MP, Rogers RM, et al. A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. Am J Respir Crit Care Med. 2000 Mar;161(3 Pt 1):807-13.

(54) Marvisi M, Brianti M, Marani G, Turrini G, Zambrelli P, Ajolfi C, et al. Acute antiarrhythmic effects of bi-level positive airway pressure ventilation in patients with acute respiratory failure

caused by chronic obstructive pulmonary disease: a randomized clinical trial. Respiration. 2004 Mar;71(2):152-8.

(55) Matic I, Sakic-Zdravcevic K, Jurjevic M. Comparison of invasive and noninvasive mechanical ventilation for patients with chronic obstructive pulmonary disease: Randomized prospective study. Period Biol. 2007;109(2):137-45.

(56) Matuska P, Pilarova O, Merta Z, Skrickova J. [Non-invasive ventilation support in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD)]. Vnitr Lek. 2006 Mar;52(3):241-8.

(57) Pastaka C, Kostikas K, Karetsi E, Tsolaki V, Antoniadou I, Gourgoulianis KI. Non-invasive ventilation in chronic hypercapnic COPD patients with exacerbation and a pH of 7.35 or higher. Eur J Intern Med. 2007;18(7):524-30.

(58) Servillo G, Ughi L, Rossano F, Leone D. Non invasive mask pressure support ventilation in COPD patients. Intensive Care Med. 1994;40(S54).

(59) Thys F, Roeseler J, Reynaert M, Liistro G, Rodenstein DO. Noninvasive ventilation for acute respiratory failure: a prospective randomised placebo-controlled trial. Eur Respir J. 2002 Sep;20(3):545-55.

(60) Wood KA, Lewis L, Von HB, Kollef MH. The use of noninvasive positive pressure ventilation in the emergency department: results of a randomized clinical trial. Chest. 1998 May;113(5):1339-46.

(61) Zhou R, Chen P, Luo H, Xiang XD. [Effects of noninvasive positive pressure ventilation on gas exchange and patients' transformation in chronic obstructive pulmonary disease and respiratory failure]. Hunan Yi Ke Da Xue Xue Bao. 2001 Jun 28;26(3):261-2.

(62) Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ. 2003 Jan 25;326(7382):185.

(63) Chen J, Qiu D, Tao D. Time for extubation and sequential noninvasive mechanical ventilation in COPD patients with acute exacerbated respiratory failure who received invasive ventilation. Zhonghua Jie He He Hu Xi Za Ahi. 2001;1(24):99-100.

(64) Ferrer M, Esquinas A, Arancibia F, Bauer TT, Gonzalez G, Carrillo A, et al. Noninvasive ventilation during persistent weaning failure: a randomized controlled trial. Am J Respir Crit Care Med. 2003 Jul 1;168(1):70-6.

(65) Girault C, Daudenthun I, Chevron V, Tamion F, Leroy J, Bonmarchand G. Noninvasive ventilation as a systematic extubation and weaning technique in acute-on-chronic respiratory failure: a prospective, randomized controlled study. Am J Respir Crit Care Med. 1999 Jul;160(1):86-92.

(66) Hill NS, Lin D, Levy M, O'Brien A. Noninvasive positive pressure ventilation (NPPV) to facilitate extubation after acute respiratory failure: a feasibility study. Am J Respir Crit Care Med. 2000;161:B18.

(67) Rabie GM, Mohamed AZ, Mohamed R. Noninvasive ventilation in the weaning of patients with acute-on-chronic respiratory failure due to COPD. Chest. 2004;126:755S.

(68) Wang X, Due X, Zhang W. Observation of the effect and the time for extubation and sequential noninvasive mechanical ventilation in COPD patients with exacerbated respiratory failure who received invasive ventilation. Shandong Medical Journal. 2004;44(7):4-6.

(69) Zheng R, Liu L, Yang Yi, et al. Prospective randomized controlled clinical study of sequential non-invasive following invasive mechanical ventilation in patients with acute respiratory failure induced by COPD. Chinese J Emerg Med. 2005;14(1):21-5.

(70) Zou SH, Zhou R, Chen P, Luo H, Xiang XD, Lu YD, et al. [Application of sequential noninvasive following invasive mechanical ventilation in COPD patients with severe respiratory failure by investigating the appearance of pulmonary-infection-control-window]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2006 Feb;31(1):120-4.

(71) Esteban A, Ferguson ND, Frutos-Vivar F, et al. Non-invasive positive pressure ventilation does not prevent reintubation and may be harmful in patients with post-extubation respiratory distress: results of a randomized controlled trial. Am J Respir Crit Care Med. 2003;167(7 Suppl):A301.

(72) Keenan SP, Powers C, McCormack DG, Block G. Noninvasive positive-pressure ventilation for postextubation respiratory distress: a randomized controlled trial. JAMA. 2002 Jun 26;287(24):3238-44.

(73) Luo H, Cheng P, Zhou R. [Sequential BiPAP following invasive mechanical ventilation in COPD patients with hypercapnic respiratory failure]. Hunan Yi Ke Da Xue Xue Bao. 2001 Dec 28;26(6):563-5.

(74) Nava S, Gregoretti C, Fanfulla F, Squadrone E, Grassi M, Carlucci A, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005 Nov;33(11):2465-70.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-7014-5 (PDF)

Ontario
Health Quality Ontario
Qualité des services
de santé Ontario

Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis

COPD Working Group

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 9, pp. 1–51, March 2012

Suggested Citation

This report should be cited as follows:

COPD Working Group. Noninvasive positive pressure ventilation for chronic respiratory failure patients with stable chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2012 Mar; 12(9): 1–51. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Ventilation_Chronic_March.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to: MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

6MWT	6 Minute Walking Test
BiPAP	Bilevel positive airway pressure
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CT	Control group
FEV_1	Forced expiratory volume in 1 second
HRQOL	Health-related quality of life
IPAP	Inspiratory positive airway pressure
kPa	kilopascal (1 kPa = 7.5 mm Hg)
LTOT	Long-term oxygen therapy
MAS	Medical Advisory Secretariat
MRC	Medical Research Council
NIV	Noninvasive ventilation
NPPV	Noninvasive positive pressure ventilation
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
TR	Treatment group, referring to NPPV
VEP	Ventilator Equipment Pool

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective

The objective of this health technology assessment was to determine the effectiveness and cost-effectiveness of noninvasive ventilation for stable chronic obstructive pulmonary disease (COPD).

Clinical Need: Condition and Target Population

Noninvasive ventilation is used for COPD patients with chronic respiratory failure. Chronic respiratory failure in COPD patients may be due to the inability of the pulmonary system to coordinate ventilation, leading to adverse arterial levels of oxygen and carbon dioxide. Noninvasive ventilation in stable COPD patients has the potential to improve quality of life, prolong survival, and improve gas exchange and sleep quality in patients who are symptomatic after optimal therapy, have hypercapnia or nocturnal hypoventilation and mild hypercapnia, and are frequently hospitalized.

Technology

Noninvasive positive pressure ventilation (NPPV) is any form of positive ventilatory support without the use of an endotracheal tube. For stable COPD, the standard of care when using noninvasive ventilation is bilevel positive airway pressure (BiPAP). Bilevel positive airway pressure involves both inspiratory and expiratory pressure, high during inspiration and lower during expiration. It acts as a pressure support to accentuate a patient's inspiratory efforts. The gradient between pressures maintains alveolar ventilation and helps to reduce carbon dioxide levels. Outpatients typically use BiPAP at night. Additional advantages of using BiPAP include resting of respiratory muscles, decreased work of breathing, and control of obstructive hypopnea.

Research Question

What is the effectiveness and cost-effectiveness of noninvasive ventilation, compared with no ventilation while receiving usual care, for stable COPD patients?

Research Methods

Literature Search

Search Strategy

A literature search was performed on December 3, 2010, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database for studies published from January 1, 2004 to December 3, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. When the reviewer was unsure of the eligibility of articles, a second clinical epidemiologist and then a group of epidemiologists reviewed these until consensus was reached.

Inclusion Criteria

- full-text English language articles,
- studies published between January 1, 2004 and December 3, 2010,
- journal articles that report on the effectiveness or cost-effectiveness of noninvasive ventilation,
- clearly described study design and methods, and
- health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs).

Exclusion Criteria

- non-English papers
- animal or in vitro studies
- case reports, case series, or case-case studies
- cross-over RCTs
- studies on noninvasive negative pressure ventilation (e.g., iron lung)
- studies that combine ventilation therapy with other regimens (e.g., daytime NPPV plus exercise or pulmonary rehabilitation)
- studies on heliox with NPPV
- studies on pulmonary rehabilitation with NPPV

Outcomes of Interest

- mortality/survival
- hospitalizations/readmissions
- length of stay in hospital
- forced expiratory volume
- arterial partial pressure of oxygen
- arterial partial pressure of carbon dioxide
- dyspnea
- exercise tolerance
- health-related quality of life

Note: arterial pressure of oxygen and carbon dioxide are surrogate outcomes.

Statistical Methods

A meta-analysis and an analysis of individual studies were performed using Review Manager Version 5. For continuous data, a mean difference was calculated, and for dichotomous data, a relative risk ratio was calculated for RCTs. For continuous variables with mean baseline and mean follow-up data, a change value was calculated as the difference between the 2 mean values.

Quality of Evidence

The quality of each included study was assessed taking into consideration allocation concealment, randomization, blinding, power/sample size, withdrawals/dropouts, and intention-to-treat analyses.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. The following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

Summary of Findings

Conclusions

The following conclusions refer to stable, severe COPD patients receiving usual care.

Short-Term Studies

- Based on low quality of evidence, there is a beneficial effect of NPPV compared with no ventilation on oxygen gas exchange, carbon dioxide gas exchange, and exercise tolerance measured using the 6 Minute Walking Test.
- Based on very low quality of evidence, there is no effect of NPPV therapy on lung function measured as forced expiratory volume in 1 second (Type II error not excluded).

Long-Term Studies

- Based on moderate quality of evidence, there is no effect of NPPV therapy for the outcomes of mortality, lung function measured as forced expiratory volume in 1 second, and exercise tolerance measured using the 6 Minute Walking Test.
- Based on low quality of evidence, there is no effect of NPPV therapy for the outcomes of oxygen gas exchange and carbon dioxide gas exchange (Type II error not excluded).

Qualitative Assessment

- Based on low quality of evidence, there is a beneficial effect of NPPV compared with no ventilation for dyspnea based on reduced Borg score or Medical Research Council dyspnea score.
- Based on moderate quality of evidence, there is no effect of NPPV therapy for hospitalizations.
- Health-related quality of life could not be evaluated.

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this health technology assessment was to determine the effectiveness and cost-effectiveness of noninvasive ventilation (NIV) for stable chronic obstructive pulmonary disease (COPD).

Clinical Need and Target Population

Ventilation Therapy in Chronic Obstructive Pulmonary Disease

Noninvasive ventilation in stable COPD patients has the potential to improve quality of life, prolong survival, and improve gas exchange and sleep quality in patients who are symptomatic after optimal therapy, have arterial carbon dioxide levels greater than 55 mm Hg, or nocturnal hypoventilation and arterial carbon dioxide levels between 50 and 54 mm Hg, and are frequently hospitalized. One of the goals of long-term ventilation at home is to persistently reduce hypercapnia. The mechanism of action of NIV is not clear but may include respiratory muscle rest, restoration of chemosensitivity, improved compliance of the chest wall and lungs, improved sleep quality, and reduced respiratory system load. (1)

Noninvasive Positive Pressure Ventilation

Mechanical ventilation is used for COPD patients with chronic respiratory failure. Respiratory failure is found only in very severe stage 4 COPD, where the arterial pressure of oxygen is less than 60 mm Hg, with or without forced expiratory volume in 1 second (FEV_1) less than 30% predicted (i.e., $FEV_1 < 50\%$ with $PaO_2 < 60$ mm Hg is also a criterion for stage 4 COPD). Therefore, respiratory failure in the absence of severe decreased lung function is a criterion for very severe COPD. Respiratory failure may lead to secondary effects on the heart, known as cor pulmonale or right heart failure. Patients at this stage are typically considered to have end-organ dysfunction related to COPD. (2) In type 1 respiratory failure, the arterial level of carbon dioxide is normal or low but the patient is in a state of hypoxemia. In type 2 respiratory failure, high levels of carbon dioxide (> 45 mm Hg) and low levels of oxygen (< 60 mm Hg) occur. In terms of pathophysiology of the respiratory system, type 1 respiratory failure may be due to failure of the lungs to provide adequate gas exchange, and type 2 respiratory failure may be due to the inability of the pulmonary system to coordinate ventilation. The clinical sign of chronic respiratory failure is shallow breathing. Respiratory failure can occur as acute, chronic, or acute-on-chronic failure. Acute-on-chronic respiratory failure occurs when there is acute deterioration of the pre-existing state of chronic respiratory failure. (3)

Ontario Context

In Ontario, ventilatory devices and positive airway pressure systems are covered under Respiratory Products of the Assistive Devices Program. There are no specific guidelines for their use; however, applicants must be assessed by a medical professional. (4) The Ventilator Equipment Pool (VEP) loans invasive (mechanical ventilators) and noninvasive positive airway (bilevel devices) systems to eligible individuals. The VEP, a Transfer Payment Agency of the Assistive Devices Program that operates out of the Kingston General Hospital, is a recycling pool that loans these devices until they are no longer required, at which time they are returned to VEP for recycling and reuse. Funding assistance is also provided for supplies when devices are used through VEP. (Personal communication, November 7, 2011) According to the VEP database, 263 patients were registered with a primary or secondary diagnosis of chronic bronchitis, emphysema, bronchiectasis, and chronic airway obstruction between 2005 and 2010. This may be an underestimate because diagnoses such as respiratory failure/respiratory insufficiency or hypoventilation are not captured in the VEP. (Personal communication, expert, February 2, 2011)

Technology

Noninvasive positive pressure ventilation (NPPV) is any form of positive ventilatory support without the use of an endotracheal tube. For stable COPD, the standard of care when using NIV is bilevel positive airway pressure (BiPAP). Bilevel positive airway pressure involves both inspiratory and expiratory positive airway pressures, high pressure during inspiration and lower pressure during expiration. This acts as a pressure support to accentuate a patient's inspiratory efforts. The gradient between these pressures maintains alveolar ventilation and helps to reduce arterial carbon dioxide levels. Additional advantages may include resting of respiratory muscles, decreased respiratory system load (work of breathing), control of obstructive hypopnea, and improved quality of sleep. It is typically used at night in outpatients. Other indications for use include obstructive sleep apnea with continuous positive airway pressure (CPAP) intolerance, obstructive sleep apnea with central sleep apnea, restrictive thoracic disorders, and obesity-hypoventilation syndrome with coexisting obstructive sleep apnea and residual hypoventilation despite CPAP.

Continuous positive airway pressure technology is not indicated for COPD; it simply acts to splint the airway open. Bilevel positive airway pressure applies a constant level of positive pressure during spontaneous breathing. When the BiPAP technology is set at 2 cm H_2O for inspiratory and expiratory settings, the BiPAP system capabilities for COPD patients is equivalent to CPAP technology; in other words, there is no ventilation support for COPD patients at these settings due to the lack of a pressure gradient. (5) (Personal communication, clinical expert, March 3, 2011)

Evidence-Based Analysis

Research Question

What is the effectiveness and cost-effectiveness of NIV, compared with no ventilation while receiving usual care, for stable COPD patients?

Research Methods

Literature Search

Search Strategy

A literature search was performed on December 3, 2010, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2004 to December 3, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. When the reviewer was unsure of the eligibility of articles, a second clinical epidemiologist and then a group of epidemiologists reviewed these until consensus was reached.

Inclusion Criteria

- full-text English language articles
- studies published between January 1, 2004 and December 3, 2010
- journal articles that report on the effectiveness or cost-effectiveness
- study design and methods must be clearly described
- health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs)

Exclusion Criteria

- non-English papers
- animal or in vitro studies
- case reports, case series, or case-case studies
- cross-over RCTs
- studies using noninvasive negative pressure ventilation (e.g., iron lung)
- studies that combine ventilation therapy with other regimens (e.g., daytime NPPV plus exercise or pulmonary rehabilitation)
- studies on heliox with NPPV
- studies on pulmonary rehabilitation with NPPV

Outcomes of Interest

- mortality/survival
- hospitalizations
- length of stay in hospital

- forced expiratory volume (FEV_1)
- arterial partial pressure of oxygen (PaO_2)
- arterial partial pressure of carbon dioxide ($PaCO_2$)
- dyspnea
- exercise tolerance
- health-related quality of life (HRQOL)

Note: arterial pressure of oxygen and carbon dioxide are surrogate outcomes.

Statistical Analysis

A meta-analysis and an analysis of individual studies were performed using Review Manager Version 5. (6) For continuous data a mean difference was calculated, and for dichotomous data a relative risk ratio was calculated for RCTs. For continuous variables with mean baseline and mean follow-up data, a change value was calculated as the difference between the 2 mean values (e.g., follow-up minus baseline). A standard deviation that accounts for the baseline standard deviation and follow-up standard deviation was calculated from 3 parameters: baseline standard deviation, follow-up standard deviation, and a correlation coefficient. The correlation coefficient represents the strength of the relationship between the 2 standard deviations. A correlation coefficient of 0.5 was used for this analysis. Graphical display of the forest plots was also examined. A *P* value of less than 0.05 was considered statistically significant. *P* values in the text have been rounded to 3 decimal places.

Quality of Evidence

The quality of each included study was assessed taking into consideration the following 7 study design characteristics:

- adequate allocation concealment,
- randomization (study must include a description of the randomization procedure used and must be a proper method),
- power/sample size (adequate sample size based on a priori calculations, underpowered studies were identified, when possible, using post hoc sample size power calculations),
- blinding (if double blinding is not possible, a single blind study with unbiased assessment of outcome was considered adequate for this criterion),
- < 20% withdrawals/dropouts,
- intention-to-treat (ITT) analysis conducted and done properly (withdrawals/dropouts considered in analysis), and
- other criteria as appropriate for the particular research question and study design.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (7) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding, and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.

- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, (8) the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

The database search yielded 2,593 studies published between January 1, 2004 and December 3, 2010, of which 3 studies and 1 systematic review met the inclusion criteria (Table 1). An additional 5 citations were identified using the systematic review. (9) An additional citation was identified from review of reference lists. Overall, there were 10 eligible studies.

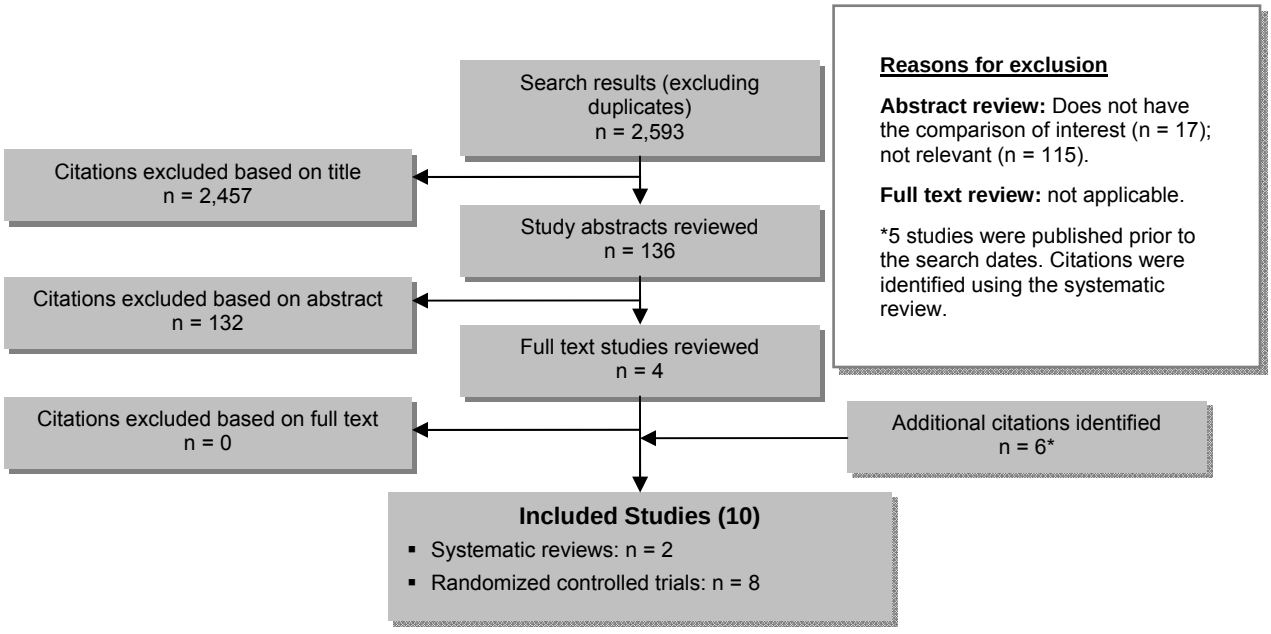


Figure 1: Citation Flow Chart

For each included study, the study design was identified and is summarized below in Table 1, which is a modified version of the hierarchy of study design by Goodman. (10)

Table 1: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies†
RCT Studies	
Systematic review of RCTs	2
Large RCT†	-
Small RCT	8
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	-
Non-RCT with contemporaneous controls	-
Systematic review of non-RCTs with historical controls	-
Non-RCT with historical controls	-
Database, registry, or cross-sectional study	-
Case series	-
Retrospective review, modelling	-
Studies presented at an international conference or other sources of grey literature	-
Expert opinion	-
Total	**10**

*Abbreviation: RCT, randomized controlled trial.
†Some citations identified were prior to the literature search dates.
‡Large RCT ≥ 150 subjects.

Systematic Reviews

A Cochrane systematic review and meta-analysis was performed to determine the effect of nocturnal NPPV using a nasal mask for at least 5 hours nightly for at least 3 consecutive weeks in patients with COPD. The relevant measured outcomes were blood gases, exercise tolerance, dyspnea, and HRQOL. The Cochrane analysis included 4 studies (years 1991–2000), 2 of which were cross-over designs and 2 of which were parallel RCT designs. The authors of the included studies reported that there were a high number of dropouts as a result of patients not tolerating the nose mask, getting infections, or no longer meeting the inclusion criteria of the individual studies. No effect of ventilation was shown for FEV_1, forced vital capacity, PaO_2, $PaCO_2$, and the 6 Minute Walking Test (6MWT test) in standard Cochrane analyses examining the mean difference of change values. There was no effect for these outcome measures when examined among the subset of parallel studies (significant results were shown for outcome measures that were not relevant for this analysis, e.g., maximum inspiratory pressure). The risk of bias scored low for all included studies. The results of the studies may have been affected by low inspiratory pressures, the extent of nocturnal hypoventilation (with studies of COPD patients with more severe hypercapnia showing the greatest improvement in daytime hypercapnia), and differences in training techniques. All studies used nocturnal BiPAP. The small sample size (< 10 subjects) may have also been a limiting factor. (11)

A systematic review and meta-analysis was performed to determine the effectiveness of bilevel NPPV in chronic respiratory failure in severe, stable COPD patients. The relevant outcome measures examined were gas exchange, lung function, dyspnea, exercise tolerance, morbidity, and HRQOL. (The outcome measures not relevant here are not discussed.) Eligible studies were categorized as RCTs and non-RCTs,

with no restrictions on how bilevel NPPV was used or length of follow-up. The search strategy included the years 2001 to 2003. The majority of studies rated high on methodological quality. For RCTs, ventilation did not affect PaO_2, $PaCO_2$, FEV_1 (data not shown), 6MWT (data not shown), mortality (data not shown), and morbidity (e.g., hospital and intensive care unit admissions), with data not meta-analyzed for morbidity due to different units of measurement (data not shown). A beneficial effect of ventilation was shown for dyspnea, although the data for dyspnea were not meta-analyzed due to different measurement scales, and HRQOL measured using St. George's Respiratory Questionnaire (SGRQ) in a single study, which was also not meta-analyzed. Only follow-up data were analyzed. A majority of studies included in the systematic review were also eligible for this report. (9)

The parallel design RCTs included in the Cochrane Review (11) were also included in the more recent systematic review (9) discussed above.

Randomized Controlled Trials

There were 5 parallel RCTs (12-16) identified from the most recent systematic review (9) and 3 parallel RCTs (17-19) identified from the literature search. Appendix 3 (Tables A3 to A8) summarizes the studies and their characteristics. The terms NPPV and NIV are used interchangeably. No studies refer to the iron lung.

A multicentre parallel RCT conducted in Australia across 4 university hospitals compared nocturnal NIV plus long-term oxygen therapy (LTOT) to LTOT alone. Patients were included if they were aged less than 80 years; had severe COPD ($FEV_1 < 50\%$) and stable hypercapnia ($PaCO_2 > 46$ mm Hg); had used LTOT for at least 3 months; and were not currently smoking. Patients were excluded if they had severe comorbidities (e.g., malignancy, left ventricular heart failure, unstable angina) that could affect the completion of the study; severe psychiatric disorder that affected use of the technology; body mass index (BMI) greater than 40 kg/m^2; and sleep apnea (> 20 episodes of apnea + hypopnea per hour of sleep). Patients with sleep apnea or obesity may have previously required the intervention and thus could no longer be randomized to a non-treatment group. Additionally, excluding individuals with sleep apnea or obesity helped to produce a more homogeneous COPD study population. The generalizability of the study results is high with respect to other populations with similarly severe COPD. The outcome measures of interest examined included mortality, hospitalizations, gas exchange, lung function, and HRQOL. Arterial blood gases were taken on room air. Follow-up was up to 5 years. A central study coordinator generated a random sequence of treatment assignments, stratified by centre and distributed in blocks of 10 sealed opaque envelopes to centres. Patients assigned to NIV were educated and familiarized with the equipment. Data were presented in a useable form for mortality only. Data on hospitalizations were given as the number of days in hospital per days on trial; data on $PaCO_2$ and FEV_1 were given, but without standard deviations; data on PaO_2 were missing; and data on HRQOL based on SGRQ were not provided but only described in the text. (Additional information on Short Form-36 health survey was provided but not included in this analysis since it is not one of the outcome measures.) (19)

A parallel RCT that included patients from university specialists' clinics in Canada compared nocturnal NIV to sham therapy. Willing patients aged 40 years or more who had a history of smoking were included in the trial if they had a clinical diagnosis of COPD ($FEV_1 < 70\%$). Patients were excluded if they had other medical conditions that could affect survival, cognitive impairment that could affect consent, left ventricular heart failure, and apnea-hypopnea (index ≥ 20 on a home-based sleep apnea test). The outcome measures of interest examined included gas exchange, lung function, and exercise-tolerance. Arterial blood gases were taken on room air. Randomization occurred at a central site. Personnel blinded to each patient's type of treatment assessed and interpreted the outcome measures. All patients received standard medical therapy and NIV training. Sham therapy was CPAP set at 4 cm H_2O. Data were presented in a useable form for the 6MWT only. There was some description of the results for $PaCO_2$ and

FEV_1, but the data were not useable. (18)

A parallel laboratory-based RCT that included patients from an outpatient clinic in Chile compared active diurnal NIV to sham therapy. Patients were included in the trial if they had stable COPD with hypercapnia ($PaCO_2 \geq 50$ mm Hg) and hypoxemia (< 60 mm Hg). They were excluded if they experienced either airway improvement or clinical exacerbation upon bronchodilation and had obstructive sleep apnea and comorbidities including left ventricular failure, peripheral vascular occlusive disease, and orthopedic disorder. Patients were nonsmokers and were using LTOT. Outcome measures of interest examined included gas exchange, lung function, dyspnea, and exercise tolerance. Arterial blood gases were taken while resting. Patients were randomly allocated to the study or the control using a table of random numbers and sealed envelopes. The treating physicians and personnel supervising the dyspnea and exercise tolerance tests were blinded to the type of treatment. Sham therapy was CPAP set at 2 cm H_2O. Ventilation was provided under direct supervision. Data were provided in a suitable format for PaO_2, $PaCO_2$, FEV_1, 6MWT, and Borg score. (17)

A multicentre parallel RCT conducted in Italy and France compared NIV plus LTOT to LTOT alone. Patients aged less than 76 years diagnosed with severe, stable COPD ($FEV_1 < 1.5$ L) were included in the trial if they experienced chronic ventilatory failure ($PaCO_2 >$ 50 mm Hg); had used LTOT for at least 6 months; had an Medical Research Council (MRC) dyspnea score of 2 or higher; and had hypoxemia ($PaO_2 <$ 60 mm Hg). Excluded were smokers who experienced airway improvement upon bronchodilation; had sleep apnea (apnea-hypopnea index > 10 episodes per hour during polysomnography); were being treated with systemic steroids; had concomitant chronic systemic diseases (e.g., chronic heart failure, diabetes) and infections, neoplasms, other chronic respiratory disease (including fibrothorax, bronchiectasis, and cystic fibrosis); and were previously using NIV or LTOT. All outcome measures of interest were examined. All patients received standard medical treatment. Arterial blood gases were taken while resting and on oxygen. A centralized randomization procedure was used. Outcome measurements were performed by personnel blinded to treatment and not involved in the study. Data were provided in a suitable format for mortality, FEV_1, and 6MWT. Results shown in graph form only for PaO_2, $PaCO_2$, dyspnea, and SGRQ were difficult to extrapolate (i.e., small scale). Data provided for hospitalizations used number of patients per year as the unit of analysis, which was not suitable for the meta-analysis. (16)

Another parallel laboratory-based RCT that was conducted in Chile included patients from an outpatient clinic and compared active diurnal NIV to sham therapy. Stable COPD patients who were nonsmoking and using LTOT were included in the trial if they had hypercapnia ($PaCO_2 \geq 50$ mm Hg) and hypoxemia (< 60 mm Hg). Patients were excluded if their airways improved upon bronchodilation; they experienced a clinical exacerbation; they were obese ($BMI \geq 30$ kg/m^2); they had a history of asthma and of obstructive sleep apnea; and they had comorbidities including left ventricular failure and bronchiectasis. Outcome measures of interest examined included gas exchange and lung function. Arterial blood gases were taken while resting. Patients were randomly allocated using a table of random numbers. Outcome measures were determined by trained nurses unaware of the purpose of the study. Sham therapy was CPAP set at 2 cm H_2O. Ventilation was supervised. Data were provided in a suitable format for PaO_2, $PaCO_2$, and FEV_1. (14)

A parallel RCT conducted in the Canary Islands compared nocturnal NIV to usual care. Stable patients with severe COPD ($FEV_1 < 45\%$) from 2 pulmonary clinics were included in the trial if they were aged 45 to 75 years and had a smoking history (> 20 pack-years). They were excluded if bronchodilation improved their airways; they refused to stop smoking; and they had sleep apnea (> 10 apnea-hypopnea episodes per hour), other etiologies of chronic airway obstruction (e.g., bronchiectasis, cystic fibrosis), and comorbidities (e.g., left ventricular failure). Outcome measures of interest included mortality, hospitalizations, gas exchange, lung function, and dyspnea. Patients were receiving supplemental oxygen.

Arterial blood gases were taken at rest. Patients were randomized by an independent office using a table of random numbers. Data were provided in a suitable format for mortality, PaO_2, $PaCO_2$, and FEV_1. Data without standard deviations were extrapolated from the graph for hospitalizations, and point estimates without standard deviations were provided for dyspnea measures. As a result, these data could not be meta-analyzed. (13)

A parallel RCT used a United States pulmonary function laboratory database of patients seen during routine clinical assessments. This trial compared nocturnal NIV to sham therapy. Included in the trial were clinically nonobese (BMI ≤ 30 kg/m^2) stable patients aged less than 80 years with severe COPD (FEV_1 < 40%) and hypercapnia ($PaCO_2$ > 45 mm Hg). Excluded were patients who were being treated with sedatives or hypnotic medications; had had lung transplantation; were currently using nocturnal ventilation or CPAP; and had major illnesses that would preclude completion of the clinical trial. Outcome measures of interest included lung function and exercise tolerance. Supplemental oxygen was used according to prior physician prescription. Patients were randomized. Sham therapy was provided using the same equipment as used for the intervention group (e.g., BiPAP), without the use of an inspiratory setting and at the lowest expiratory setting. Data were in a suitable format for 6MWT, though FEV_1 data were in litres and therefore not analyzed. (15)

A parallel RCT conducted using the medical records of a pulmonary function laboratory compared NIV to sham therapy. Patients were included in the trial if they had stable, severe COPD (FEV_1 < 50%). They were excluded if they had congestive heart failure, asthma, lung cancer, thoracic cage abnormalities, prior thoracic surgery, restrictive pulmonary disease, obstructive sleep apnea, and degenerative joint disease. Also excluded were those who had had an exacerbation within the preceding 6 weeks. Outcome measures of interest included gas exchange, dyspnea, and exercise tolerance. Arterial blood gases were taken at rest while patients were breathing air or home oxygen. Patients were randomized. Sham therapy was provided using the same equipment as used by the intervention group (e.g., BiPAP) with inspiratory and expiratory pressures set at the minimum of 2 cm H_2O. None of the data were available in a suitable format for meta-analysis. (12)

Meta-Analysis

An analysis was performed to address the following research question: What is the effectiveness of noninvasive ventilation compared with no ventilation, while receiving usual care, for stable COPD patients? The potential outcomes examined were mortality, hospitalizations, FEV_1, PaO_2, $PaCO_2$, dyspnea, exercise tolerance, and HRQOL. The gas exchange measures were considered surrogate outcomes. From among the 8 eligible studies, suitable data were found for mortality, FEV_1, PaO_2, $PaCO_2$, and 6MWT. The outcome measures of hospitalizations, dyspnea, and HRQOL were analyzed qualitatively. The authors were contacted for their data but these were not received or, in one instance, the data were received in a format that was still unsuitable for analysis. For FEV_1, PaO_2, $PaCO_2$, and 6MWT, the results shown (Figures 2 to 6) are for change values that make use of the maximum amount of data (e.g., compared with analysis on follow-up data only). Change was calculated as the difference between the mean baseline value and the mean follow-up value. Due to the different lengths of follow-up and the possibility of clinical heterogeneity, where possible, data were examined in subgroups based on the length of follow-up as less than or equal to 3 months (i.e., short-term), 4 to 11 months, or greater than or equal to 12 months (i.e., long-term). (Personal communication, clinical expert, March 8, 2011) The estimates for FEV_1, PaO_2, $PaCO_2$, and 6MWT were interpreted as the change over time (≤ 3 months vs. > 3 months) for a given factor. The interpretation of the results differs based on the direction of change and the outcome measure. A positive change over time is favourable for FEV_1, PaO_2, and 6MWT, suggesting an increase in respiratory capacity; a negative change over time is favourable for $PaCO_2$, suggesting a decrease in an adverse respiratory factor. For mortality, the presentation of the analysis defines a beneficial effect of NPPV compared with no ventilation (i.e., the control) as an increased risk for the group of no ventilation

(i.e., relative risk > 1).

For consistency, a beneficial effect of NPPV is shown on the right-hand side of the zero line of the forest plots, and a negative effect on the left-hand side.

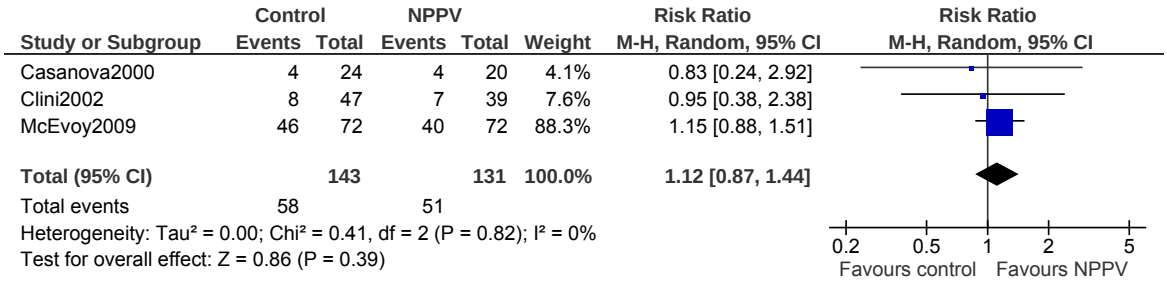


Figure 2: Mortality (Number of Events) – All Studies With Follow-up Greater Than 3 Months*,†,‡

*Abbreviations: CI, confidence interval; hrs, hours; IPAP, inspiratory positive airway pressure; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation.
†Mean IPAP values include Casanova et al (13): 12 cm H_20; Clini et al (16): 14 cm H_20; McEvoy et al (19): 13 cm H_20.
‡Mean hours of NPPV use include Casanova et al (13): 6.1 hrs/night; Clini et al (16): 9 hrs/night; McEvoy et al (19): 4.5 hrs/night.

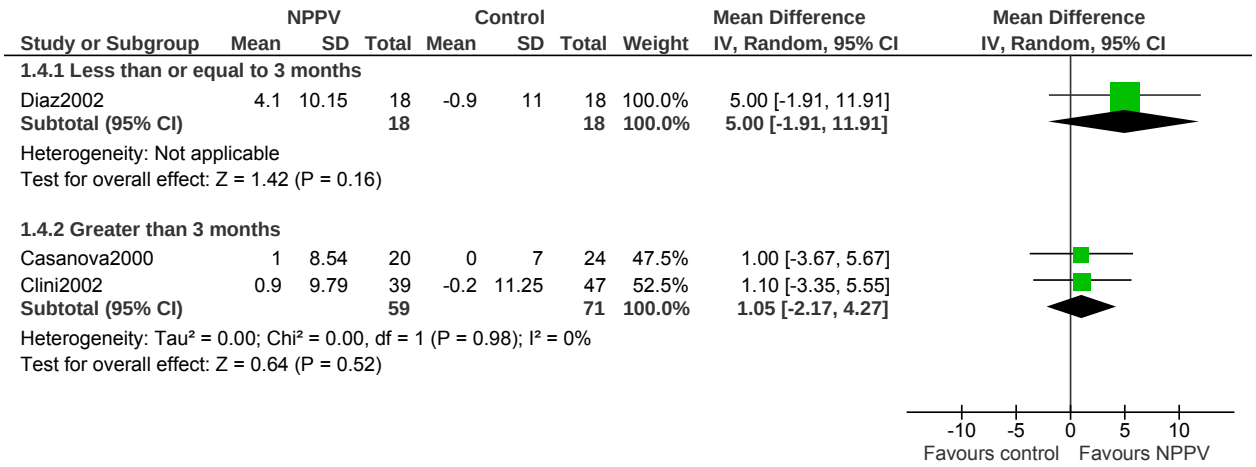


Figure 3: Forced Expiratory Volume in 1 Second (% Predicted)*,†,‡

*Abbreviations: CI, confidence interval; hrs, hours; IPAP, inspiratory positive airway pressure; IV, inverse variance; NPPV, noninvasive positive pressure ventilation; SD, standard deviation.
†Mean IPAP values include Diaz et al (14): 18 cm H20; Casanova et al (13): 12 cm H20; Clini et al (16): 14 cm H20.
‡Mean hours of NPPV use include Diaz et al (14): 3 hrs/day, 5 days-wk; Casanova et al (13): 6.1 hrs/night; Clini et al (16): 9 hrs/night.

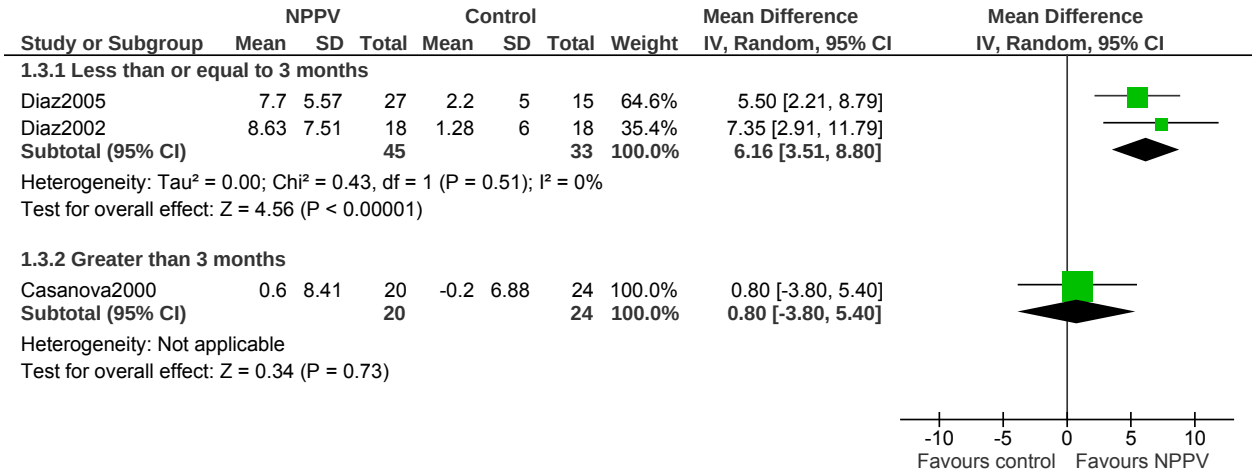


Figure 4: Arterial Pressure of Oxygen (mm Hg)*,†,‡

*Abbreviations: CI, confidence interval; hrs, hours; IPAP, inspiratory positive airway pressure; IV, inverse variance; NPPV, noninvasive positive pressure ventilation; SD, standard deviation.

†Mean IPAP values include Diaz et al (17): 18 cm H_20; Diaz et al (14): 18 cm H_20; Casanova et al (13): 12 cm H_20.

‡Mean hours of NPPV use include Diaz et al (17): 3 hrs/day, 5 days-wk; Diaz et al (14): 3 hrs/day, 5 days-wk; Casanova et al (13): 6.1 hrs/night.

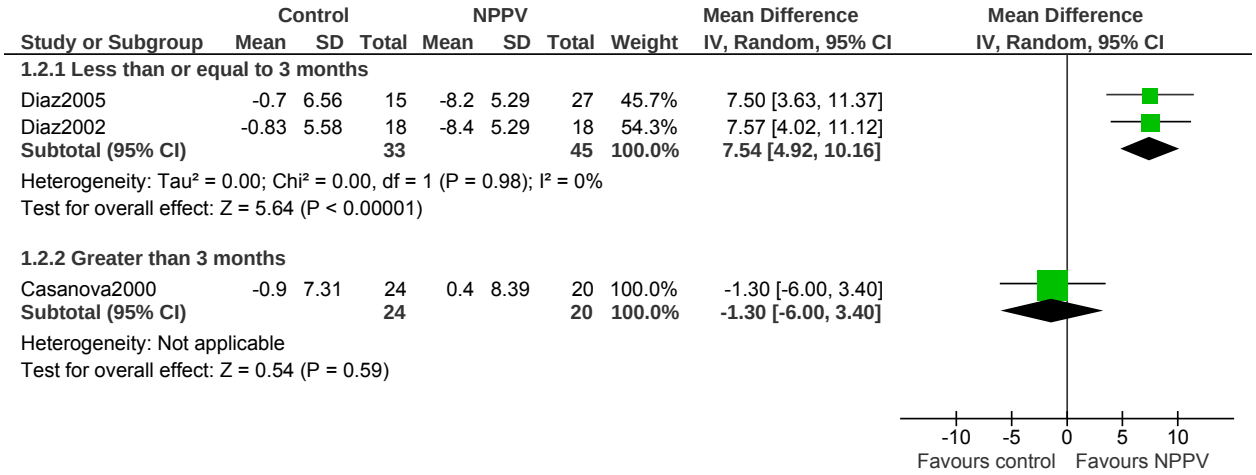


Figure 5: Arterial Pressure of Carbon Dioxide (mm Hg)*,†,‡

*Abbreviations: CI, confidence interval; hrs, hours; IPAP, inspiratory positive airway pressure; IV, inverse variance; NPPV, noninvasive positive pressure ventilation; SD, standard deviation.

†Mean IPAP values include Diaz et al (17): 18 cm H_20; Diaz et al (14): 18 cm H_20; Casanova et al (13): 12 cm H_20.

‡Mean hours of NPPV use include Diaz et al (17): 3 hrs/day, 5 days-wk; Diaz et al (14): 3 hrs/day, 5 days-wk; Casanova et al (13): 6.1 hrs/night.

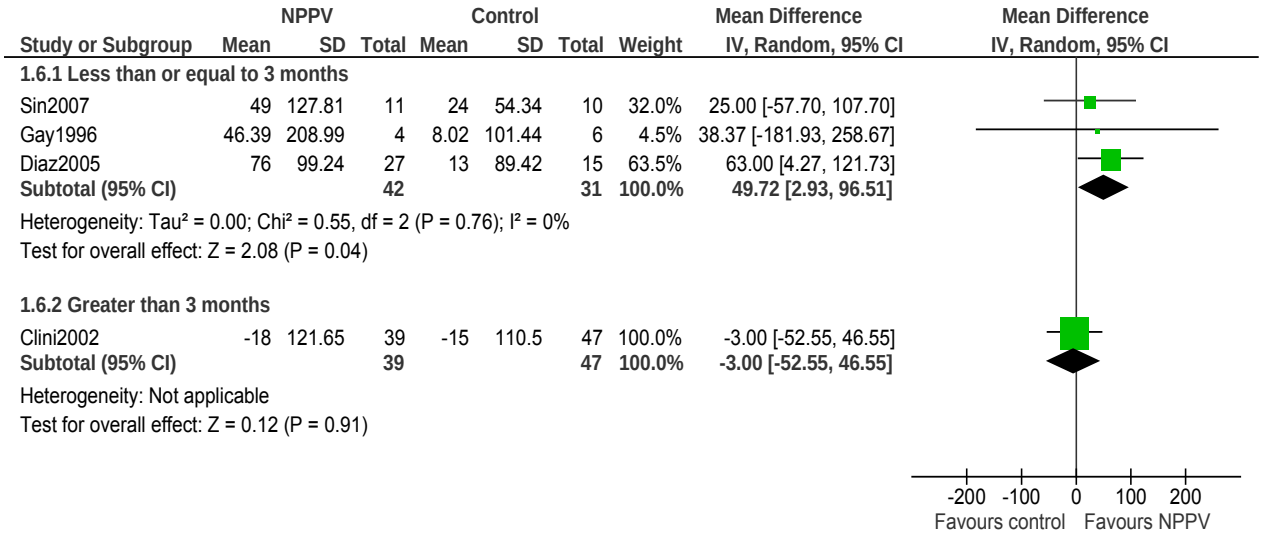


Figure 6: Six Minute Walking Test (Metres)*,†,‡

*Abbreviations: CI, confidence intervals; hrs, hours; IPAP, inspiratory positive airway pressure; IV, inverse variance; NPPV, noninvasive positive pressure ventilation; SD, standard deviation.

†Mean IPAP values include Sin et al (18): 15.5; Gay et al (15): 10; Diaz et al (17): 18; Clini et al (16): 14 cm H_20.

‡Mean hours of NPPV use include Sin et al (18): unknown; Gay et al (15): 4.5 hrs/night; Diaz et al (17): 3 hrs/day, 5 days-wk; Clini et al (16): 9 hrs/night.

Results of Meta-Analysis

The results of the analyses are shown in Figures 2 to 6. Noninvasive positive pressure ventilation had a short-term beneficial effect on PaO_2 (mean difference [MD], 6.16; 95% CI, 3.51–8.80 mm Hg; $P < 0.001$); $PaCO_2$ (MD, 7.54; 95% CI, 4.92–10.16 mm Hg; $P < 0.001$); and 6MWT (MD, 49.72; 95% CI, 2.93–96.51 m; $P = 0.04$). The result for the 6MWT was statistically significant and clinically relevant (minimally clinically important difference: 25–54 m). (20-22) Although the results for PaO_2 and $PaCO_2$ were statistically significant, the point estimate did not meet the minimum for clinical relevance, a change of at least 10 mm Hg. (Personal communication, clinical expert, April 14, 2011) However the gas exchange measures are considered surrogate outcomes. Noninvasive positive pressure ventilation had no effect on FEV_1 in the short term.

Noninvasive positive pressure ventilation did not have any long-term effect on mortality, FEV_1, PaO_2, $PaCO_2$, or 6MWT.

Qualitative Assessment

Some studies examined the outcomes of interest but did not have data suitable for a meta-analysis. In that case, or if there was only one study that had data suitable for meta-analysis for a given outcome, these were assessed qualitatively in aggregate by outcome, as shown below.

Hospitalizations

Two studies had information on hospitalizations. These showed no overall effect of NPPV on hospitalizations. McEvoy et al (19) found no difference between NPPV and usual care based on days in hospital and days on trial (rate ratio, 0.96; 95% CI, 0.90–1.02; $P = 0.16$). Casanova et al (13) found no differences in the number of hospital admissions between the NPPV group and usual care at the 12-month follow-up (both ~ 20%); however, there was an apparent difference between the groups at 3 months (treatment group [TR]: ~ 5% vs. control [CT]: ~ 15%), although the statistical significance for both were

not reported. The 2 studies had different lengths of follow-up (5 years vs. 3 and 12 months), and characterized hospitalizations differently, which precluded a meta-analysis.

Dyspnea

Four studies had information on dyspnea. Overall, there was a beneficial effect of NPPV therapy on dyspnea as indicated by a reduction in Borg score or MRC dyspnea score for the NPPV group compared with the control group. Diaz et al (17) found an increased reduction in Borg score between baseline and follow-up at 3 weeks in the NPPV group compared with the no ventilation group when assessed during walking (TR: −1.5 vs. CT: −0.1; $P < 0.001$). Clini et al (16) found that MRC dyspnea score decreased in the NPPV group compared with usual care at the 2-year follow-up, indicating improved dyspnea ($P = 0.01$). This information was reported in graph format only. Casanova et al (13) found no difference between the NPPV group and usual care in the mean MRC dyspnea score at the 6-month follow-up (TR: 2 vs. CT: 2). In the same study, the NPPV group showed a statistically significant higher level of dyspnea when measured on the Borg scale (TR: 5 vs. CT: 4; $P = 0.03$). However, no standard deviations were provided. In Renston et al (12) the NPPV group showed a decreased modified Borg score in arbitrary units (data in graph format) and a decreased MRC dyspnea score at 5 days of follow-up compared with no ventilation (TR: 2.6, standard deviation [SD]: 0.5 vs. CT: 3.3, SD: 0.4; *P* not given), suggesting improved dyspnea for the NPPV group. Dyspnea tests were administered with participants at rest in all the studies except Diaz et al. (17) The 2 short-term studies with 5 days (12) and 3 weeks (17) of follow-up characterized their outcome measures differently, which precluded a meta-analysis. For the 2 long-term studies with 6 months (13) and 2 years (16) of follow-up, there were insufficient data to perform a meta-analysis.

The 2007 systematic review (9) examined dyspnea, and additional data were available. Review of these found there was information from one study on MRC dyspnea scores (16) that could be combined with data presented in the original paper of another study. (12) However, since the data for these studies were for 2 years (long-term) and 5 days (short-term) of follow-up, respectively, a meta-analysis was not performed.

Health-Related Quality of Life

Although 2 studies included HRQOL among their outcome measures, the data were not substantial enough to form a conclusion. McEvoy et al (19) found no difference between NPPV and usual care groups; however, they did not show the data for this outcome measure. Clini et al (16) found improved scores at the 2-year follow-up; however, there was no significant difference between the NPPV and usual care groups (*P* not given). Data were presented in a graph.

The results of the studies are summarized in Appendix 3, Tables A3 to A5. The consistency of the qualitative assessment of the evidence is summarized in Appendix 3, Table A7.

Summary of the Literature Review

The results of this evidence-based analysis show short-term beneficial effects of NPPV on oxygen and carbon dioxide levels and on exercise tolerance. There was no short-term beneficial effect of NPPV on FEV_1. However, because the primary sample size calculation was not for FEV_1, type II error cannot be excluded. There were no long-term beneficial effects of NPPV on mortality, FEV_1, oxygen levels, carbon dioxide levels, and exercise tolerance. The qualitative assessment indicated a beneficial effect of NPPV on breathlessness but no effect on hospitalizations. The data on HRQOL were not substantial enough to form a conclusion.

From the 8 studies included, 5 used nocturnal NPPV (13;15;16;18;19) and 3 used diurnal NPPV therapy. (12;14;17) Of the 3 studies that used diurnal NPPV therapy, 2 were predominately based in pulmonary

laboratories where NPPV use was closely supervised. (14;17) The studies that used nocturnal NPPV were not directly observed. Increased quality assurance would be expected in a laboratory environment. (Personal communication, clinical expert, March 23, 2011) All studies included no ventilation as the comparator, with 3 studies using CPAP (14;17;18) and 2 studies using BiPAP without a pressure gradient. (12;15) These "sham therapy" types of studies were designed to minimize a placebo effect for the patient and to ensure personnel were blinded to treatment. However, the CPAP equipment differs from the BiPAP equipment, as do the settings for use: the BiPAP equipment cycles audibly between high inspiratory and low expiratory settings, which are likely to be noticed. Some studies indicated in their methods that the personnel performing the outcome assessment were blinded to the allocation of treatment or the research question. (14;16-18) The 2 studies that used BiPAP equipment as the comparator (12;15) (though at low settings) likely achieved a higher level of patient and personnel blinding. (Personal communication, clinical expert, March 18, 2011) Sham therapy was generally given with usual care. Thus, these types of studies are comparable to the non-sham-based studies that examined long-term oxygen use and usual care as the comparator, since in these studies what was compared was NPPV therapy to no ventilation therapy while receiving usual care.

The studies included in this evidence-based analysis addressed the limitations of previous systematic reviews. Patients had severe to very severe COPD with hypercapnia and thus the greatest potential to benefit from NPPV therapy. Patients also underwent NPPV training prior to study initiation. However, low inspiratory levels may have been a limiting factor (< 15 cm H_2O). When there was a trend for a beneficial effect of NPPV on PaO_2 and $PaCO_2$, the 2 studies that contributed to the estimate were distinct in that they were pulmonary laboratory-based studies with NPPV in use for 3 hours per day, 5 days a week at an IPAP of 18 cm H_2O. (14;17) This suggests that proper use, as can be expected in a pulmonary laboratory–based setting, and high IPAP values are necessary in order to see the benefit of NPPV therapy. (23) Studies that used nocturnal NPPV may not have been adequately designed. (13;15;16;18;19) The study design concerns may be less relevant when examining the 6MWT. The heterogeneity in study design, as well as measurement and characterization of hospitalizations, dyspnea, and HRQOL, precluded a meta-analysis; however, there was some consistency in the results for dyspnea suggesting a beneficial effect of NPPV.

The evidence for the outcomes that could be meta-analyzed (mortality, PaO_2, $PaCO_2$, FEV_1, 6MWT) was graded as very low to moderate quality of evidence. The evidence for the outcome of hospitalizations, which was not meta-analyzed, was graded as of moderate quality, and the evidence for the outcome of dyspnea, which was also not meta-analyzed, was graded as low quality. There was a lack of substantial data to grade the outcome of HRQOL. Grade quality of evidence for all outcomes is shown in Appendix 2.

Given the grade quality of evidence, the generalizability of the study results is high with respect to other severe to very severe COPD populations. For a majority of studies, individuals with sleep apnea were excluded as they may require the intervention and would not be able to be randomized to a non-treatment group. Additionally, the exclusion of individuals with sleep apnea or obesity helped to produce a more homogeneous COPD study population. Disease conditions that may affect the completion of the study (e.g., severe comorbidity), or the ability to use the technology (e.g., psychiatric conditions) were also excluded.

The characteristics of the studies identified in the literature review are shown in Appendix 3, Tables A3 to A8.

Economic Analysis

The results of the economic analysis are summarized in issue 12 of the COPD series entitled *Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model*. This report can be accessed at: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Economic_March.pdf.

The results from the systematic review of the clinical evidence for NPPV for chronic respiratory failure in stable COPD patients were not included in the economic model because it was not shown to be clinically effective.

Conclusions

The following conclusions refer to stable, severe COPD patients receiving usual care.

Short-Term Studies

- Based on low quality of evidence, there is a beneficial effect of NPPV compared with no ventilation on oxygen gas exchange, carbon dioxide gas exchange, and exercise tolerance measured using the 6MWT.
- Based on very low quality of evidence, there is no effect of NPPV therapy on lung function measured as FEV_1 (Type II error not excluded).

Long-Term Studies

- Based on moderate quality of evidence, there is no effect of NPPV therapy for the outcomes of mortality, lung function measured as FEV_1, and exercise tolerance measured using the 6MWT.
- Based on low quality of evidence, there is no effect of NPPV therapy for the outcomes of oxygen gas exchange and carbon dioxide gas exchange (Type II error not excluded).

Qualitative Assessment

- Based on low quality of evidence, there is a beneficial effect of NPPV compared with no ventilation for dyspnea based on reduced Borg score or MRC dyspnea score.
- Based on moderate quality of evidence, there is no effect of NPPV therapy for hospitalizations.
- HRQOL could not be evaluated.

Existing Guidelines for Noninvasive Positive Pressure Ventilation

An overview of existing guidelines for NPPV were identified from one journal article by Hill et al. (24) For Ontario, the Ministry of Health and Long-Term Care website was reviewed for existing guidelines. (4) The following guidelines are arranged according to the source of the guidelines: Consensus Conference Guidelines, (24) Centers for Medicare and Medicaid Services Guidelines, (24) and the Ministry of Health and Long-Term Care Guidelines. (4)

Consensus Conference Guidelines

For severe, stable COPD:

- symptomatic after optimal therapy
- sleep apnea excluded
- $PaCO_2 \geq 55$ mm Hg or
- $PaCO_2$ 50–54 mm Hg and evidence of nocturnal hypoventilation based on nocturnal oximetry showing sustained desaturation to < 89% for ≥ 5 min on oxygen use
- repeated hospitalizations

Centers for Medicare and Medicaid Services Guidelines

For severe, stable COPD:

- $PaCO_2 \geq 52$ mm Hg and
- evidence of nocturnal hypoventilation based on nocturnal oximetry showing sustained desaturation to < 89% for ≥ 5 min on oxygen use
- sleep apnea excluded

Ministry of Health and Long-Term Care Guidelines

- no specific criteria
- assessment by medical professional (i.e., a doctor who works at a sleep clinic registered with the Assistive Devices Program)

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity (FVC)	The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.

Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.
Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[1]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.
Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.

[1] The mild-to-moderate classification was created for the purposes of the report.

Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.
Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Medical Information Officer

Kellee Kaulback

Editorial Staff

Joanna Odrowaz
Irina Alecu

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

Appendices

Appendix 1: Literature Search Strategies

Search date: December 3, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane Library, Cumulative Index to Nursing & Allied Health Literature (CINAHL), Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database(s): Ovid MEDLINE(R) 1950 to November Week 3 2010
Search Strategy:

#	Searches	Results
1	exp Pulmonary Disease, Chronic Obstructive/	15011
2	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab.	21909
3	(copd or coad).ti,ab.	16795
4	chronic airflow obstruction.ti,ab.	493
5	exp Emphysema/	7051
6	((chronic adj2 bronchitis) or emphysema).ti,ab.	22960
7	or/1-6	54680
8	exp Respiration, Artificial/	51221
9	((artificial or non-invasive or noninvasive or invasive or nasal or mechanical or volume-controlled or pressure controlled or positive) adj2 (ventilat* or respiration)).ti,ab.	29829
10	(NIV or NPPV or NIPPV or NIAV or continous positive airway pressure or CPAP or bi-level positive pressure or ventilation support or BiPAP or endotracheal intubation or ventilat* failure).ti,ab.	10735
11	exp Ventilator Weaning/	2368
12	limit 11 to "all adult (19 plus years)"	1062
13	or/8-10	68682
14	7 and 13	3314
15	12 or 14	4228
16	limit 15 to (english language and humans and yr="2004 -Current")	1206

Database(s): EMBASE 1980 to 2010 Week 47
Search Strategy:

#	Searches	Results
1	exp chronic obstructive lung disease/	48840
2	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab.	26482
3	(copd or coad).ti,ab.	21755
4	chronic airflow obstruction.ti,ab.	551

5	exp emphysema/	25753
6	exp chronic bronchitis/	6600
7	((chronic adj2 bronchitis) or emphysema).ti,ab.	25596
8	or/1-7	89245
9	exp artificial ventilation/	86836
10	((artificial or non-invasive or noninvasive or invasive or nasal or mechanical or volume-controlled or pressure controlled or positive) adj2 (ventilat* or respiration)).ti,ab.	36697
11	(NIV or NPPV or NIPPV or NIAV or continous positive airway pressure or CPAP or bi-level positive pressure or ventilation support or BiPAP or endotracheal intubation or ventilat* failure).ti,ab.	13569
12	(ventilat* adj2 wean*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	971
13	limit 12 to (adult <18 to 64 years> or aged <65+ years>)	357
14	or/9-11	102073
15	8 and 14	6573
16	13 or 15	6871
17	limit 16 to (human and english language and yr="2004 -Current")	2094

CINAHL

#	Query	Results
S14	(S11 or S12) Limiters - Published Date from: 20040101-20101231; English Language	416
S13	(S11 or S12)	794
S12	s6 and s10	585
S11	(MH "Ventilator Weaning") Limiters - Age Groups: Aged: 65+ years	235
S10	S7 or S8 or S9	12790
S9	NIV or NPPV or NIPPV or NIAV or continous positive airway pressure or CPAP or bi-level positive pressure or ventilation support or BiPAP or endotracheal intubation or ventilat* failure	1689
S8	artificial N2 ventil* or non-invasive N2 ventil* or noninvasive N2 ventil* or invasive N2 ventil* or nasal N2 ventil* or mechanical N2 ventil* or volume-controlled N2 ventil*or pressure controlled N2 ventil*or positive N2 ventil* or artificial N2 respirat* or non-invasive N2 respirat* or noninvasive N2 respirat* or invasive N2 respirat* or nasal N2 respirat* or mechanical N2 respirat* or volume-controlled N2 respirat*or pressure controlled N2 respirat*or positive N2 respirat*	9597
S7	(MH "Respiration, Artificial+")	10081
S6	S1 or S2 or S3 or S4 or S5	7579
S5	chronic bronchitis or emphysema	1606
S4	(MH "Emphysema+")	982
S3	copd or coad	4153

S2	(chronic obstructive and (lung* or pulmonary or airway* or airflow or respiratory) and (disease* or disorder*))	5747
S1	(MH "Pulmonary Disease, Chronic Obstructive+")	4462

Appendix 2: GRADE Evidence Tables

Table A1: GRADE Evidence Assessment for Outcomes of Mortality and Lung Function*

Quality Assessment							Summary of Findings					Importance
							No. of patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	NIV	No NIV	RR (95% CI)	Absolute	Quality	
Mortality												
3	Randomized trials	Serious†,‡,§	No serious inconsistency	No serious indirectness	No serious imprecision	Long term only	51/131 (38.9%)	58/143 (40.6%) 17%	RR 0.91 (0.7 to 1.19)	37 fewer per 1000 (from 122 fewer to 77 more) 15 fewer per 1000 (from 51 fewer to 32 more)	⊕⊕⊕O MODERATE	
$PaCO_2$ Surrogate Outcome												
3	Randomized trials	Serious†,§	No serious inconsistency	Pulmonary lab in the short term	Small sample in the long term‖	Short term Long term	45 20	33 24	-	MD 7.54 lower (10.16 lower to 4.92 lower) MD 1.30 higher (3.40 lower to 6.00 higher)	⊕⊕OO LOW ⊕⊕OO LOW	
PaO_2 Surrogate Outcome												
3	Randomized trials	Serious†,§	No serious inconsistency	Pulmonary lab in the short term	Small sample in the long term‖	Short term Long term	45 20	33 24	-	MD 6.16 higher (3.51 higher to 8.80 higher) MD 0.80 higher (3.80 lower to 5.40 higher)	⊕⊕OO LOW ⊕⊕OO LOW	

Quality Assessment							Summary of Findings					Importance
							No. of patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	NIV	No NIV	RR (95% CI)	Absolute	Quality	
FEV_1												
3	Randomized trials	Serious†,§	No serious inconsistency	Pulmonary lab in the short term	Small sample in the short term‖	Short term Long term	18 59	18 71	-	MD 5.00 higher (1.91 lower to 11.91 higher) MD 1.05 higher (2.17 lower to 4.27 higher)	⊕OOO VERY LOW ⊕⊕⊕O MODERATE	
6MWT												
4	Randomized trials	Serious¶.#'	No serious inconsistency	Pulmonary lab in the short term	No serious imprecision	Short term Long term	42 39	31 47	-	MD 49.72 higher (2.93 higher to 96.51 higher) MD 3.00 lower (52.55 lower to 46.55 higher)	⊕⊕OO LOW ⊕⊕⊕O MODERATE	

*Abbreviations: 6MWT, 6 Minute Walking Test; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; MD, mean difference; NIV, noninvasive ventilation; no., number; $PaCO_2$, arterial pressure of carbon dioxide; PaO_2, arterial pressure of oxygen; RR, relative risk.

†Lack of blinding of patients and/or assessors: mortality, (13;19); PaO_2, (13); $PaCO_2$, (13); FEV_1, (13).

‡Significant losses to follow-up in 1 study: mortality, (16).

§Allocation concealment was not well described in 2 studies (mortality, (13;16); PaO_2, (13;14); $PaCO_2$, (13;14)), or 3 studies (FEV_1, (13;14;16)).

‖Small sample size per arm (< 25 subjects) in the context of the low number of individuals using noninvasive ventilation (e.g., 263 in Ontario according to the Ventilation Equipment Pool): short term studies, FEV_1, (14) ; long term studies, PaO_2, $PaCO_2$, (13).

¶High attrition: 6MWT, (15;16).

#Allocation concealment was not well described in 3 studies (6MWT, (15;16;18) and the process of randomization was not well described in 2 studies (6MWT, (15;18)).

Table A2: GRADE Evidence Assessment for Outcomes of Hospitalizations, Dyspnea, and SGRQ*

Quality Assessment							Summary of Findings					Additional Comments
							No of patients		Effect		Quality	
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	NIV	No NIV	Relative (95% CI)	Absolute		
Hospitalizations												
2	Randomized trials	Serious†,‡	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕O MODERATE	3 and 12 months, and 5 years of follow-up, data could not be pooled across the 2 studies with different lengths of follow-up (qualitative assessment)
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Dyspnea												
4	Randomized trials	Very serious†,§,‖,¶	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	5 days, 3 weeks, 6 months, and 2 years of follow-up, data could not be pooled, different characterization of outcome by follow-up (qualitative assessment)
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
SGRQ												
n/a	n/a	n/a	n/a	n/a	n/a	n/a					n/a	Insufficient data on which to base a conclusion

*Abbreviations: CI, confidence interval; NIV, noninvasive ventilation; No., number; RR, relative risk; SGRQ, St. George's Respiratory Questionnaire.

†Lack of blinding of patients and/or assessors: hospitalizations, (13;19); dyspnea, (13).

‡Allocation concealment was not well described: hospitalizations, (13).

§Allocation concealment was not well described in 3 studies (dyspnea, (12;13;16) and the process of randomization in 1 study (dyspnea, (12)).

‖High attrition in 1 study (dypsnea, (16)).

¶Unknown if randomization was achieved in 1 study (dyspnea, (12)).

Appendix 3: Summary Tables

Table A3: Summary of Study Characteristics (N = 8 Studies)*

Author, Year	Study Location	COPD Severity†	Study Design	Length of Follow-up	Treatment/Control (no.)	Losses to Follow-up‡
McEvoy et al, 2009 (19)	University hospitals, Australia	Severe	Parallel RCT	5 years	72/72	4/4
Sin et al, 2007 (18)	Specialists' clinics, University of Alberta	Moderate	Parallel RCT	3 months	10/11	2/0
Diaz et al, 2005 (17)	Universidad Catolica de Chile, Chile	Severe	Parallel RCT	3 weeks	27/15	0/0
Clini et al, 2002 (16)	Respiratory units, Italy and France	Severe	Parallel RCT	2 years	39/47	8/15
Diaz et al, 2002 (14)	Universidad Catolica de Chile, Chile	Severe	Parallel RCT	3 weeks	18/18	0/0
Casanova et al, 2000 (13)	Pulmonary clinics, Canary Islands	Severe	Parallel RCT	1 year	20/24	5/2
Gay et al, 1996 (15)	Database, United States	Severe	Parallel RCT	3 months	7/6	3/0
Renston et al, 1994 (12)	Pulmonary lab records, United States	Severe	Parallel RCT	5 days	9/8	n/a

*Abbreviations: COPD, chronic obstructive pulmonary disease; no., number; RCT, randomized controlled trial.
†COPD severity based on study entry criteria. Final study population may differ. See Appendix 3, Table A8 for baseline values.
‡Losses to follow-up refer to treatment/control (no.).

Table A4: Summary of Study Design Characteristics From Studies Identified From the Literature Search (N = 3 Studies)*

Author, Year	Comparator	Study Population	Intervention	Results	Additional Comments
McEvoy et al, 2009 (19)	N-NIV + LTOT vs. LTOT	144† COPD patients, < 80 yrs, severe (FEV_1 < 50%), stable, hypercapnic ($PaCO_2$ > 46 mm Hg), FU: 5 yrs	N-NIV, patient triggered BiPAP, IPAP to max tolerable, EPAP of 3 cm H_2O, IPAP-EPAP difference of ≥10 cm H_2O	Mean age: ~68 yrs; median FU, TR: 28.5 vs. CT: 20.5 mo, no diff in LTOT use (~19 hrs); mean NIV use: 4.5 hrs/night; mean IPAP: 13 cm H_2O Mortality, HR: 0.63, 95% CI: 0.40-0.99, *P* = 0.045, (TR: 40/72 (55.6%) vs. 46/72 (63.9%)); no diff in hospitalization rates based on days on trial Lung function: no diff for PaO_2 (DNS), $PaCO_2$, FEV_1 at 12 mo, *P*? HRQOL: no diff for SGRQ at 12 mo (DNS)	LTOT for at least 3 mo, nasal or face mask, sleep apnea excluded, nonsmoking, plus usual care in both arms, close contact for FU, subgroup analysis for NIV > 4 hrs, NIV training, 8/144 R-DO (5.6%) (TR: 4/72 (5.6%) vs. CT: 4/72 (5.6%))
Sin et al, 2007(18)	N-NIV vs. CPAP	23 COPD patients, > 39 yrs, moderate (FEV_1 < 70%), stable? near hypercapnic (from baseline: ~44.2 mm Hg), FU: 3 mo	N-NIV, BiPAP, IPAP to max tolerable, EPAP of 4 cm H_2O	Mean age: ~65 yrs; mean NIV use? Mean IPAP: 15.5 cm H_2O 6MWT at 3 mo, no diff (TR: 367 vs. CT: 311 m, *P* = 0.311); No suitable data for $PaCO_2$ and FEV_1 (within group comparison from baseline)	O_2 use as needed, nasal or face mask, sleep apnea excluded, smokers, std medical, close contact for FU, NIV training, 2/23 R-DO (8.7%) (TR: 2/13 (15.4%) vs. 0/10 CT (0%))
Diaz et al, 2005 (17)	NIV vs. CPAP	62 COPD patients, all ages, severe (at baseline), stable, hypercapnic ($PaCO_2$ ≥ 50 mm Hg), FU: 3 wks	NIV, spontaneous mode, BiPAP, IPAP to max tolerable, EPAP of 2 cm H_2O, 3 hrs/day, 5 days/wk	Mean age: ~68 yrs; use of NIV as in lab; mean IPAP: 18 cm H_2O Change in $PaCO_2$, TR: -8.2 vs. CT: -0.7 mm Hg, *P* < 0.0001; PaO_2, TR: 7.7 vs. CT: 2.2 mm Hg, *P* < 0.001; FEV_1, TR: 0.08 vs. CT: 0 litres, *P* < 0.001; 6MWT, TR: 76 vs. CT: 13 m, *P* < 0.0001; Borg, TR: -1.5 vs. CT: -0.1, *P* < 0.0001	LTOT use, no prior NIV use, sleep apnea excluded, current medication (e.g., bronchodilators), O_2 for all controls, face mask, nonsmoking, pulmonary lab, 0 R-DO

*Abbreviations: 6MWT, 6 Minute Walking Test; BiPAP, bilevel positive airway pressure; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRQ, Chronic Respiratory Questionnaire; CT, control group; diff, difference; DNS, data not shown; DO, dropout; EPAP, expiratory positive airway pressure; FEV_1, forced expiratory volume in 1 second; FU, follow-up; HR, hazard ratio; HRQOL, health-related quality of life; hrs, hours; IPAP, inspiratory positive airway pressure; LTOT, long-term oxygen therapy; mm Hg, millimetres of mercury; NIV, noninvasive ventilation; N-NIV, nocturnal noninvasive ventilation; O_2, supplementary oxygen; $PaCO_2$, arterial pressure of carbon dioxide; PaO_2, arterial pressure of oxygen; R-DO, dropouts from randomization; SGRQ, St. George's Respiratory Questionnaire; TR, treatment group; wk, week.

†After exclusions. Remaining numbers refer to the initial COPD study population.

Table A5: Summary of Study Design Characteristics From Eligible Studies (N = 5 Studies)*,†

Author, Year	Comparator	Study Population	Intervention	Results	Additional Comments
Clini et al, 2002 (16)	N-NIV + LTOT vs. LTOT	122 COPD patients < 76 yrs, severe (FEV_1 <1.5 L), stable, hypercapnic ($PaCO_2$ >50 mm Hg), FU: 2 yrs	N-NIV, spontaneous/timed mode, BiPAP, IPAP to max tolerable, EPAP of 2–5 cm H_2O	Mean age: ~65 yrs; mean LTOT use (~20 hrs); mean NIV use: 9 hrs/night; mean IPAP: 14 cm H_2O Mortality: no diff (TR: 18 vs. CT: 17%) Lung function: no diff for FEV_1 and PaO_2 at 12 and 24 mo; $PaCO_2$ diff at 12 and 24 mo (24 mo, TR: 55 vs. CT: 60 mm Hg, *P* = 0.002); MRC dyspnea diff at 12 and 24 mo (24 mo, TR: 2.2 vs. CT: 3, *P* = 0.013); no diff for 6MWT at 12 and 24 mo HRQOL: no diff for SGRQ at 12 and 24 mo	LTOT for at least 6 mo, nasal, no prior use of NIV, sleep apnea and smokers excluded, SM (e.g., bronchodilators), close contact for FU, NIV training, 23/86 R-DO (26.7%) (TR: 8/39 (20.5%) vs. CT: 15/47 (31.9%)), $PaCO_2$ and HRQOL on usual O_2, MRF-28 available
Diaz et al, 2002 (14)	NIV vs. CPAP	56 COPD patients, all ages, severe (?FEV_1), stable, hypercapnic ($PaCO_2$ >50 mm Hg), FU: 3 wks	NIV, spontaneous mode, BiPAP, IPAP to max tolerable, EPAP of 2 cm H_2O, laboratory/direct supervision (outpatient), 3 hrs/day, 5 days-wk	Mean age: ~67 yrs, use of NIV as in lab; mean IPAP: 18 cm H_2O Lung function at 3 wks, $PaCO_2$, TR: 6.5 vs. CT: 7.3 kPa; PaO_2, TR: 7.1 vs. 6.7 kPa; FEV_1, TR: 35.8 vs. 36.7% (*P*? for all)	All controls needed O_2 (offered to NIV but not needed), face mask, sleep apnea excluded, SM (e.g., bronchodilators), no prior use of NIV, nonsmoking, std medical, pulmonary lab, 0 R-DO
Casanova et al, 2000 (13)	N-NIV + SM vs. SM	80 COPD patients, 45-75 yrs, severe (< 45%), stable, hypercapnic (from baseline: ~52 mm Hg), FU: 1 yr	N-NIV, spontaneous mode, BiPAP, IPAP of 12 cm H_2O, EPAP of 4 cm H_2O	Mean age: ~66 yrs; mean NIV use: 6.1 hrs/day, mean IPAP: 12 cm H_2O Morbidity, no sign diff at 1 yr (e.g., hospital admissions, ~20%) Mortality, no sign diff at 1 yr (TR: 4/20 (20%) vs. CT: 4/24 (16.7%), *P*?) Lung function (gases and FEV_1), no sign diff at 6 mo (e.g., FEV_1, TR: 30 vs. 31%)	SM as bronchodilators, antibiotics, corticosteroids, and LTOT use, nasal, O_2 as needed, sleep apnea excluded, stopped smoking, NIV training, 7/52 R-DO (13.5%) (TR: 5/26 (19.2%) vs. CT: 2/26 (7.7%))

Author, Year	Comparator	Study Population	Intervention	Results	Additional Comments
Gay et al, 1996 (15)	N-NIV vs. CPAP	85 COPD patients, < 80 yrs, severe (FEV_1 < 40%), stable, hypercapnic ($PaCO_2$ > 45 mm Hg), FU: 3 mo	N-NIV, spontaneous mode, BiPAP, IPAP: 10 cm H_20, EPAP of 2 cm H_2O	Mean age: ~69 yrs; NIV use: ~4.5 hrs/night, IPAP: 10 cm H_2O Lung function, FEV_1, TR: 0.60 vs. CT: 0.71 litres, *P*? data are difficult to extrapolate for $PaCO_2$; 6MWT, TR: 309.2 vs. CT: 306.9 m, *P*?)	LTOT use, nasal, NIV training, medications, 3/13 R-DO (23.1%) (TR: 3/7 (42.9%) vs. CT: 0/6)
Renston et al, 1994 (12)	NIV vs. CPAP	17 COPD patients, all ages, severe (FEV_1 <50%), stable, hypercapnic? FU: 5 days	NIV, spontaneous mode, BiPAP, IPAP: 15-20 cm H_2O, EPAP of 2 cm H_2O	Mean age: ~65 yrs; NIV use: 2 hrs/day, Mean IPAP? Lung function, $PaCO_2$, PaO_2: no sign diff at FU (extrapolated from graph), Borg, TR: 0.6 vs. CT: 1.3, *P*? (extrapolated from graph, au), 6MWT, Change, TR: 32 vs. CT: 0 m, *P*? (extrapolated from graph)	Home oxygen use, nasal, sleep apnea excluded, very short duration study, 0 R-DO

*Abbreviations: 6MWT, 6 Minute Walking Test; au, arbitrary units; BiPAP, bilevel positive airway pressure; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CT, control group; diff, difference; EPAP, expiratory positive airway pressure; FEV_1, forced expiratory volume in 1 second; FU, follow-up; HRQOL, health-related quality of life; hrs, hours; kPa, kilopascal; IPAP, inspiratory positive airway pressure; LTOT, long-term oxygen therapy; mm Hg, millimetres of mercury; mo, months; MRC, Medical Research Council; MRF-28, Maugeri Foundation Respiratory Failure Questionnaire; NIV, noninvasive ventilation; N-NIV, nocturnal noninvasive ventilation; O_2, supplementary oxygen; $PaCO_2$, arterial pressure of carbon dioxide; PaO_2, arterial pressure of oxygen; R-DO, dropouts from those randomized (early dropouts excluded from denominator); SGRQ, St. George's Respiratory Questionnaire; SM, standard medical; TR, treatment group; yrs, years.

†*Source: Kolodziej et al, 2007 (9)*

Table A6: Study Design Strengths and Limitations*

Study, Year	Study Design Strengths and Limitations†									
	COPD Study Population	Adequate Sample Size‡	Exclusions Detailed	Randomization Achieved	Blinding§	Adequately Measured Compliance	All-Cause Mortality	Survival Analysis	Intent-to-Treat Analysis	Minimal Attrition‖
McEvoy et al, 2009 (19)	✓		✓	✓		✓	✓	✓	✓	✓
Sin et al, 2007 (18)	✓		✓	✓	✓	✓				✓
Diaz et al, 2005 (17)	✓		✓	✓	✓	✓			✓¶	✓
Clini et al, 2002 (16)	✓	✓	✓	✓	✓	✓	✓		✓	
Diaz et al, 2002 (14)	✓	✓	✓	✓	✓	✓			✓¶	✓
Casanova et al, 2000 (13)	✓	✓	✓	✓#		✓	✓	✓		✓
Gay et al, 1996 (15)	✓		✓		✓**	?				
Renston et al, 1994 (12)	✓		✓		✓**	✓			✓¶	✓

*Abbreviations: BiPAP, bilevel positive airway pressure; COPD, chronic obstructive pulmonary disease; ✓, study design strengths; ? compliance of NIV use was determined but not reported.
†Allocation concealment was not adequate for Clini (2002), Diaz (2002), Sin (2007), Casanova (2000), Gay (1996), and Renston (1994) and the process of generating randomized schedules was not adequate for Sin (2007), Gay (1996) and Renston (1994).
‡Lack of sample size based on reported sample size calculation for primary association of interest.
§Personnel performing outcome assessment were blinded to allocation of treatment or research question. Placebo effect for the patient cannot be ruled out.
‖Minimal attrition based on examination of total and per arm losses to follow-up/dropouts, with less than 20% attrition deemed to be adequate.
¶For a short length of follow-up, with zero dropouts.
#Slight differences for age only.
**Blinding based on use of sham-BiPAP.

Table A7: Summary of the Results from the Qualitative Assessment*

Outcome Measures	Assessment
1) Dyspnea	
4 Studies	
Diaz et al, 2005 (17)	+
Clini et al, 2002 (16)	+
Casanova et al, 2000 (13)	-/=
Renston et al, 1994 (12)	+
2) Hospitalizations	
2 Studies	
McEvoy et al, 2009 (19).	=
Casanova et al, 2000 (13)	=
3) Health-Related Quality of Life	
2 Studies	
McEvoy et al, 2009 (19).	=
Clini et al, 2002 (16)	=

*= indicates evidence that showed no difference between technologies;
+ indicates evidence favouring the technology;
- indicates evidence favouring the control.

Table A8: Summary of Key Study Characteristics*

	Summary of Key Study Characteristics†									
Study, Year	**FEV_1 Total Baseline‡ (% pred)**	**FEV_1 TR Baseline‡ (% pred)**	**FEV_1 CT Baseline‡ (% pred)**	**PaO_2 Total Baseline§ (mm Hg)**	**PaO_2 TR Baseline§ (mm Hg)**	**PaO_2 CT Baseline§ (mm Hg)**	**$PaCO_2$ Total Baseline‖ (mm Hg)**	**$PaCO_2$ TR Baseline‖ (mm Hg)**	**$PaCO_2$ CT Baseline‖ (mm Hg)**	**Mean (SD) FU or Range (years)**
McEvoy et al, 2009 (19)	24.1	25	23.1	53.7	54.8	52.5	53.5	52.6	54.4	2.0¶
Sin et al, 2007 (18)	31.2	37.6	24.8	60	59.3	60.7	44.2	45.2	43.1	?
Diaz et al, 2005 (17)	32.5	30	35	46.6	45.3	47.9	56.6	56.5	56.7	n/a
Clini et al, 2002 (16)	29	27	31	49.9	50.3	49.5	54.8	54	55.5	?
Diaz et al, 2002 (14)	0.8#	0.7#	0.8#	47.2	45.2	49.2	56	56.8	55.2	n/a
Casanova et al, 2000 (13)	0.9#	0.8#	0.9#	56.6	55.7	57.5	52.0	50.7	53.2	?
Gay et al, 1996 (15)	0.7#	0.6#	0.7#	62.1	66.4	57.8	51.6	54.7	48.5	?
Renston et al, 1994 (12)	34.5	32	37	65	65**	65**	48.5	50**	47**	n/a

*Abbreviations: COPD, chronic obstructive pulmonary disease; CT, control group; FEV_1, forced expiratory volume in 1 second; FU, follow-up; mm Hg, millimetres of mercury; n/a, not applicable; $PaCO_2$, arterial pressure of carbon dioxide; PaO_2, arterial pressure of oxygen; pred, predicted; SD, standard deviation; TR, treatment group; ? indicates data not provided.

†Data were reported as means and standard deviations unless otherwise indicated; total was either taken from the original paper or calculated as the mean from the two arms of the trial; total refers to the study population as a whole including the treatment group and control group.

‡COPD Stage: Mild, $FEV_1 \geq 80\%$ predicted; Moderate, $FEV_1 < 80\%$ and $FEV_1 \geq 50\%$ predicted; Severe, $FEV_1 < 50\%$ and $FEV_1 \geq 30\%$ predicted; Very Severe, $FEV_1 < 30\%$.

§Hypoxemia: Severe, ≤ 55 mm Hg; Mild-Moderate, ~ 56-65 mm Hg.

‖Hypercapnia: > 45-60 mm Hg.

¶Median, average of both arms.

#FEV_1 in litres. Severe COPD defined as $FEV_1 < 1.5$ litres.

**Extrapolated from graph.

References

(1) Diaz-Lobato S, Alises SM, Rodriguez EP. Current status of noninvasive ventilation in stable COPD patients. Int J Chron Obstruct Pulmon Dis. 2006;1(2):129-35.

(2) Gold PM. The 2007 GOLD Guidelines: a comprehensive care framework. Respir Care. 2009;54(8):1040-9.

(3) Budweiser S, Jorres RA, Pfeifer M. Treatment of respiratory failure in COPD. Int J Chron Obstruct Pulmon Dis. 2008;3(4):605-18.

(4) Ministry of Health and Long-Term Care. Assistive Devices Program: Respiratory Products [Internet]. Ontario: Queen's Printer of Ontario. 2004 Jun 1 [cited: 2011 Jan 6]. 3 p. Available from: http://www.health.gov.on.ca/english/public/pub/adp/resp.html

(5) Theerakittikul T, Ricaurte B, Aboussouan LS. Noninvasive positive pressure ventilation for stable outpatients: CPAP and beyond. Cleve Clin J Med. 2010;77(10):705-14.

(6) Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen (DK): The Nordic Cochrane Centre, The Cochrane Collaboration; 2011.

(7) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490.

(8) Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.

(9) Kolodziej MA, Jensen L, Rowe B, Sin D. Systematic review of noninvasive positive pressure ventilation in severe stable COPD. Eur Respir J. 2007;30(2):293-306.

(10) Goodman, C. Literature searching and evidence interpretation for assessing health care practices. Stockholm, Sweden: Swedish Council on Technology Assessment in Health Care. 1996. 81p. SBU Report No. 119E.

(11) Wijkstra PPJ, Lacasse Y, Guyatt GH, Goldstein R, Struik F. Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD002878. DOI: 10.1002/14651858.CD002878.

(12) Renston JP, DiMarco AF, Supinski GS. Respiratory muscle rest using nasal BiPAP ventilation in patients with stable severe COPD. Chest. 1994;105(4):1053-60.

(13) Casanova C, Celli BR, Tost L, Soriano E, Abreu J, Velasco V et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest. 2000;118(6):1582-90.

(14) Diaz O, Begin P, Torrealba B, Jover E, Lisboa C. Effects of noninvasive ventilation on lung hyperinflation in stable hypercapnic COPD. Eur Respir J. 2002;20(6):1490-8.

(15) Gay PC, Hubmayr RD, Stroetz RW. Efficacy of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. Mayo Clin Proc. 1996;71(6):533-42.

(16) Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J. 2002;20(3):529-38.

(17) Diaz O, Begin P, Andresen M, Prieto ME, Castillo C, Jorquera J, et al. Physiological and clinical effects of diurnal noninvasive ventilation in hypercapnic COPD. Eur Respir J. 2005;26(6):1016-23.

(18) Sin DD, Wong E, Mayers I, Lien DC, Feeny D, Cheung H, et al. Effects of nocturnal noninvasive mechanical ventilation on heart rate variability of patients with advanced COPD. Chest. 2007;131(1):156-63.

(19) McEvoy RD, Pierce RJ, Hillman D, Esterman A, Ellis EE, Catcheside PG et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax. 2009;64(7):561-6.

(20) Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. Am J Respir Crit Care Med. 1997;155(4):1278-82.

(21) Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. Arch Phys Med Rehabil. 2010;91(2):221-5.

(22) Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schunemann HJ. Interpretation of treatment changes in 6-minute walk distance in patients with COPD. Eur Respir J. 2008;32(3):637-43.

(23) Budweiser S, Jorres RA, Pfeifer M. Noninvasive home ventilation for chronic obstructive pulmonary disease: indications, utility and outcome. Curr Opin Pulm Med. 2008;14(2):128-34.

(24) Hill NS. Noninvasive ventilation for chronic obstructive pulmonary disease. Respir Care. 2004;49(1):72-87.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-7015-2 (PDF)

Ontario
Health Quality Ontario
Qualité des services de santé Ontario

Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis

BR McCurdy

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 10, pp. 1–65, March 2012

Suggested Citation

This report should be cited as follows:

McCurdy BR. Hospital-at-home programs for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2012 Mar; 12(10):1–65. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Hospital_at_Home_March.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to: MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit:
http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses:
http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
H	Inpatient hospital group
HaH	Hospital-at-home group
HR	Hazard ratio
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
ED	Emergency department
EDHaH	Early discharge hospital-at-home program
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQOL	Health-related quality of life
MAS	Medical Advisory Secretariat
NICE	National Institute for Health and Clinical Excellence
RCT	Randomized controlled trial
RR	Relative risk
SpO_2	Oxygen saturation level of arterial blood measured by pulse oximetry
SGRQ	St. George's Respiratory Questionnaire

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients with Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective

The objective of this analysis was to compare hospital-at-home care with inpatient hospital care for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) who present to the emergency department (ED).

Clinical Need: Condition and Target Population

Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a disease state characterized by airflow limitation that is not fully reversible. This airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The natural history of COPD involves periods of acute-onset worsening of symptoms, particularly increased breathlessness, cough, and/or sputum, that go beyond normal day-to-day variations; these are known as acute exacerbations.

Two-thirds of COPD exacerbations are caused by an infection of the tracheobronchial tree or by air pollution; the cause in the remaining cases is unknown. On average, patients with moderate to severe COPD experience 2 or 3 exacerbations each year.

Exacerbations have an important impact on patients and on the health care system. For the patient, exacerbations result in decreased quality of life, potentially permanent losses of lung function, and an increased risk of mortality. For the health care system, exacerbations of COPD are a leading cause of ED visits and hospitalizations, particularly in winter.

Technology

Hospital-at-home programs offer an alternative for patients who present to the ED with an exacerbation of COPD and require hospital admission for their treatment. Hospital-at-home programs provide patients with visits in their home by medical professionals (typically specialist nurses) who monitor the patients, alter patients' treatment plans if needed, and in some programs, provide additional care such as pulmonary rehabilitation, patient and caregiver education, and smoking cessation counselling.

There are 2 types of hospital-at-home programs: admission avoidance and early discharge hospital-at-home. In the former, admission avoidance hospital-at-home, after patients are assessed in the ED, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional. In early discharge hospital-at-home, after being assessed in the ED, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged into a hospital-at-home program before the exacerbation has resolved. In both cases, once the exacerbation has resolved, the patient is discharged from the hospital-at-home program and no longer receives visits in his/her home.

In the models that exist to date, hospital-at-home programs differ from other home care programs because they deal with higher acuity patients who require higher acuity care, and because hospitals retain the medical and legal responsibility for patients. Furthermore, patients requiring home care services may require such services for long periods of time or indefinitely, whereas patients in hospital-at-home programs require and receive the services for a short period of time only.

Hospital-at-home care is not appropriate for all patients with acute exacerbations of COPD. Ineligible patients include: those with mild exacerbations that can be managed without admission to hospital; those

who require admission to hospital; and those who cannot be safely treated in a hospital-at-home program either for medical reasons and/or because of a lack of, or poor, social support at home.

The proposed possible benefits of hospital-at-home for treatment of exacerbations of COPD include: decreased utilization of health care resources by avoiding hospital admission and/or reducing length of stay in hospital; decreased costs; increased health-related quality of life for patients and caregivers when treated at home; and reduced risk of hospital-acquired infections in this susceptible patient population.

Ontario Context

No hospital-at-home programs for the treatment of acute exacerbations of COPD were identified in Ontario. Patients requiring acute care for their exacerbations are treated in hospitals.

Research Question

What is the effectiveness, cost-effectiveness, and safety of hospital-at-home care compared with inpatient hospital care of acute exacerbations of COPD?

Research Methods

Literature Search

Search Strategy

A literature search was performed on August 5, 2010, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database for studies published from January 1, 1990, to August 5, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists and health technology assessment websites were also examined for any additional relevant studies not identified through the systematic search.

Inclusion Criteria

- English language full-text reports;
- health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials (RCTs);
- studies performed exclusively in patients with a diagnosis of COPD or studies including patients with COPD as well as patients with other conditions, if results are reported for COPD patients separately;
- studies performed in patients with acute exacerbations of COPD who present to the ED;
- studies published between January 1, 1990, and August 5, 2010;
- studies comparing hospital-at-home and inpatient hospital care for patients with acute exacerbations of COPD;
- studies that include at least 1 of the outcomes of interest (listed below).

Cochrane Collaboration reviews have defined hospital-at-home programs as those that provide patients with active treatment for their acute exacerbation in their home by medical professionals for a limited period of time (in this case, until the resolution of the exacerbation). If a hospital-at-home program had not been available, these patients would have been admitted to hospital for their treatment.

Exclusion Criteria

- < 18 years of age
- animal studies
- duplicate publications
- grey literature

Outcomes of Interest

Patient/clinical outcomes

- mortality
- lung function (forced expiratory volume in 1 second)
- health-related quality of life
- patient or caregiver preference
- patient or caregiver satisfaction with care
- complications

Health system outcomes

- hospital readmissions
- length of stay in hospital and hospital-at-home
- ED visits
- transfer to long-term care
- days to readmission
- eligibility for hospital-at-home

Statistical Methods

When possible, results were pooled using Review Manager 5 Version 5.1; otherwise, results were summarized descriptively. Data from RCTs were analyzed using intention-to-treat protocols. In addition, a sensitivity analysis was done assigning all missing data/withdrawals to the event. *P* values less than 0.05 were considered significant. A priori subgroup analyses were planned for the acuity of hospital-at-home program, type of hospital-at-home program (early discharge or admission avoidance), and severity of the patients' COPD. Additional subgroup analyses were conducted as needed based on the identified literature. Post hoc sample size calculations were performed using STATA 10.1.

Quality of Evidence

The quality of each included study was assessed, taking into consideration allocation concealment, randomization, blinding, power/sample size, withdrawals/dropouts, and intention-to-treat analyses.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. The following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Summary of Findings

Fourteen studies met the inclusion criteria and were included in this review: 1 health technology assessment, 5 systematic reviews, and 7 RCTs.

The following conclusions are based on low to very low quality of evidence. The reviewed evidence was based on RCTs that were inadequately powered to observe differences between hospital-at-home and inpatient hospital care for most outcomes, so there is a strong possibility of type II error. Given the low to very low quality of evidence, these conclusions must be considered with caution.

- Approximately 21% to 37% of patients with acute exacerbations of COPD who present to the ED may be eligible for hospital-at-home care.
- Of the patients who are eligible for care, some may refuse to participate in hospital-at-home care.
- Eligibility for hospital-at-home care may be increased depending on the design of the hospital-at-home program, such as the size of the geographical service area for hospital-at-home and the hours of operation for patient assessment and entry into hospital-at-home.
- Hospital-at-home care for acute exacerbations of COPD was associated with a nonsignificant reduction in the risk of mortality and hospital readmissions compared with inpatient hospital care during 2- to 6-month follow-up.
- Limited, very low quality evidence suggests that hospital readmissions are delayed in patients who received hospital-at-home care compared with those who received inpatient hospital care (mean additional days before readmission comparing hospital-at-home to inpatient hospital care ranged from 4 to 38 days).
- There is insufficient evidence to determine whether hospital-at-home care, compared with inpatient hospital care, is associated with improved lung function.
- The majority of studies did not find significant differences between hospital-at-home and inpatient hospital care for a variety of health-related quality of life measures at follow-up. However, follow-up may have been too late to observe an impact of hospital-at-home care on quality of life.
- A conclusion about the impact of hospital-at-home care on length of stay for the initial exacerbation (defined as days in hospital or days in hospital plus hospital-at-home care for inpatient hospital and hospital-at-home, respectively) could not be determined because of limited and inconsistent evidence.
- Patient and caregiver satisfaction with care is high for both hospital-at-home and inpatient hospital care.

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this analysis was to compare hospital-at-home care with inpatient hospital care for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) who present to the emergency department (ED).

Clinical Need and Target Population

Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a disease state that is characterized by a limitation in airflow that is not fully reversible. This airflow limitation is usually both progressive and associated with abnormal inflammatory response of the lungs to noxious particles or gases. (1) The natural history of COPD involves periods of worsening symptoms known as acute exacerbations. There is debate about the best definition for exacerbations; a consensus definition developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines an acute exacerbation as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication." (2) Patients may also experience a variety of other symptoms such as worsening exercise tolerance, fatigue, malaise, and decreased oxygen saturation. (3)

Two-thirds of COPD exacerbations are caused by an infection of the tracheobronchial tree or by air pollution; the cause is unknown in the remaining cases. (2;4) Risk factors for exacerbations include disease severity, winter months, and a previous exacerbation in the previous 8 weeks. (3;5) The frequency of exacerbations seems to vary with disease severity. Using data from the Inhaled Steroids in Obstructive Lung Disease Study (ISOLDE Study), the European Respiratory Society Study on COPD, and the Copenhagen City Lung Study, Donaldson et al (3) found that patients with severe disease (GOLD category III) experienced an average of 3.43 exacerbations per year, whereas patients with moderate disease (GOLD category II) experienced an average of 2.68 exacerbations per year. (3)

Exacerbations have an important impact on patients and on the health care system. For patients, exacerbations result in decreased quality of life, potential permanent loss in lung function, and increased risk of mortality. For patients with severe exacerbations that require hospitalization, estimates of inpatient mortality range from 4% to 30%. Higher hospital mortality rates are observed for patients admitted with respiratory failure. Mortality following discharge is also high: data from the United Kingdom shows a 14% mortality rate within 3 months of readmission, and data from the United States shows a 43% mortality rate after 12 months. (3) Furthermore, exacerbations of COPD are a leading cause of ED visits and hospitalizations, particularly in winter. The health care burden associated with exacerbations is high; inpatient costs for exacerbations have been estimated to account for 70% of total health care costs for COPD treatment. (6;7)

Technology

Hospital-at-home programs offer an alternative to inpatient hospital programs for patients who present to the ED with an exacerbation of COPD that requires hospital admission for treatment. In general, when patients are enrolled in hospital-at-home for COPD exacerbations programs, medical professionals (typically specialist nurses) visit the patients in their home to monitor them, alter their treatment plans if needed, and in some programs, provide additional care such as pulmonary rehabilitation, patient and caregiver education, smoking cessation counselling, etc., and support services. In the programs discussed in the literature, patients remain under the legal and medical responsibility of the hospital while being treated at home.

There are 2 types of hospital-at-home programs: admission avoidance and early discharge hospital-at-home. In admission avoidance hospital-at-home, after being assessed in the ED, patients are prescribed any necessary medications and additional care (e.g., oxygen therapy) and then sent home where they receive visits from medical professionals. Alternatively, patients may be referred directly to admission avoidance hospital-at-home care by their general practitioner, bypassing the ED visit. In contrast, in early discharge hospital-at-home, after being assessed in the ED, patients are admitted to the hospital where they receive the initial phase of their treatment. Following this, they are discharged into hospital-at-home before the exacerbation has resolved. In both cases, once the exacerbation has resolved, the patient is discharged from the hospital-at-home program and no longer receives visits at his/her home.

Cochrane reviews have defined hospital-at-home programs as services that provide patients with active treatment by health care professionals in the patient's home for a condition that otherwise would require acute inpatient hospital care for a limited time period. In other words, if hospital-at-home is not available, the patient would be admitted to an acute hospital ward. (8;9)

Figure 1 shows a comparison of inpatient hospital care and hospital-at-home care (including admission avoidance and early discharge) pathways for acute exacerbations of COPD, as well as admission avoidance and early discharge hospital-at-home options.

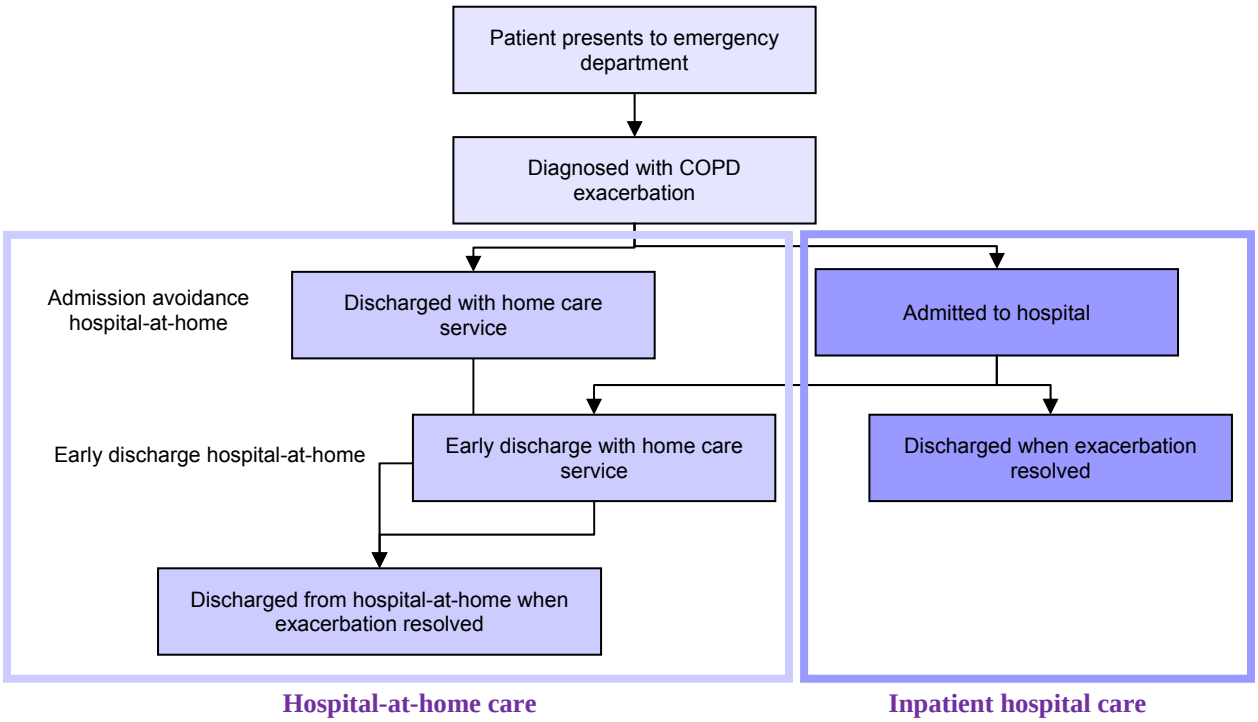


Figure 1: Hospital-at-Home Program Versus Inpatient Hospital Care

Hospital-at-home programs differ from other home care programs partly because they deal with higher acuity patients who require higher acuity care—in this case, patients with severe acute exacerbations of COPD who would otherwise require hospitalization to treat their condition—and partly because hospitals retain the medical and legal responsibility for patients (at least in the COPD models that have existed to date). Furthermore, patients requiring home care services may need these services for long periods of time or perhaps indefinitely; patients in hospital-at-home programs require and receive services for a limited period of time (e.g., until the acute exacerbation has resolved).

Hospital-at-home care is not appropriate for all patients with acute exacerbations of COPD. First, patients with less severe exacerbations that can be managed without admission to hospital are not eligible for hospital-at-home care; this includes those patients who do not present to the ED for their exacerbation or those that can be discharged with some changes in medication only. Second, some patients require admission to the hospital and cannot be safely treated in a hospital-at-home program whether for medical reasons (e.g., diminished consciousness) or lack of adequate social support at home. The issue of appropriate eligibility for hospital-at-home programs is addressed in both the results and in the summary of current hospital-at-home guidelines sections of the evidence-based review section.

The proposed possible benefits of hospital-at-home for exacerbations of COPD include: decreased health care resource utilization through avoided hospital admissions and/or reduced length of stay in the hospital; lower costs; increased health-related quality of life (HRQOL) for both patients and caregivers when patients are treated at home; and reduced risk of hospital-acquired infections in this susceptible patient population.

Ontario Context

No hospital-at-home programs for the treatment of acute exacerbations of COPD were identified in Ontario based on conversations with experts.

Evidence-Based Analysis

Research Question

What is the effectiveness, cost-effectiveness, and safety of hospital-at-home care compared with inpatient hospital care of acute exacerbations of COPD?

Research Methods

Literature Search

Search Strategy

A literature search was performed on August 5, 2010, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews Dissemination database for studies published from January 1, 1990, to August 5, 2010. The search strategy is shown in Appendix 1.

Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists and health technology assessment websites were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English language full-text reports;
- health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials (RCTs);
- studies performed exclusively in patients diagnosed with COPD or studies that included patients with COPD as well as patients with other conditions, if results are reported for COPD patients separately;
- studies performed in patients with acute exacerbations of COPD who present to the ED;
- studies published between January 1, 1990, and August 5, 2010;
- studies comparing hospital-at-home and inpatient hospital care for patients with acute exacerbations of COPD;
- studies that report at least 1 of the outcomes of interest (listed below).

This review adopted the Cochrane definition of hospital-at-home used by Shepperd et al (8;9). As such, studies were only included if the hospital-at-home programs provided patients with active treatment for their acute exacerbation in their home by medical professionals for a limited period of time (in this case, until the resolution of the exacerbation). If a hospital-at-home program had not been available, these patients would have been admitted to hospital for their treatment.

Exclusion Criteria

- < 18 years of age
- animal studies
- duplicate publications
- grey literature

Outcomes of Interest

Patient/clinical outcomes

- mortality
- lung function
- HRQOL
- patient or caregiver preference
- patient or caregiver satisfaction with care
- complications

Health system outcomes

- hospital readmissions
- length of stay in hospital and hospital-at-home
- ED visits
- transfer to long-term care
- days to readmission
- eligibility for hospital-at-home

Statistical Analysis

When possible, results were pooled using Review Manager 5 Version 5.1 (10) to calculate relative risks (RRs) using the Mantel–Haenszel method and a random effects model. If the data could not be pooled, the results were summarized descriptively. Data from RCTs were analyzed using intention-to-treat protocols. *P* values less than 0.05 were considered significant. Post hoc sample size calculations were performed using STATA 10.1.

To account for clinical heterogeneity between the studies, it was decided a priori to conduct subgroup analyses to reflect important differences between studies. These included acuity of hospital-at-home program, type of hospital-at-home program (early discharge or admission avoidance), and the severity of COPD of the patients included in the study. Additional subgroup analyses were completed as needed based on the identified literature.

Quality of Evidence

The quality of each included study was assessed, taking into consideration the following 7 study design characteristics:

- adequate allocation concealment;
- randomization (study must include a description of the randomization procedure used and must be a proper method);
- power/sample size (adequate sample size based on a priori calculations; underpowered studies were identified, when possible, using post hoc sample size power calculations);
- blinding (if double blinding is not possible, a single blind study with unbiased assessment of outcome was considered adequate for this criterion);
- < 20% withdrawals/dropouts;
- intention-to-treat (ITT) analysis conducted and done properly (withdrawals/dropouts considered in analysis); and

- other criteria as appropriate for the particular research question and study design.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (11) as presented below.

- Quality indicates the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency indicates the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness indicates the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

The database search yielded 3,142 citations published between January 1, 1990, and August 5, 2010 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 2 shows the breakdown of when and for what reason citations were excluded in the analysis.

Ten studies (3 systematic reviews and 7 RCTs) met the inclusion criteria. The reference lists of included studies and health technology assessment websites were hand-searched to identify any additional potentially relevant studies. In these, 3 additional citations (1 health technology assessment and 2 systematic reviews) were found, making a total of 13 included citations.

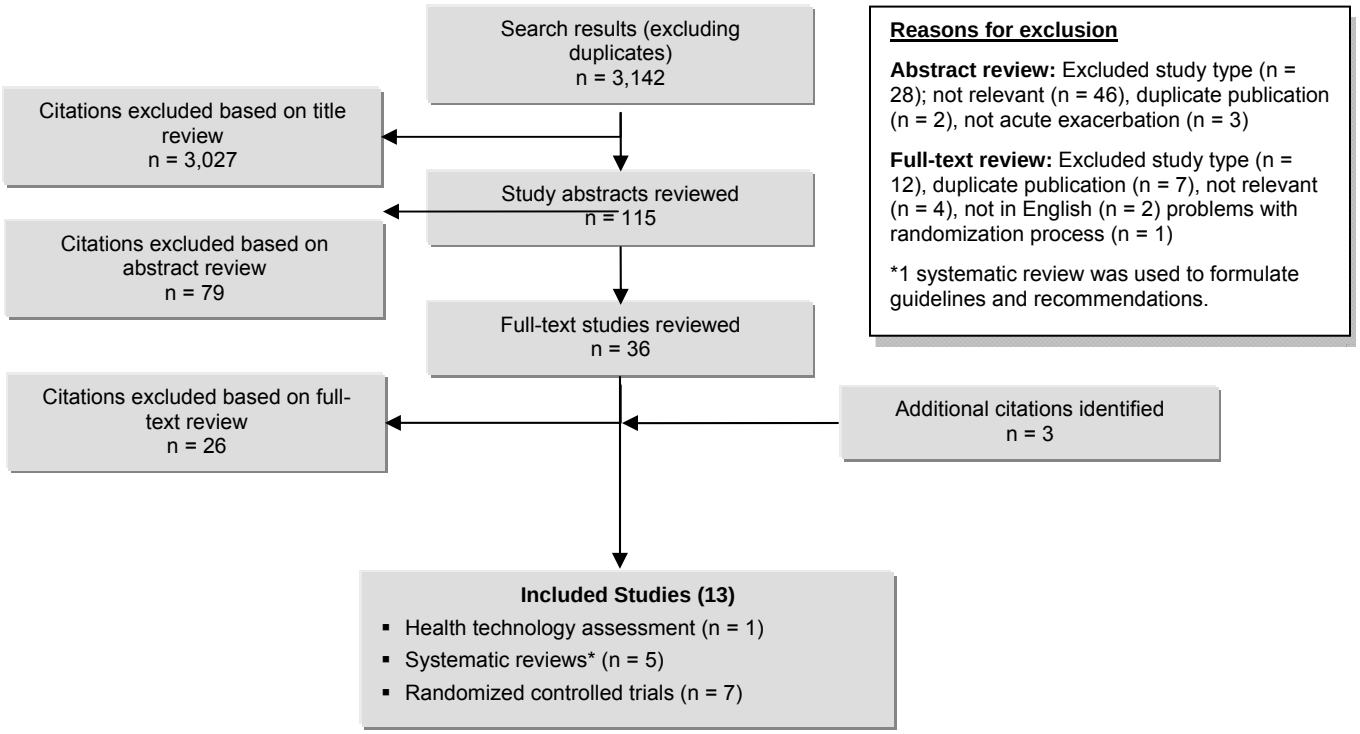


Figure 2: Citation Flow Chart

For each included study, the study design was identified and is summarized below in Table 1, which is a modified version of the hierarchy of study design by Goodman. (12)

Table 1: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	6†
Large RCT‡	3
Small RCT	4§
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	
Total	13

*Abbreviations: RCT, randomized controlled trial.
†Includes 1 health technology assessment and 5 systematic reviews.
‡Large RCT was defined as a trial with more than 100 patients.
§Two of the small RCTs reported results for the same study.

Health Technology Assessments

The National Institute for Clinical Excellence (NICE) in the United Kingdom conducted a systematic review of the effectiveness and cost-effectiveness of numerous interventions for COPD, including hospital-at-home care versus inpatient hospital care for acute exacerbations of COPD. (13) Guidelines and recommendations were developed based on the findings of the systematic reviews. Literature published in MEDLINE (1966 to 2003), EMBASE (1980 to 2003), and CINAHL (1982 to 2003) was reviewed, and 4 RCTs, 1 qualitative study, 1 survey, and 1 service evaluation relevant to the hospital-at-home versus inpatient hospital care question were identified. (13)

The main findings of the systematic review are summarized below:

- There were no significant differences between those patients cared for as part of a hospital-at-home program and those cared for in hospital for the following outcomes:
  - forced expiratory volume in 1 second (FEV_1) (Ib evidence)[1]
  - readmission rates (Ib evidence)
  - number of additional days readmitted patients spent in hospital (Ib evidence)
  - number of days in care (Ib evidence)
  - mortality rates (Ib evidence)
  - symptom scores (Ib evidence)

[1] NICE defines Ib evidence as evidence from at least 1 RCT. (13)

  - additional support services (Ib evidence)
  - patient and caregiver satisfaction scores (Ib evidence) (13)
- The HRQOL results were conflicting: 2 studies showed no statistically significant difference, whereas 1 study showed a significant improvement in the St. George's Respiratory Questionnaire (SGRQ) and Chronic Respiratory Disease Questionnaire between the hospital-at-home and inpatient hospital groups. (13)
- There was limited and inconsistent evidence on the comparative cost of hospital-at-home compared with inpatient hospital care, with 1 study showing an increased cost and another a decreased cost associated with hospital-at-home care. (13)

Based on the results of the systematic review, NICE made the following recommendations:

R138: "Admission discharge and early discharge hospital-at-home programs are safe and effective and should be used as an alternative way of caring for those patients with exacerbations of COPD who would otherwise need to be admitted to or stay in hospital." (GRADE A)[2] (13)

R139: "The multiprofessional team required to operate these schemes should include allied health professionals with experience in managing COPD, and may include nurses, physiotherapists, occupational therapists, and generic health workers." (GRADE D)[3] (13)

R140: "There are currently insufficient data to make firm recommendations about which patients with an exacerbation are most suited for hospital-at-home or early discharge. Patient selection should depend on the resources available and on the absence of factors associated with worse prognosis, for example, acidosis." (GRADE D) (13)

R141: "Patients' preferences for treatment at home or in hospital should be considered." (GRADE D) (13)

MAS Comments

Recommendation 138 is based on the lack of significant differences between hospital-at-home and inpatient hospital care for most of the outcomes examined in this review. Since the included studies were designed as superiority trials, nonsignificant results cannot be used to conclude that hospital-at-home is a safe and effective alternative; such a conclusion requires evidence from equivalency trials.

Systematic Reviews

Of the 11 studies that met the inclusion criteria, 3 were systematic reviews conducted by the Cochrane Collaboration. Ram et al (14) conducted a systematic review of the evidence for hospital-at-home care compared with inpatient hospital care for acute exacerbations of COPD published until August 2003. Seven RCTs were included.

Only the results for the 2 primary outcomes—readmission rates and mortality—could be pooled due to substantial differences in the way the secondary outcomes were measured across studies. The main results comparing hospital-at-home and inpatient hospital care are as follows:

- Based on 7 studies (n = 754), the difference in hospital readmission rates for the hospital-at-home and inpatient hospital care groups was not statistically significant (relative risk [RR], 0.89; 95% confidence interval [CI], 0.72–1.12; $P = 0.33$). (14)

[2] NICE defines GRADE A as evidence based on hierarchy I evidence, which includes systematic reviews, meta-analyses of RCTs, or RCTs. (13)

[3] NICE defines GRADE D as evidence based on hierarchy IV evidence, which includes evidence from expert committee reports or options and/or clinical experience of respected authorities or evidence that is extrapolated from hierarchy I, II, or III. (13)

- Based on 6 studies (n = 729) with 2- to 3-month follow-up, individuals in the hospital-at-home group were 39% less likely to die than those in the inpatient hospital group (RR, 0.61; 95% CI, 0.36–1.05; *P* = 0.08). (14)
- One study identified a statistically significant reduction in the risk of hospital ED visits (with no inpatient admission) in the hospital-at-home group (RR, 0.44; 95% CI, 0.22–0.86; *P* values not reported) over 2 months of follow-up. (14)
- One study found that hospital-at-home patients who were readmitted to hospital during the 3-month follow-up tended to have longer durations of stay than patients in the inpatient hospital group, but this difference was not statistically significant (median days of readmission, 5 vs. 0; *P* = 0.08). (14)
- The studies that measured lung function did not find any statistically significant differences in the changes in FEV_1, forced vital capacity (FVC), or in FEV_1/FVC ratio between the 2 groups. (14) Three studies found no difference in HRQOL between the 2 groups based on the SGRQ. (14)
- No statistically significant difference was observed between the 2 groups in terms of patient or caregiver satisfaction with care (patient satisfaction: RR, 1.04; 95% CI, 0.88–1.24; caregiver satisfaction: RR, 0.97; 95% CI, 0.79–1.19; *P* values not reported). (14)
- More of those patients who were treated at home and more of their caregivers preferred hospital-at-home than patients (RR, 1.17; 95% CI, 1.17–2.04) who were treated in hospital and their caregivers (RR, 1.52; 95% CI, 1.08–2.14). (14)
- A pooled analysis of 2 studies that reported a mean cost analysis found a cost savings of £540 (GBP) per patient with hospital-at-home care compared with inpatient hospital care. (14)
- The reported economic analyses in the included studies were heterogeneous. One study did find a higher mean hospital cost in the hospital-at-home group, but this difference was not statistically significant (£1,389 [GBP] vs. £1,198 [GBP]). (14)
- In the 7 included studies, 26.7% (744/2786) of the patients who presented to the ED for acute exacerbations of COPD were eligible for hospital-at-home care. (14)

The authors concluded that there was no significant difference between hospital-at-home care and inpatient hospital care based on readmission and mortality rates 2 to 3 months after the initial exacerbation. Although hospital-at-home care was determined to be safe, effective, and the preferred option for suitable patients, Ram et al (14) identified the need for further research to determine which patient groups are most suitable; what components of care (including who should deliver the care) provide the greatest benefits; and the cost-effectiveness (considering both the direct and indirect costs) of hospital-at-home care for the treatment of acute exacerbations of COPD. (14)

MAS Comments

The conclusion of this systematic review that hospital-at-home care is safe and effective for suitable patients is based on statistically nonsignificant results from superiority trials, and is hence inappropriate.

The 2 other Cochrane reports were systematic reviews of RCT evidence published up to January 2008 on early discharge hospital-at-home programs and admission avoidance hospital-at-home programs. (8;9) These reviews were conducted in parallel and together represent an update to a previous 2005 Cochrane review. Both reviews analyzed published and unpublished data consisting of individual patient data that were obtained from the authors of many of the included studies.

The Shepperd et al (8) review of early discharge hospital-at-home studies identified 26 RCTs, of which 13 contributed individual patient data. Three of these studies included patients with COPD, whereas the

remainder also included patients with a variety of other medical conditions such as recovery from stroke, hip fractures, and total knee replacement. The analyses stratified the results into 3 groups: patients recovering from strokes, older people with a mix of conditions, and patients having elective surgery. The COPD studies were included in the second group. (8)

Shepperd et al (8) found the following[4]:

- There was a nonsignificant small increase in mortality in the hospital-at-home group using the individual patient data (hazard ratio [HR], 1.06; 95% CI, 0.69–1.61) and published data (RR, 1.12; 95% CI, 0.77–1.63) for the subgroup of older people with a mix of conditions. (8) The direction of the pooled analysis of the published data for the COPD studies alone was the opposite, showing a statistically nonsignificant reduction in mortality in the hospital-at-home group (RR, 0.50; 95% CI, 0.23–1.09). (8)
- There was a significant increase in hospital readmissions for the older people with a mix of conditions in the hospital-at-home care group based on the individual patient data (HR, 1.57; 95% CI, 1.10–2.24) and the published data (RR, 1.35; 95% CI, 1.03–1.76). (8)
- Only 1 of these studies included patients with COPD, and COPD was the diagnosis for only 6% (32/538) of patients in the study. In this study, a nonsignificant increase in hospital readmissions was found in both the COPD patients only and in the study as a whole. (15) (8)
- The COPD trials that measured functional status and/or quality of life found no statistically significant difference between the 2 groups. (8)
- The 5 trials (1 of which included COPD patients) that measured psychological well-being in the subgroup of older people with a mix of conditions found no significant differences between the groups at follow-up. (8)
- Three trials (including 2 with COPD patients) in the subgroup of older people with a mix of conditions found statistically significant increased levels of satisfaction in the hospital-at-home group, although the results in 1 of these studies found improved patient satisfaction for only some of the measured domains. (8)
- Three trials (2 of which included COPD patients) found no statistically significant differences in terms of caregiver satisfaction or burden; however, 1 of the COPD trials found that a significantly greater number of caregivers in the hospital-at-home group were happier with hospital-at-home care. (8)
- The 3 COPD trials found a reduction in hospital stay (range, 1.5–3 days) for the hospital-at-home group, but this reduction was statistically significant in only 1 study. (8)
- Two of the COPD trials measured total days in care, which included both days in hospital and in hospital-at-home care, and found a statistically significant increase in total days of care in the hospital-at-home group. (8)
- Two of the 3 studies with COPD patients found a lower mean health service cost using the average cost per bed-day for patients in the hospital-at-home group, but the third study reported a significant increase in costs when the different resources used during a patient's inpatient admission were taken into account (mean difference, £1,132.00 [GBP]; $P < 0.01$). (8)

Based on the evidence for all of the medical conditions examined, Shepperd et al (8) concluded that there was insufficient objective evidence of economic benefit or improved health outcomes associated with early discharge hospital-at-home programs. Further primary research was recommended in the area of early discharge hospital-at-home for patients recovering from a stroke, patients with an acute exacerbation of COPD, and older patients with medical conditions requiring an acute inpatient hospital stay. (8)

[4] Since only the results that include the COPD patients are relevant for this analysis, the other results are not discussed here.

MAS Comments
The overall conclusions are based on a combination of studies that included patients with conditions other than COPD, so the conclusions may not all be appropriate for the COPD patient population specifically.

The related review on admission avoidance hospital-at-home compared with inpatient hospital care by Shepperd et al (9) identified 10 studies, 5 of which contributed individual patient data. Two of the studies included COPD patients only, whereas the other studies recruited patients with other conditions—recovering from stroke (2 studies), with cellulitis (1 study), with community-acquired pneumonia (1 study), and frail, elderly with dementia (1 study). The results from the studies were pooled and are summarized below[5]:

- The individual patient data from 5 studies (1 of which included COPD patients) showed a nonsignificant reduction in mortality at 3 months (HR, 0.77; 95% CI, 0.54–1.09; $P = 0.15$) and a significant reduction at 6 months (HR, 0.62; 95% CI, 0.45–0.87; $P = 0.005$). (9)
- Three trials (1 of which included COPD patients) found a statistically nonsignificant increase in the rate of hospital readmissions in the hospital-at-home group at the 3-month follow-up (HR, 1.49; 95% CI, 0.96–2.33) using the individual patient data and the published data (RR, 1.18; 95% CI, 0.83–1.67). (9)
- The 5 studies that measured functional ability (including 1 with COPD patients) found nonsignificant differences in most measures. (9)
- One of the COPD studies found that patients in the hospital-at-home group were significantly more likely to be prescribed an antibiotic (difference, 18%; 95% CI, 1.4%–34.6%). (9)
- One of the COPD studies found a lower mean health service cost for patients in the hospital-at-home group using diagnostic-related group categorization to calculate hospital costs (cost per episode mean difference, – £1,798 [GBP], $P < 0.01$). (9)
- One of the COPD trials found an increase in referrals for social support in the hospital-at-home group compared with the inpatient group (24% vs. 6%; difference, 18%; 95% CI, 7.3%–28.6%). (9)

Based on the evidence for admission avoidance hospital-at-home, Shepperd et al (9) concluded that there was no evidence to suggest that admission avoidance hospital-at-home leads to outcomes that differ from inpatient hospital care. As such, they concluded that admission avoidance hospital-at-home can provide an effective alternative to inpatient care for a selected group of elderly patients requiring hospital admission.

MAS Comments
The conclusions of this review are based on nonsignificant results from superiority trials, which is inappropriate. In addition, the overall conclusions are based on a combination of studies that included patients with conditions other than COPD, so the conclusions may not all be appropriate for the COPD patient population.

Soderstrom et al (16) focused on the health and cost effects of hospital-at-home care in a systematic review of the literature published between 1975 and early 1998 on hospital-at-home care for acute conditions, including COPD acute exacerbations. One RCT, which included COPD patients, was identified and rated as a class 1 study based on 6 internal validity criteria developed by the authors (class 1 studies are believed to present valid results despite some methodological issues). This study reported no

[5] Since only the results that include COPD patients are relevant for this analysis, the other results are not discussed here.

difference between hospital-at-home care and inpatient hospital care with regard to patients' health, caregivers' health, or caregivers' and patients' costs. A statistically significant effect, however, was found for social costs[6] and health system costs. (16) The review concluded that hospital-at-home care had no notable effect on health outcomes compared with inpatient hospital care, although the effects on social and health system costs vary by condition. The study recommended further research to determine the appropriate use of acute hospital-at-home care. (16)

> ***MAS Comments***
> The overall conclusions are based on a combination of studies that included patients with conditions other than COPD, so the conclusions may not all be appropriate for the COPD patient population specifically.

The final systematic review identified was published by the British Thoracic Society Guideline Development Group; (17) however, the systematic review component of this paper reviewed the literature on certain questions related to hospital-at-home for COPD exacerbations such as how, where, and by whom should patients be assessed for suitability, and what should comprise hospital-at-home care for the purposes of making recommendations and guidelines. Therefore, the results of this paper are presented in the Guideline section of this evidence-based analysis.

Randomized Controlled Trials

Seven RCTs that met the inclusion criteria were identified and included in this review. Two of the studies reported on the same trial by Shepperd et al (15;18); these papers were not counted as a duplicated publication because they reported on different outcomes, but they are treated as 1 combined study in the following tables and discussion. The general study characteristics, such as the type of hospital-at-home service, and details of the characteristics of the patients included in the studies are shown in Tables A1, A2, and A3 in Appendix 2.

Overall, 3 studies evaluated early discharge programs, 2 studies evaluated admission avoidance hospital-at-home programs, and 2 studies included both early discharge and admission avoidance hospital-at-home programs. In 6 of the 7 studies, specialist nurses conducted the hospital-at-home visits, whereas 1 study used a combination of both physicians and nurses for patient follow-up. The acuity of care provided at home varied widely across the studies; patients in some studies received only basic care and monitoring, whereas patients in others received a variety of additional services including education, counselling, and rehabilitation.

A comparison of the baseline patient population characteristics in Tables A2 and A3 (Appendix 2) show some differences across the study populations:

- In the study by Aimonino Ricauda et al (19), the mean age of patients was higher, the percentage of current smokers was lower, the percentage of nonsmokers was higher, and the percentage of patients with support at home was higher compared with the other studies.
- There was a lower percentage of men in the Shepperd et al (15;18) study compared with the other studies.
- The percentage of patients using home oxygen before the exacerbation was lower in the Skwarska et al (6) study.
- The mean FEV_1 was lower in the Davies et al and Skwarska et al (6;20) trials.

[6] The social cost effect was defined as the effect of home care on public and private costs, including the hospital cost savings from shorter inpatient stays, the public and private costs of the home care program including drugs, supplies, services, etc., and the change in non-health-system costs borne by patients and caregivers including babysitting, transportation, and value of time to manage the condition. (16)

The majority of the identified differences were related to the baseline population characteristics rather than the patients' clinical parameters; however, since the clinical parameters, such as partial pressure of oxygen, were less consistently reported, a thorough comparison of the patient populations is not possible. These differences may account for some of the heterogeneity observed when the results are pooled in the analyses below.

Hospital-at-Home Care Follow-Up Details

The average number of follow-up visits that patients in the hospital-at-home programs received varied substantially between studies (Table 2). Patients in the Aimonino Ricauda et al trial (19) tended to receive the most follow-up home visits, especially as they received visits from both nurses and physicians, whereas patients in the Skwarska et al trial (6) tended to have the fewest visits.

Table 2: Hospital-at-Home Follow-Up Details*

Author, Year	Number of Follow-Up Home Visits, Mean (SD)	Mean Duration of HaH Care, days
Cotton et al, 2000 (21)	Median, 11	Median, 24
Davies et al, 2000 (20)	11 (3)	14†
Ojoo et al, 2002 (22)	NR	NR
Aimonino Ricauda et al, 2008 (19)	Nurse visits: 14.1 (range, 3 – 38); median, 11 Physician visits: 9.9 (range, 2 – 28); median, 8	NR
Shepperd et al, 1998 (15;18)	NR	NR
Skwarska et al, 2000 (6)	3.8	NR

*Abbreviations: HaH, hospital-at-home; NR; not reported; SD, standard deviation.
†Exacerbations settled within 14 days in 96 patients (20).

Eligibility for Hospital-at-Home

In the included studies, only a portion of the patients presenting to the ED or admitted to hospital wards for acute exacerbations of COPD were eligible for hospital-at-home care. The reasons for exclusion varied by study (see Table 3), but the most common reasons were absence of or poor home/social support, severe acidosis or alkalosis, severe comorbidities (e.g., cancer, dementia, renal failure, etc.), and acute chest radiograph changes. Overall, the percentage of patients with COPD exacerbations who were eligible for hospital-at-home care ranged from 20.7% to 36.7% (Table 3).

Table 3: Percentage of Patients Eligible for Hospital-at-Home Care and Refusals

Author, Year	Eligible Patients, % (n)*	Refused Patients, % (n)†
Cotton et al, 2000 (21)	36.7 (151)	24.5 (37)
Davies et al, 2000 (20)	32.9 (192)	21.9 (42)
Ojoo et al, 2002 (22)	34.4 (182)	42.9 (78)
Aimonino Ricauda et al, 2008 (19)	20.7 (208)	11.5 (24)
Shepperd et al 1998 (15;18)	29.0 (95)	36.8 (35)
Skwarska et al, 2000 (6)	–	–

*Eligible Patients indicates the percentage of patients assessed who were deemed eligible for hospital-at-home programs.
†Refused Patients indicates the percentage of patients who were eligible to participate in the trial but who declined.

However, this may underestimate the true number of patients with acute exacerbations of COPD who are eligible for hospital-at-home programs. The early discharge studies generally included only patients who could be discharged within several days of hospitalization (for example, patients in the Davies et al (20) study had to be discharged within 3 days of admission to hospital). Also, many of the programs excluded patients who lived further than a particular distance from the hospital (for example, in Ojoo et al (22), patients were excluded if they lived more than 15 miles from the hospital; in Aimonino Ricauda et al (19), 28% of patients [148 of 529 patients assessed] were excluded because they lived outside of the hospital area). Furthermore, almost all of the trials only included patients who presented to the ED or were admitted to the hospital during particular hours of the day and/or days of the week. In practice, the number of eligible patients could be increased by including patients who have been admitted for longer periods of time in early discharge hospital-at-home programs, by expanding hospital boundaries, particularly in urban areas, and by including patients assessed/admitted on evenings and weekends.

Moreover, not all eligible patients were willing to participate in hospital-at-home programs: 11.5% to 42.9% of eligible patients refused to participate in the included trials (Table 3). It is possible that some of the refusals related to unwillingness to participate in a study rather than an established program.

Length of Stay

The length of stay in hospital-at-home care (includes both days spent in hospital for early discharge hospital-at-home programs and days spent in the hospital-at-home program) and inpatient hospital groups varied across the studies (Table 4). As a result of differences in reporting and measuring, length of stay could not be pooled across the studies. While Shepperd et al (15;18) observed similar lengths of stay in both groups, and Cotton et al (21) observed a shorter length of stay in the hospital-at-home group compared with the inpatient hospital group, 3 other studies observed longer lengths of stay in the hospital-at-home group. However, since many of the hospital-at-home programs did not require home visits every day, patients may have been enrolled in the program longer than was medically necessary simply because the nurse or physician did not visit the patient every day. (6)

Table 4: Length of Stay in First Admission (Hospital + Hospital-at-Home or Hospital)*

	Length of Stay, Mean (SD), days		
Author, Year	**HaH**	**H**	***P* Value**
Cotton et al, 2000 (21)	3.2 (range, 1 – 16)	6.1 (range, 1 – 13)	NR
Davies et al, 2000 (20)	NR	Median, 5 (IQ range, 4 – 7)	NR
Ojoo et al, 2002 (22)	7.4	5.9	0.14
Aimonino Ricauda et al, 2008 (19)	15.5 (9.5)	11.0 (7.9)	0.01
Shepperd et al, 1998 (15;18)	12.27 (3.69)†	12.12 (7.49)	NR
Skwarska et al, 2000 (6)	Median, 7‡	Median, 5	< 0.01

*Abbreviations: H, inpatient hospital care; HaH, hospital-at-home care; IQ, interquartile range; NR, not reported; SD, standard deviation.
†The mean total length of stay includes both days in hospital care and in hospital-at-home care (mean ± SD days in hospital: 6.93 ± 3.39; mean ± SD days in hospital-at-home care: 5.33 ± 3.94). (15;18)
‡Nurse hospital-at-home visits were not always daily, so patients may be in the hospital-at-home program longer than needed. (6)

Mortality

Table 5 shows the number of deaths in the hospital-at-home and inpatient hospital groups. The pooled results (Figure 3) show a nonsignificant reduction in the risk of death during the overall follow-up period (range, 2–6 months) in the hospital-at-home group compared with the inpatient hospital group (RR, 0.68; 95% CI, 0.41–1.12; $P = 0.13$).

Table 5: Mortality Results*

Author, Year	Number of Deaths (%) HaH	H	*P* Value
Cotton et al, 2000 (21)	1 (2.4)	2 (5)	Difference, 2.6% (95% CI, −5.7% to 10.8%)
Davies et al, 2000 (20)	9 (9)	4 (8)	NS
Ojoo et al, 2002 (22)	1 (3.7)	3 (11)	NS
Aimonino Ricauda et al, 2008 (19)	9 (17)	12 (23)	0.72
Shepperd et al, 1998(15;18)	3 (20)	3 (18)	Difference, 2% (95% CI, −25% to 30%); *P* = NS
Skwarska et al, 2000† (6)	4 (3.3)	7 (11.3)	NR

*Abbreviations: CI, confidence interval; H, inpatient hospital care; HaH, hospital-at-home care; NR, not reported; NS, not significant

†All deaths in the hospital-at-home group occurred after discharge from the hospital-at-home program. One death in the inpatient hospital group occurred during the hospitalization period, and the others occurred after discharge from the hospital. (6)

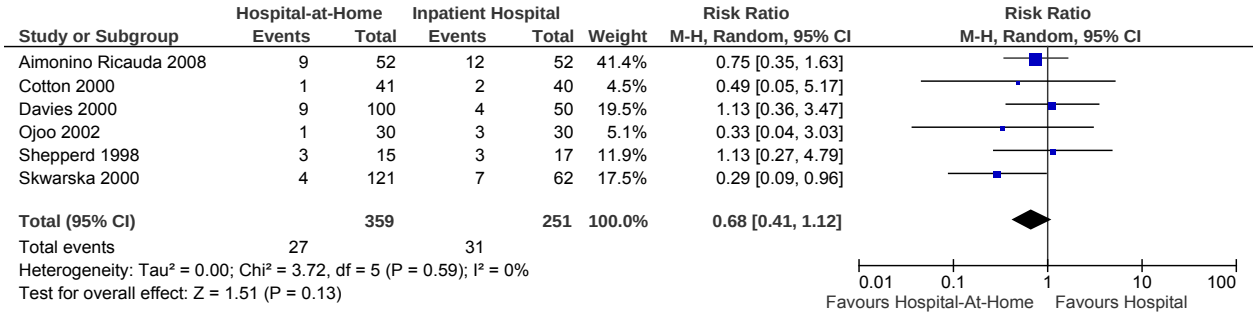


Figure 3: Forest Plot of Pooled Mortality Results*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.

When the results are stratified by the length of the follow-up period (Figure 4), there is a statistically significant reduction in the risk of death at the 2-month follow-up (RR, 0.32; 95% CI, 0.11–0.93; *P* = 0.04), but the results for the 3- and 6-month follow-up remain nonsignificant (3 months: RR, 0.95; 95% CI, 0.42–2.17; *P* = 0.91; 6 months: RR, 0.75; 95% CI, 0.35–1.63; *P* = 0.47). The 2-month results may be more meaningful than the longer follow-up time points because hospital-at-home care is an acute intervention for a complex disease that may not have lasting effects once an exacerbation is treated.

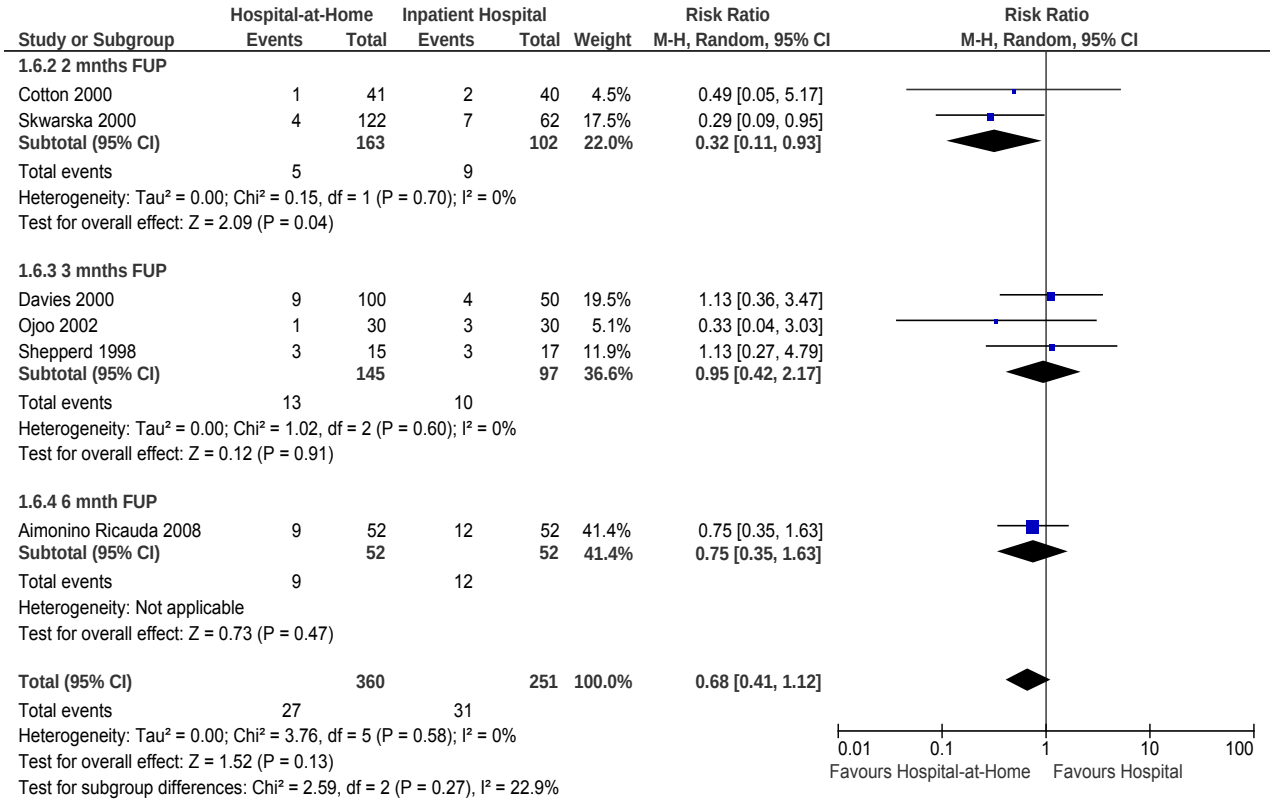


Figure 4: Forest Plot of Pooled Mortality Data by Time Point*

*Abbreviations: CI, confidence interval; FUP, follow-up; M–H, Mantel–Haenszel; mnth, month.

Figures 5 and 6 show the stratified pooled mortality rates by type of program (admission avoidance versus early discharge hospital-at-home) and level of acuity of hospital-at-home care[7]. The trend of a nonsignificant reduction in the risk of death in the hospital-at-home group compared with the inpatient hospital group was maintained for most of the subgroups, but a significant reduction was observed for the early discharge hospital-at-home group (RR, 0.33; 95% CI, 0.13–0.85; $P = 0.02$).

[7]Low acuity hospital-at-home programs were defined as programs in which patients were monitored and treatment adjusted as needed, but no additional care was provided; high acuity programs included additional services such as social support, physical therapy, pulmonary rehabilitation, education, etc.

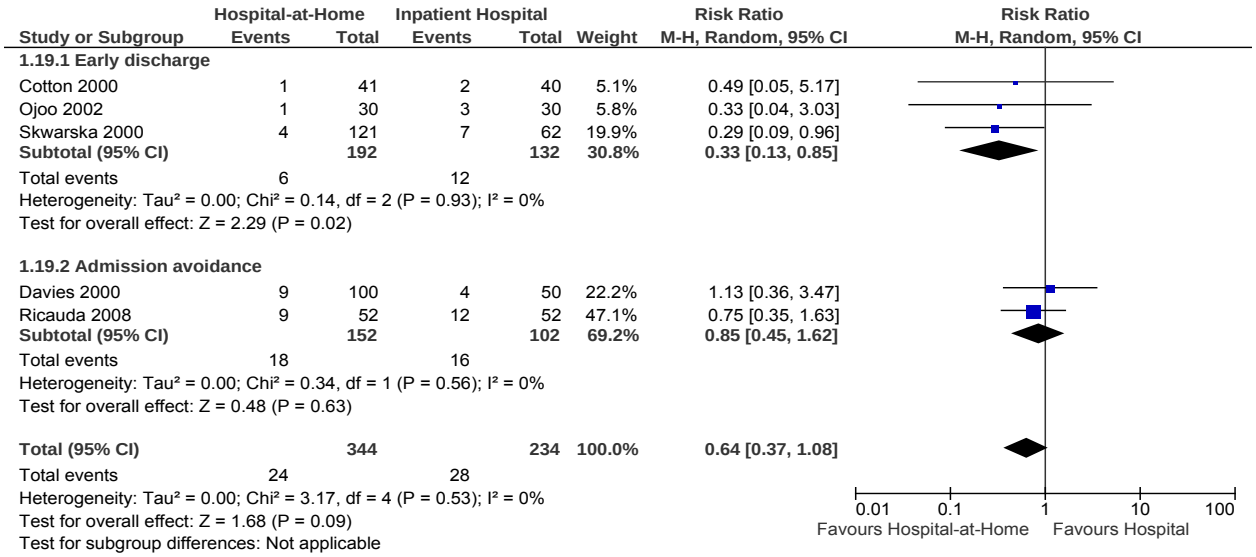


Figure 5: Forest Plot of Pooled Mortality Results by Type of Hospital-at-Home Program*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.
Note: Results for Shepperd et al (15;18) are excluded from the forest plot because this program included both early discharge and admission avoidance hospital-at-home programs.

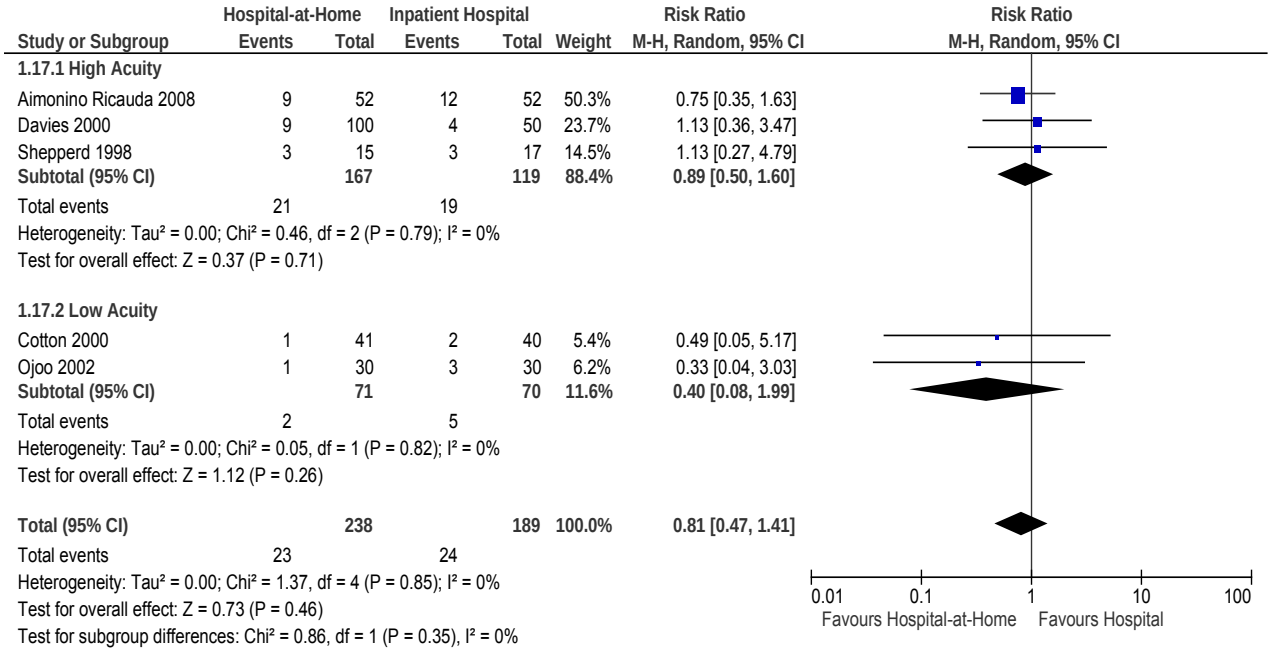


Figure 6: Forest Plot of Pooled Mortality Data by Acuity of Hospital-at-Home Program

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.
Note: Results for Skwarska et al (6) are removed from the pooled data by acuity of hospital-at-home program because it was unclear from the published study whether it involved high or low acuity care.

Hospital Readmissions

Table 6 summarizes the number of patients readmitted to hospital in the hospital-at-home and inpatient hospital groups in the included studies (readmissions to hospital include any patients that were readmitted to the hospital after discharge in the inpatient hospital group and any patients readmitted to the hospital after entry into the hospital-at-home group or after discharge from the hospital-at-home program).

Table 6: Hospital Readmission Results*

Author	Number of Readmissions (%)		
	HaH	H	*P* Value
Cotton et al, 2000 (21)	12 (29.3)	12 (30)	NR
Davies et al, 2000 (20)	37 (37)†	17 (34)	NS
Ojoo et al, 2002 (22)	12 (40.0)‡	13 (44.4)	NS
Aimonino Ricauda et al, 2008 (19)	20 (38)§	34 (87)	0.001‖
Shepperd et al, 1998 (15;18)	8 (53)	6 (35)	NS
Skwarska et al, 2000 (6)	39 (32.0)¶	21 (33.9)#	NR

*Abbreviations: H, inpatient hospital care; HaH, hospital-at-home care; NR, not reported; NS, not significant; SD, standard deviation.

†It is unclear from the study results whether the 37 patients readmitted to hospital included the 9 patients readmitted during the first 14 days after randomization or if it only includes patients readmitted after being discharged from hospital-at-home care. So as to not count these patients twice, it was assumed that the 9 patients were included in this total. The authors were contacted to confirm this assumption, but no response has yet been received.

‡While the trial reported only 10 patients (33.3%) in the hospital-at-home group, 2 patients in this group were readmitted to hospital due to clinical deterioration before being discharged from hospital-at-home care. The authors counted these patients as failures to complete the trial, although it would be more appropriate to count them as readmissions to hospital. As a result, they have been added to the 10 other readmissions reported in the table above.

§While the published results reported only 17 patients being readmitted, this did not include the 3 patients in the hospital-at-home group who were readmitted not because of their own health but because of their caregivers' failing health. As a result, 20 readmissions are counted in this analysis.

‖The reported *P* value is based on the comparison between 17 patients in the hospital-at-home group and 34 in the inpatient hospital group and does not take into account the additional 3 patients in the hospital-at-home group who were readmitted during the hospital-at-home treatment phase.

¶ Of the readmitted patients, 12 were readmitted during the hospital-at-home follow-up period (9 for respiratory reasons and 3 for nonrespiratory reasons) and 27 were readmitted during the follow-up period after discharge from the hospital-at-home program (23 for respiratory reasons and 4 for nonrespiratory reasons). (6) Statistical significance was calculated only for readmissions after hospital-at-home discharge and before final follow-up; this comparison was not statistically significant.

#All 21 patients were readmitted during the follow-up period after discharge from the hospital, 19 for respiratory reasons and 2 for nonrespiratory reasons.

When the readmission results are pooled (Figure 7), there is a nonsignificant reduction in the risk of hospital readmissions during the overall follow-up period (2 to 6 months) in the hospital-at-home group compared with the inpatient hospital group (RR, 0.90; 95% CI, 0.70–1.16; $P = 0.41$).

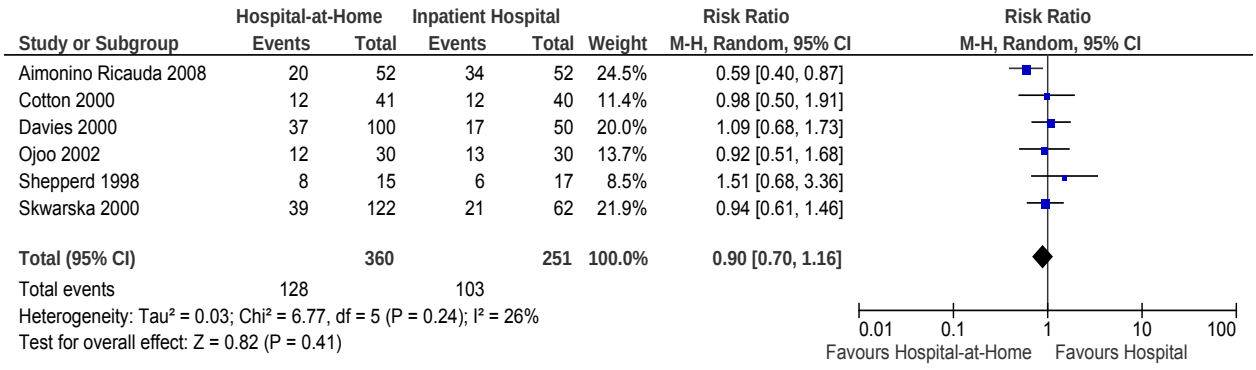


Figure 7: Forest Plot of Pooled Hospital Readmissions*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.

In the hospital-at-home group, patients could be readmitted to the hospital either "early" during the hospital-at-home care period or "late" during the follow-up period (after discharge from hospital-at-home but before final follow-up). As shown in Table 7, both early and late readmissions occurred; readmissions during the hospital-at-home period accounted for 13% to 50% of the total readmissions in the hospital-at-home group (weighted average, 24.0%). These results should be considered with caution because readmissions were not always clearly defined as early and late in the published results[8], so some assumptions had to be made to reach the results shown in Table 7.

Table 7: Early Versus Late Readmissions in the Hospital-at-Home Group

Author, Year	Number of Early Readmissions* (% of total readmissions)	Number of Late Readmissions* (% of total readmissions)	Total Number of Readmissions
Cotton et al, 2000 (21)	6† (50)	6† (50)	12
Davies et al, 2000 (20)	9‡ (24)	28‡ (76)	37
Ojoo et al, 2002 (22)	2§ (17)	10§ (83)	12§
Aimonino Ricauda et al, 2008 (19)	3‖ (15)	17‖ (85)	20‖
Shepperd et al, 1998 (15;18)	1 (13)	7 (88)	8
Skwarska et al, 2000 (6)	9 (25)	27 (75)	36

*Early readmissions were defined as those that occurred before patients were discharged from the hospital-at-home program. Late readmissions were defined as readmissions that occurred after discharge from hospital-at-home and before final follow-up.
†The number of patients readmitted early compared with those readmitted late is not specified in the published results. Using the information that the average length of stay in hospital was 3.2 days and the median duration of nurse follow-up was 24 days, and according to Table 3 in the paper, 6 patients in the hospital-at-home group were readmitted to hospital within the first 30 days from the index admission. (21) The study authors were contacted to determine the exact number of early versus late readmissions, but no response has yet been received.
‡It is unclear from the results whether the 37 patients readmitted to hospital includes the 9 patients readmitted during the first 14 days after randomization, or if this only includes patients readmitted after being discharged from hospital-at-home care. So as not to count these patients twice, it was assumed that the 9 patients were included in this total, resulting in 28 patients being admitted in the late readmission category. The authors were contacted to confirm this assumption, but no response has yet been received.
§It is unclear in the published results whether any of the 10 reported readmissions occurred during the hospital-at-home period. Two patients in the hospital-at-home group were, however, excluded from the results of the trial because they were readmitted to hospital as a result of clinical deterioration. Given that the deterioration led to readmission, these 2 patients should have been treated as readmissions rather than excluded from the trial. It was assumed that none of the 10 readmissions reported occurred during the early follow-up period as they would have also been excluded. The authors of the study have been contacted for clarification, but no response has been received to date.
‖The 3 patients reported as being readmitted before discharge from the hospital-at-home program were readmitted due to failing caregiver health and not the patients' health. Based on information received from the authors of the study, these 3 patients were not included in the 17 reported readmissions.

When the results are stratified by the length of the follow-up period (Figure 8), there is a statistically significant reduction in the risk of hospital readmissions at the 6-month follow-up (RR, 0.59; 95% CI, 0.40–0.87; $P = 0.009$). The results remain nonsignificant at 2 and 3 months; however, the 3-month time point shows a nonsignificant increase in the risk of hospital readmissions in the hospital-at-home group instead of a reduced risk as shown at 2- and 6-months follow-up.

[8] Authors were contacted to clarify the number of early and late readmissions in their studies, but no responses have been received to date.

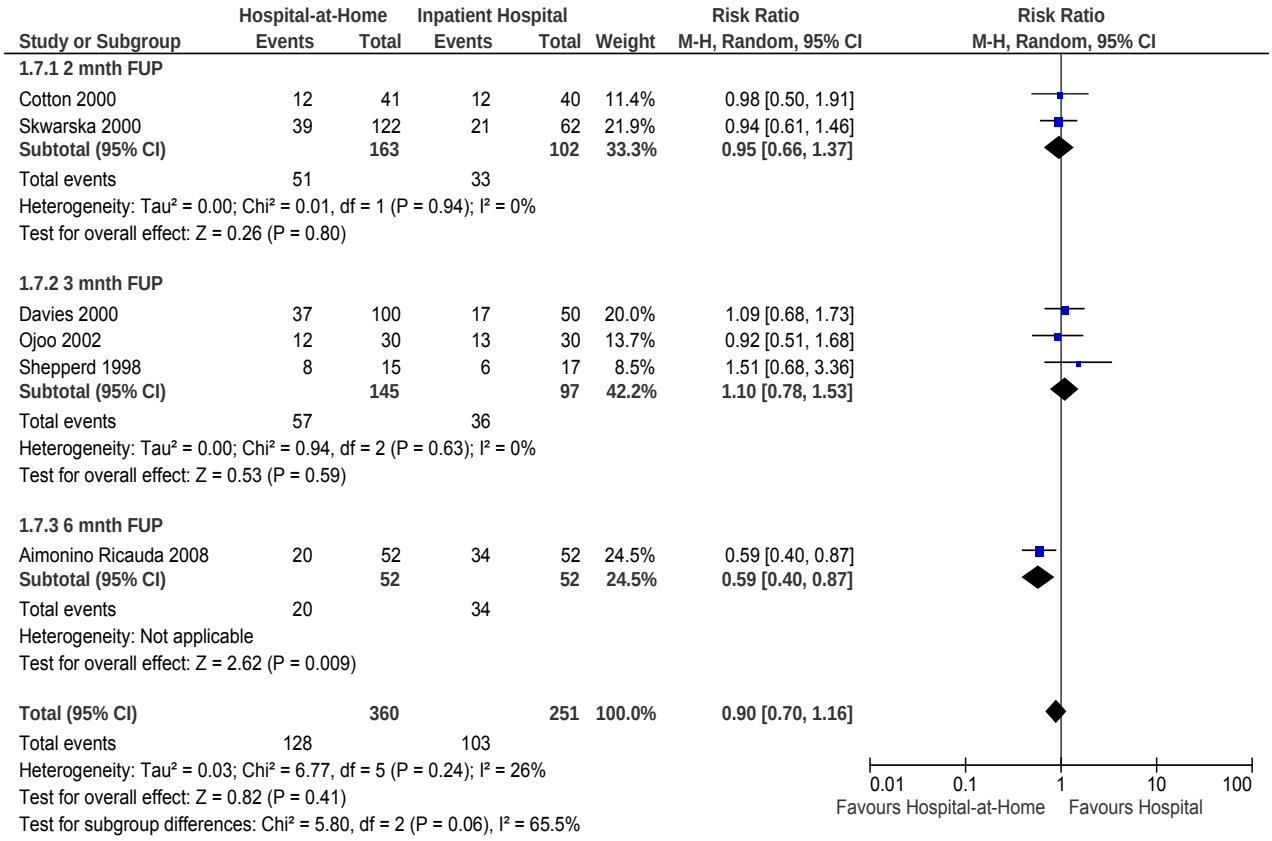


Figure 8: Forest Plot of Pooled Hospital Readmissions by Time Period*

*Abbreviations: CI, confidence interval; FUP, follow-up; M–H, Mantel–Haenszel; mnth, month.

When the results were stratified by type of hospital-at-home program and acuity of hospital-at-home care (Figures 9 and 10), there was a nonsignificant reduction in the risk of hospital readmissions for hospital-at-home care in all the subgroups.

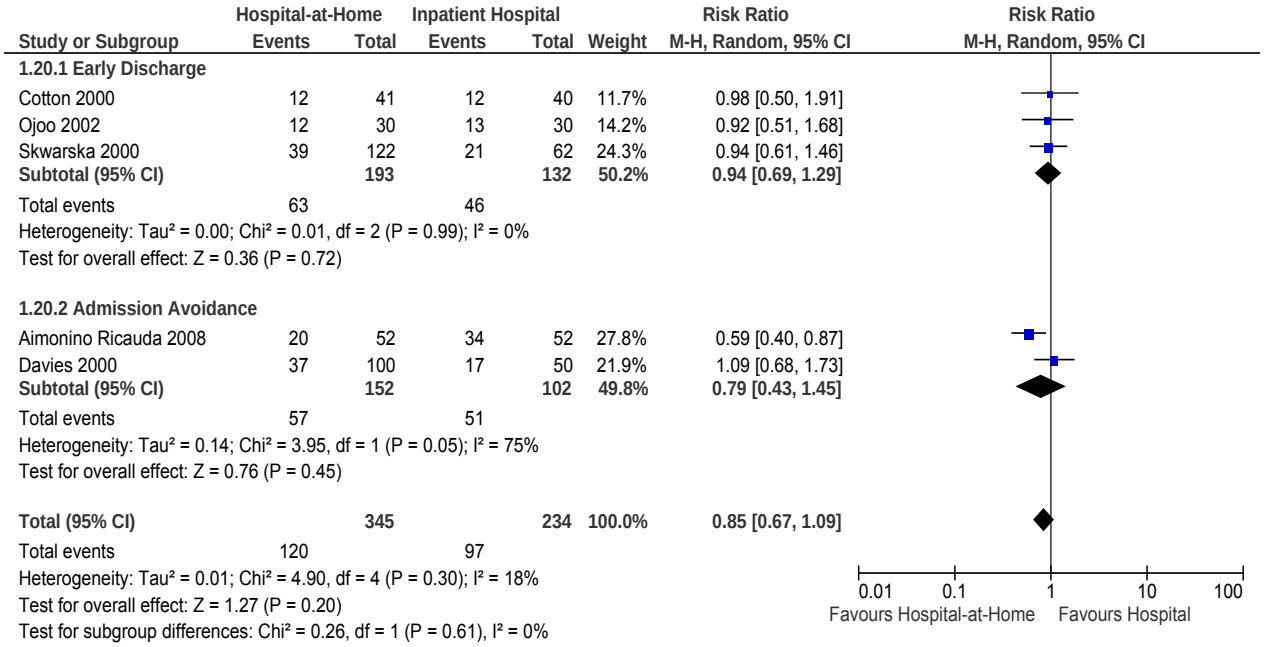


Figure 9: Forest Plot of Pooled Hospital Readmissions by Type of Hospital-at-Home Program*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.
Note: The results from Shepperd et al (15;18) are excluded from the above analysis as it includes both early discharge and admission avoidance hospital-at-home programs.

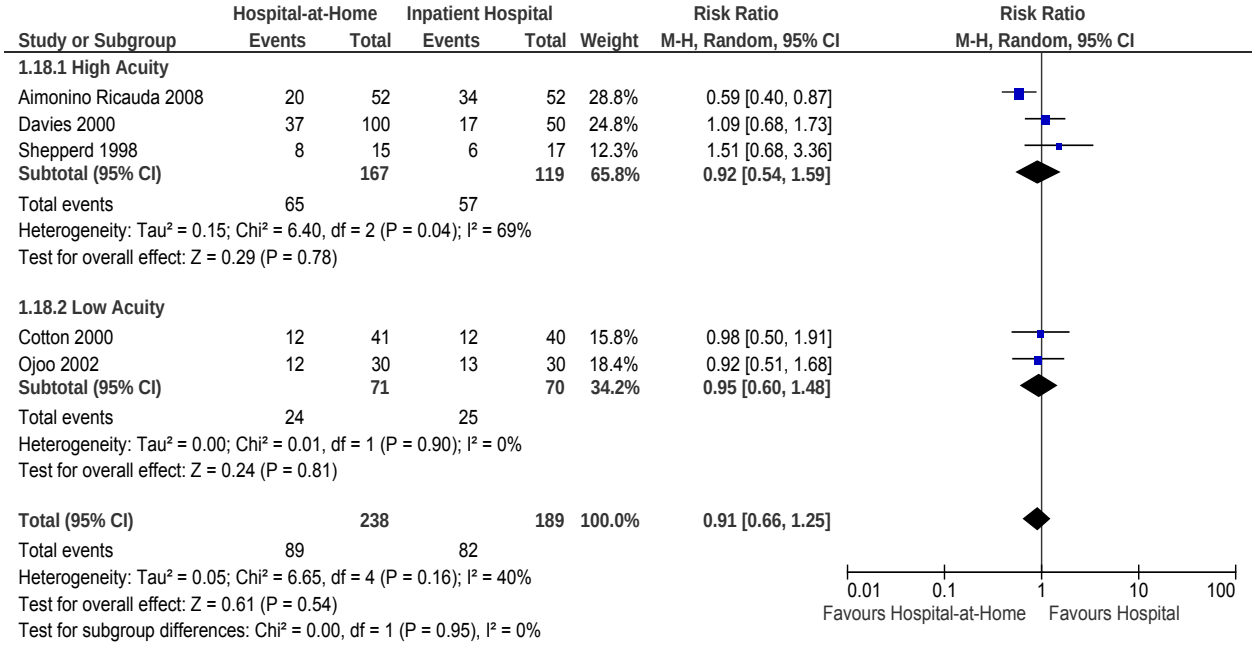


Figure 10: Forest Plot of Pooled Hospital Readmissions by Acuity of Hospital-at-Home Program*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.
Note: The results from Skwarska et al (6) were excluded from the above analysis as it was unclear from published results if the hospital-at-home program provided low or high acuity care.

Days to Readmission

Two studies reported the mean number of days to readmission. Both found a longer mean number of days before admission in the hospital-at-home group compared with the inpatient hospital group (29.6 days vs. 25.6 days in Cotton et al (21) and 75 ± 55 days vs. 37 ± 29 days in Aimonino Ricauda et al (19)). Therefore, comparing hospital-at-home and inpatient hospital care groups, the mean additional days before readmission ranged from 4 to 38 days. It was not possible to pool these results, however, because the studies reported different time periods (days from the day of the first admission in Cotton et al (21) versus days from the first day of discharge in Aimonino Ricauda et al (19)).

While both studies show that readmissions were delayed in patients in the hospital-at-home group, the absolute benefit varied greatly (difference: hospital-at-home group [HaH], 45.4 days; inpatient hospital group [H], 11.4 days). One reason for this variation is the difference between the hospital-at-home programs in the 2 trials. In the Cotton et al trial (21), the hospital-at-home program was limited to assessing and monitoring patients and did not include any additional services; in contrast, in the Aimonino Ricauda et al trial, the hospital-at-home patients received a range of additional services including physical therapy, occupational therapy, education and nutritional advice, as well as a full geriatric assessment. (19) These additional services may lead to benefits in patients' COPD disease management as well as management of other comorbidities and result in a longer delay in the amount of time before hospital readmissions.

Number of Additional Days in Hospital

Two studies also reported the mean number of additional days in hospital for the patients who were readmitted. Cotton et al (21) found that patients in the hospital-at-home group spent fewer additional days in the hospital than patients in the inpatient hospital group (7.83 vs. 8.75 days; difference, 0.92; 95% CI, −6.5 to 8.3). In contrast, Shepperd et al (18) found that the median number of days before readmission was longer in the hospital-at-home group compared with the inpatient hospital group (HaH: 5.00 days; interquartile range [IQ], 0.00–10.00; H, 0.00 days; IQ, 0.00–3.00), but this difference was not significant ($P = 0.08$).

Lung Function

Forced Expiratory Volume in One Second

Lung function was measured in 3 of the included studies, but it was not possible to pool these results because of different outcomes and methods of measurement. Two of the studies reported the mean change in FEV_1. Davies et al (20) reported the mean change in postbronchodilator FEV_1 between admission and the 3-month follow-up, and Ojoo et al (22) reported the mean change in FEV_1 between admission and discharge. As shown in Table 8, both studies observed mean improvements in FEV_1 in the hospital-at-home and inpatient hospital groups.

Table 8: Lung Function Results Using Mean Change in FEV_1*

		Change in FEV_1, Mean (SD), L		
Author, Year	Time of Assessment	HaH	H	*P* Value
Davies et al, 2000 (20)	3-months FUP	0.11 (0.34)	0.14 (0.32)	NR
Ojoo et al, 2002 (22)	At discharge	0.16 (0.26)	0.06 (0.27)	NS

*Abbreviations: FEV_1, forced expiratory volume in 1 second; FUP, follow-up; H, inpatient hospital; HaH, hospital-at-home; L, litres; NR, not reported; NS, not significant; SD, standard deviation.

Skwarska et al (6) reported FEV_1 at baseline, discharge, and final follow-up for comparisons within the hospital-at-home and inpatient hospital groups between baseline and discharge and discharge and final follow-up. In the hospital-at-home group, the study found a significant improvement in FEV_1 between baseline and discharge (mean change, 0.16 litres [L]; $P < 0.01$). The other changes in FEV_1 in the hospital-at-home and inpatient hospital groups were not significant. The study did not compare FEV_1 values or the mean changes in FEV_1 between the hospital-at-home and hospital groups; however, the FEV_1 at the time of discharge was substantially higher in the hospital-at-home group than in the hospital group (HaH, 0.92 L; H, 0.72 L), and it remained slightly higher at the end of follow-up (HaH, 1.05 L; H, 0.94 L).

Other Lung Function Measures

Skwarska et al (6) also measured the change in respiratory rate, peak expiratory flow, and oxygen saturation between admission and discharge and between discharge and final follow-up for the hospital-at-home and inpatient hospital groups. There were significant mean improvements between admission and discharge for respiratory rate, peak expiratory flow, and oxygen saturation in both hospital-at-home and inpatient hospital groups, and for the mean change in oxygen saturation between discharge and final follow-up in the inpatient hospital group. The mean change between the 2 arms of the study was not compared, but the peak expiratory flow was substantially lower in the inpatient hospital group at all time points (H vs. HaH: 146.8 L vs. 175.3L; 168.8 L vs. 215.6 L; 171.0 L vs. 233.3 L; and 181.3 L vs. 220.7 L at admission, discharge, discharge, and final follow-up, respectively). (6)

Ojoo et al (22) measured the mean improvement in FVC between admission and discharge and found no significant difference between the hospital-at-home and inpatient hospital groups (mean improvement [SD]: 0.12 [0.65] vs. 0.17 [0.55]; *P* = not significant).

Health-Related Quality of Life

Five studies reported HRQOL results. Since each used different scales or reported the results differently, it was not possible to pool the results. Table 9 summarizes the results by study. Overall, the HRQOL results are inconsistent across the included studies: 1 study observed statistically significant improvements in the hospital-at-home group for some HRQOL measures, whereas 4 studies found no statistically significant differences in HRQOL between the groups.

Table 9: Summary of HRQOL Results*

Author	HRQOL Measure	Overall Results
Davies et al, 2000 (20)	SGRQ	No significant difference between baseline and follow-up values in either H or HaH groups for all domains†
Ojoo et al, 2002 (22)	Symptom score‡	No significant difference between groups
Aimonino Ricauda et al, 2008 (19)	Geriatric Depression Scale Nottingham Health Profile Activities of Daily Living score Instrumental Activities of Daily Living score Mini-Mental State Examination score Mini-Nutritional Assessment score Relatives' Stress Scale score	Significant improvement in Geriatric Depression Scale ($P < 0.01$) and Nottingham Health Profile score ($P = 0.04$) in the HaH group compared with the H group
Shepperd et al, 1998 (15;18)§	Dartmouth CO-OP Charts Chronic Respiratory Disease Questionnaire	No significant differences observed between groups for any domains of the Dartmouth CO-OP Charts or Chronic Respiratory Disease Questionnaire
Skwarska et al, 2000 (6)	Chronic Respiratory Disease Questionnaire	No significant difference between the groups on any domain‖

*Abbreviations: H, inpatient hospital; HaH, hospital-at-home; HRQOL, health-related quality of life; SGRQ, St. George's Respiratory Questionnaire.
†No comparison between the mean change in score between the hospital-at-home and the inpatient hospital groups was provided in the paper. (21)
‡Symptom score was calculated by assessing breathlessness, cough, ability to walk, anxiety, sputum production, sputum consistency, and sputum colour. (22)
§HRQOL baseline results were defined as HRQOL measurements at 1-month follow-up. (15;18)
‖Actual results were not provided in the paper. (6)

With the exception of Ojoo et al (22), the studies examined HRQOL at the end of the follow-up period, ranging from 2 to 6 months after the patient was enrolled in the study. The nonsignificant differences between the groups could be due to the time point at which HRQOL was measured. An improvement in HRQOL attributable to treatment at home instead of in the hospital might be best measured during or immediately after the treatment of the exacerbation, rather than several months later, by which time, the exacerbation has resolved and the patient is back in his/her home. Furthermore, the trials that examined HRQOL were not powered to look at this outcome, so type II error may explain a lack of significant difference between the groups.

Although Ojoo et al (22) examined HRQOL at a more appropriate time point—comparing mean symptom scores at admission and discharge—the paper was unclear as to whether the calculated symptom score was a validated tool that was adequately sensitive to detect differences in HRQOL between the groups.

Patient and Caregiver Preference

Ojoo et al (22) measured preference of hospital-at-home versus inpatient hospital care by asking patients and caregivers in the respective groups whether they would prefer hospital-at-home care. Patients in the hospital-at-home group were significantly ($P = 0.001$) more likely to prefer hospital-at-home care than patients in the inpatient hospital group: 96.3% (26/27) of patients in the hospital-at-home group preferred hospital-at-home care, whereas only 59.3% (16/27) of patients in the inpatient hospital group preferred hospital-at-home care. (22) Similarly, caregivers in the hospital-at-home group were significantly ($P = 0.01$) more likely to prefer hospital-at-home care than caregivers in the inpatient hospital group: 85.7% (17/20) compared with 42.9% (6/14) caregivers preferred hospital-at-home care in the hospital-at-home and inpatient hospital groups, respectively. (22) The authors suggest that these results are due to the positive experiences that patients/caregivers are receiving in the hospital-at-home program.

Since Ojoo et al (22) measured patient and caregiver preference after completion of the care, the study does not provide information on patients' preference for hospital-at-home care before their enrolment in a program. The results suggest that once patients have experienced hospital-at-home care, they are substantially more likely to prefer this treatment option for future exacerbations. The results also suggest that some patients and caregivers may be hesitant to enter hospital-at-home, which reinforces the previous finding that 12% to 43% of patients may refuse to enter hospital-at-home programs. (This refusal rate may be falsely high because the hospital-at-home programs were in the context of RCTs and may lack external validity.) While this information may be useful if such a program were implemented, also needed is a comparison of patients' and caregivers' preference for hospital-at-home care between the groups at baseline.

Patient and Caregiver Satisfaction with Care

Of the included studies, 3 measured patient satisfaction with care and 1 measured caregiver satisfaction with care. (6;19;22) Overall, most patients were satisfied with the care in both the hospital-at-home and inpatient hospital groups (Table 10). None of the studies observed a significant difference between the 2 groups. Similarly, Ojoo et al (22) did not find a significant difference between the hospital-at-home and inpatient hospital caregivers' satisfaction (mean satisfaction score: HaH, 92.70%; H, 91.30%). Type II error must be taken into consideration, however, because the studies were not adequately powered to examine satisfaction with care.

Table 10: Summary of Patient Satisfaction Results*

		Satisfaction Results (% of Patients)		
Author	**Satisfaction Measure**	**HaH**	**H**	***P* value**
Ojoo et al, 2002 (22)	Mean satisfaction score (%)	91.7	88.1	NS
Aimonino Ricauda et al, 2008 (19)	Number of patients (%) who rated care as very good/excellent at discharge	49 (94)	46 (88)	0.83
	% patients completely satisfied with care	95	–†	n/a
Skwarska et al, 2000 (6)	% patients felt they were cared for as well or better than care would have been if hospitalized	90	–†	n/a

*Abbreviations: H, inpatient hospital; HaH, hospital-at-home; n/a, not applicable; NS, not significant
†Patients in the inpatient hospital group were not asked about their satisfaction with care.

Other Reported Outcomes

Medical Complications

Aimonino Ricauda et al (19) found a significant reduction in the incidence of urinary tract infections in the hospital-at-home group compared with the inpatient hospital group (HaH vs. H: 6% vs. 1%; $P = 0.049$). The incidence rates for other medical complications were not significantly different between the groups, but these results must be considered with caution because the risk of type II error is high. (19)

Place of Residence after Discharge

Aimonino Ricauda et al (19) observed a nonsignificant reduction in the risk of transfer to long-term care after resolution of the exacerbation: 6 patients in the inpatient hospital group (n = 52 patients) were transferred to long-term care after discharge compared with no patients in the hospital-at-home group (n = 52). While this difference was not statistically significant, the risk of type II error for this outcome is high.

Additional Health Care Use

Skwarska et al (6) compared visits to general practitioners and informal caregiver visits between the hospital-at-home and inpatient groups during the follow-up period. While the number of general practitioner visits per 100 patient-days (1.07 vs. 0.70) and the number of caregiver visits (36 vs. 21) were higher in the inpatient hospital group compared with the hospital-at-home group, these differences were not significant. (6) Once again, the risk of type II error for these outcomes is high.

Quality of Evidence

The analysis is based on RCT evidence, but, according to the information available in the published papers,[9] the majority of the studies had serious methodological issues, including lack of allocation concealment, unclear methods used for randomization, unclear blinding of those conducting outcome assessment, inadequate sample sizes to eliminate type II error (based on post hoc sample size calculations when possible), and improper ITT analyses (withdrawals/dropouts ignored) (summarized in Table A4 in Appendix 3).

The quality of the overall body of evidence on hospital-at-home care for acute exacerbations of COPD was evaluated using the GRADE system (Table A5 in Appendix 3) and was found to be **low to very low**. (11) Due to the uncertainty associated with low and very low quality evidence, further research is likely to have an impact on the confidence in the estimate of effect and is likely to change the estimate. (11)

[9] It is possible that some of the methodological flaws which were identified in these studies were not actual flaws but the result of incomplete reporting in the published methods.

Economic Analysis

The results of the economic analysis are summarized in issue 12 of the COPD series entitled *Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model*. This report can be accessed at: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Economic_March.pdf.

The results from the systematic review of the clinical evidence for hospital-at-home programs for the treatment of acute exacerbations of COPD were not included in the economic model because of the low to very low quality of evidence and the lack of significant findings for the model inputs.

Conclusions

The following conclusions are based on low to very low quality of evidence. The reviewed evidence was based on RCTs that were inadequately powered to observe differences between hospital-at-home and inpatient hospital care for most outcomes, so there is a strong possibility that type II error is an issue. Given the low to very low quality of evidence, these conclusions must be considered with caution.

- Approximately 21% to 37% of patients with acute exacerbations of COPD who present to the ED may be eligible for hospital-at-home care.
- Of the patients who are eligible for care, some patients may refuse to participate in hospital-at-home care.
- Eligibility for hospital-at-home care may be increased depending on the design of the hospital-at-home program such as the size of the geographical service area for hospital-at-home and the hours of operation for patient assessment and entry into hospital-at-home.
- Hospital-at-home care for acute exacerbations of COPD was associated with a nonsignificant reduction in the risk of mortality and hospital readmissions compared with inpatient hospital care during 2- to 6-months follow-up.
- Limited, very low quality evidence suggests that hospital readmissions are delayed after hospital-at-home care compared with inpatient hospital care (mean additional days before readmission comparing hospital-at-home to inpatient hospital care ranged from 4 to 38 days).
- There is insufficient evidence to determine whether hospital-at-home care, compared with inpatient hospital care, is associated with improved lung function.
- The majority of studies did not find significant differences between hospital-at-home and inpatient hospital care for a variety of HRQOL measures at follow-up. The follow-up time point chosen to measure HRQOL, however, may be too late to observe an impact of hospital-at-home care on HRQOL.
- Due to limited and inconsistent evidence, conclusions about the effect of hospital-at-home care on length of stay (defined as days in hospital or days in hospital plus hospital-at-home care for inpatient hospital and hospital-at-home, respectively) for the initial exacerbation, could not be determined.
- Patient and caregiver satisfaction with care is high for both hospital-at-home and inpatient hospital care.

Existing Guidelines for Hospital-at-Home for Acute Exacerbations of COPD

The British Thoracic Society Guideline Development Group developed guidelines for hospital-at-home care for COPD acute exacerbations using the National Institute for Health and Clinical Excellence (NICE) Guideline Development Methods to answer the following questions:

- How, where, and by whom should patients be assessed for suitability for hospital-at-home?
- Should hospital-at-home aim to avoid admission or to implement early supported discharge?
- Should the service be limited to 9:00 to 17:00 hours Monday to Friday or should its hours of operation be more extended?
- What proportion of patients with exacerbations of COPD will be suitable for hospital-at-home?
- Should the hospital-at-home team be composed of specialist practitioners or could it be generic?
- Does hospital-at-home require modification of treatment policy?
- What competencies are necessary to deliver hospital-at-home?
- What should comprise hospital-at-home care?
- How many visits will be necessary and for how long?
- Would stable COPD patients benefit from intermediate care? (17)

The Guideline Development Group conducted a systematic review of the literature published between 1966 and April 2005 (as well as any additional studies identified by members of the group published after the inclusion dates) to identify studies that helped to answer the above questions. (17) Based on review of the evidence and using the NICE levels of evidence and recommendations, the Guideline Development Group recommended that:

- A hospital should use an assessment proforma, protocol, or integrated care pathway (ICP) if setting up an integrated care service in order to deliver uniform care and facilitate audit. (Grade D) (17)
- Hospital-at-home should not be offered to patients with:
  - impaired level of consciousness (Grade C),
  - acute confusion (Grade C),
  - pH < 7.35, if arterial blood gases have been measured (Grade C),
  - acute changes on chest radiograph (Grade C),
  - concomitant medical problem requiring inpatient stay (Grade C),
  - insufficient social support, no telephone, residence geographically removed from hospital (Grade C), and/or
  - new hypoxemia (saturation level of oxygen in haemoglobin measured by pulse oximetry [SpO_2] ≤ 90%) – a contraindication if oxygen cannot be provided at home (Grade D). (17)
- Blood tests need not be routinely performed when considering patients for home management of their exacerbation but should be available if they are indicated after assessment. (Grade D) (17)
- Routine sputum culture before referral to hospital-at-home is not necessary. (Grade D) (17)
- An electrocardiogram need not be routinely performed when considering a patient for home management of their exacerbation but is indicated if the resting heart rate is < 60 beats/minute or > 110 beats/minute. (Grade D) (17)

- Pulse oximetry should be performed on all subjects being considered for home management. Arterial blood gas measurements should be performed if SpO_2 is < 90%. These should be repeated after 1 hour on the intended therapeutic flow rate of oxygen aiming for 90% < SpO_2 < 94% and an arterial blood pH > 7.35. (Grade NICE) (17)
- A chest radiograph should be performed on all subjects being considered for home management. (Grade D) (17)
- Baseline spirometry should be carried out to confirm the diagnosis in cases where this is the patient's first presentation with presumed COPD. (Grade D) (17)
- In busy inner city hospitals, if staffing levels permit, the combined approach of admission avoidance and early supported discharge is practicable but might be expensive. Eligibility for hospital-at-home varies from 30% to 35%, with readmission from hospital-at-home care of 10%. (Grade A) (17)
- In hospitals with fewer admissions for COPD or limited respiratory staffing levels, early inpatient assessment for supported discharge is the favoured model for hospital-at-home. Eligibility for hospital-at-home varies from 35% to 40%. (Grade A) (17)
- Recruitment for hospital-at-home following direct referral from a general practitioner is not recommended because of large numbers of inappropriate referrals. (Grade C) (17)
- For inner city hospitals with high COPD admission rates, a 24-hour/7-day service should be set up in order to maximize admission avoidance. (Grade C) (17)
- For hospitals with fewer COPD admissions, hours of operation should correspond to the peak times of COPD referrals and a Monday-to-Friday service may be most cost-effective. (Grade C) (17)
- After recruitment to hospital-at-home, clinical responsibility and out-of-hours cover should be undertaken by the acute trust. (Grade C) (17)
- When the patient is discharged from hospital-at-home, clinical responsibility should be formally transferred back to primary care either by fax or by email. (Grade C) (17)
- The lead clinician should be a consultant respiratory physician, supported by trainee junior medical staff. (Grade C) (17)
- The hospital-at-home care team should be lead by a specialist respiratory nurse, physiotherapist, or appropriately qualified health professional. (Grade C) (17)
- Inner city hospitals should aim for specialist teams, but district hospitals in provincial or rural areas should consider generic teams which may deal with several hospital-at-home services. (Grade C) (17)
- Key skills for members of the hospital-at-home teams include:
  - ability to take a comprehensive clinical history,
  - proficiency in assessing clinical condition,
  - familiarity with pharmacological and nonpharmacological approaches,
  - knowledge of current guidelines in COPD management,
  - excellent communication skills,
  - excellent team working skills. (Grade D based on consensus) (17)
- Useful but nonessential team member skills include:
  - ability to perform chest auscultation,
  - venous and arterial blood sampling,
  - performance of and basic interpretation of an electrocardiogram,

  - interpretation of a chest radiograph,
  - performance of spirometry,
  - understanding of airway clearance techniques. (Grade D based on consensus) (17)
- The first visit should be carried out on the day after recruitment to hospital-at-home. (Grade D) (17)
- Details of levels of dyspnea, cough, and sputum volume/colour should be recorded. (Grade D) (17)
- Vital signs, including pulse, blood pressure, respiratory rate, and temperature, should be measured. (Grade D) (17)
- Oxygen saturation should be measured by oximetry and the SpO_2 documented alongside the fraction of inspired oxygen (F_{IO2}). (Grade D) (17)
- A copy of the clinical notes and observations should be left in the patient's home. (Grade D) (17)
- Serial spirometry may be useful as objective confirmation of improvement or worsening during an exacerbation and should always be measured before discharge. (Grade D) (17)
- Treatment compliance and nebulizer/oxygen usage should be assessed. (Grade D) (17)
- Telephone contact with respiratory practitioner should be encouraged. (Grade D) (17)
- Weekly team meetings should be held. (Grade D) (17)
- Hospital-at-home care should be completed in fewer than 14 days and with fewer than 10 visits. (Grade C) (17)
- Failure to comply with the above recommendations requires team discussion. (Grade C) (17)
- There should be written agreement between management and medical/nursing staff defining the scope and objectives of an early discharge service. (Grade D) (17)
- Patients should be given an information leaflet about the service. (Grade D) (17)
- The process of discharge should be streamlined. (Grade D) (17)
- There is insufficient evidence to justify setting up telemetry in hospital-at-home at present. (Grade C) (17)
- Plans for new hospital-at-home services should include a formal health economics evaluation. (Grade C) (17)
- Regular administration of short-acting bronchodilators (β-agonist/anticholinergic or both) should be administered to all patients during hospital-at-home care. (Grade NICE) (17)
- Nebulized delivery is the mode of choice in hospital-at-home. (Grade C) (17)
- Prednisolone 30 mg/daily should be given for 7 to 14 days to all patients unless there is a specific contraindication to steroid therapy. (Grade NICE) (17)
- Oxygen therapy is a cornerstone of treatment of an exacerbation of COPD and should be made available to patients if they are hypoxemic. (Grade C) (17)
- Supplementary oxygen should be administered in a controlled fashion aiming for $90\% < SpO_2 < 94\%$. (Grade C) (17)
- Patients who remain in respiratory failure should be referred for consideration of long-term oxygen therapy. (Grade C) (17)
- Antibiotic therapy should be offered to patients with 2 or more symptoms of breathlessness, increased sputum, and increased sputum purulence. (Grade A) (17)
- Patients with a high risk of treatment failure or unusual pathogens benefit from tailored antibiotic therapy. (Grade B) (17)

- Hospital-at-home should not prevent patients gaining access to broader COPD care such as pulmonary rehabilitation or smoking cessation programmes. (Grade D) (17)
- Selected physiotherapeutic techniques and nutritional support may be beneficial. (Grade D) (17)

Grade C recommendations are directly based on evidence from nonexperimental descriptive studies such as comparative studies, correlation studies, and case control studies, or extrapolated from higher quality of evidence. Grade D recommendations are directly based on evidence from expert committee reports or opinions and/or clinical experience of respected authorities or extrapolated from high quality evidence. (13;17) As indicated by the recommendation grades noted with each recommendation, the majority are based on low quality evidence or extrapolated from RCTs that were not specifically designed to test the specific issues dealt with by the recommendations, such as the components of care. For example, recommendations regarding which individuals should be excluded from hospital-at-home care are based on the inclusion and exclusion criteria in the various RCTs that compare hospital-at-home care with inpatient hospital care. These studies, however, do not actually test whether these patients are the most appropriate patients to exclude from care. Furthermore, as most of these studies were carried out in Europe and the recommendations are designed to fit with the British health care system, some recommendations may not be generalizable to Ontario. For these reasons, the recommendations must be considered with caution in the context of developing a hospital-at-home program in Ontario.

Based on the evidence and recommendations, the Guideline group reached the following conclusions:

- Hospital-at-home care should be offered to patients with exacerbations of COPD unless there is impairment of consciousness, confusion, acidosis, serious co-morbidity, or inadequate social support. (17)
- After suitability for hospital-at-home is confirmed by assessment in hospital, a treatment package is prescribed that includes antibiotics, steroids, nebulized bronchodilators, and oxygen if necessary. (17)
- Hospital-at-home care should be delivered by specialist respiratory nurses/physiotherapists or in generic teams by district nurses. (17)
- For most hospitals the preferred model of hospital-at-home should be early supported discharge rather than admission avoidance. (17)
- The role of intermediate care in stable COPD is not yet clearly defined and initiatives in this area should be conducted as experimental and controlled interventions. (17)

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity (FVC)	The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.
Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.

Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[10]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.
Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.
Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.

[10] The mild-to-moderate classification was created for the purposes of the report.

Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Medical Information Officer

Kellee Kaulback

Editorial Staff

Joanna Odrowaz
Irina Alecu

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

Appendices

Appendix 1: Literature Search Strategies

Search date: August 5, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to July Week 4 2010>
Search Strategy:
---
1 exp Pulmonary Disease, Chronic Obstructive/ (14057)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (20996)
3 (copd or coad).ti,ab. (15985)
4 chronic airflow obstruction.ti,ab. (486)
5 exp Emphysema/ (6925)
6 ((chronic adj2 bronchitis) or emphysema).ti,ab. (22569)
7 or/1-6 (53015)
8 exp Community Health Services/ (416785)
9 exp Community Health Centers/ (8823)
10 exp After-Hours Care/ (637)
11 exp House Calls/ (1945)
12 (community* or home care or hospital at home).ti,ab. (210944)
13 or/8-12 (579476)
14 7 and 13 (2849)
15 limit 14 to (english language and humans and yr="1990 -Current") (2007)

Database: EMBASE <1980 to 2010 Week 30>
Search Strategy:
---
1 exp chronic obstructive lung disease/ (46998)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (25339)
3 (copd or coad).ti,ab. (20580)
4 chronic airflow obstruction.ti,ab. (548)
5 exp emphysema/ (25279)
6 exp chronic bronchitis/ (6508)
7 ((chronic adj2 bronchitis) or emphysema).ti,ab. (25265)
8 or/1-7 (86627)
9 exp home care/ (43432)
10 exp community care/ (81462)
11 (community* or home care or hospital at home).ti,ab. (240281)
12 or/9-11 (320084)
13 8 and 12 (2959)
14 limit 13 to (human and english language and yr="1990 -Current") (2014)

Database: CINAHL

#	Query	Results
S12	S11 Limiters - Published Date from: 19900101-20101231	958
S11	S9 and S10	995
S10	(S1 or S2 or S3 or S4 or S5)	7280
S9	S6 or S7 or S8	193
S8	(community* or home care or hospital at home)	106964
S7	(MH "Home Health Care+")	24877
S6	(MH "Community Health Services+")	177846
S5	chronic bronchitis or emphysema	1556
S4	(MH "Emphysema+")	951
S3	copd or coad	4025
S2	(chronic obstructive and (lung* or pulmonary or airway* or airflow or respiratory) and (disease* or disorder*))	5497
S1	(MH "Pulmonary Disease, Chronic Obstructive+")	4248

Appendix 2: Summary Tables

Table A1: General Study Characteristics*

Author, Year	Sample Size	Type of Service	Service Details				HaH Details (Patient Follow-up)				Reasons for Ineligibility for HaH
			Referral	Who Evaluates Patients	When are Patients Evaluated	Hours of Operation	Who	Frequency	After Hours Coverage	Types of Care Offered	
Cotton et al, 2000 (21)	81	EDHaH	Hospital medical wards	Specialist respiratory nurse	Mornings after admission	Monday -- Friday (hours NR)	Specialist respiratory nurse Changes in txt adjusted by respiratory med staff member discussed with nurse	Morning after discharge then discretion of nurse	Patients' GP	Assessment of pt progress based on subjective feelings, pulse, blood pressure, respiratory rate, temperature, oxygen saturation, chest auscultation, spirometry, sputum appearance, advice on use of meds. No additional services, such as social services or rehabilitation, were provided	Not resident of Glasgow, homeless (including hostel dwellers), unable to give informed consent, no access to telephone, patients required inpatient management or investigation for some other medical problem, patients with life-threatening respiratory failure (H* > 45 nM) at time of assessment, not waiting for results from investigational tests
Davies et al, 2000 (20)	150	AA	ED	Specialist nurses with additional COPD training	During operating hours	7 d/wk, 8 AM – 6 PM	Specialist nurse	2 visits/day for first 3 days then at discretion of the nurse	Agreement with district nurses	Social support if needed, nebulized ipratropium bromide, salbutamol with a compressor, oral prednisolone for 10 days, antibiotics for 10 days, additional services or testing performed NR	Personal history of asthma, marked use of accessory muscles, suspected underlying malignancy on chest x-ray film, pneumothorax or pneumonia, uncontrolled left ventricular failure, acute changes on ECG, requires full-time nursing care, requires IV therapy, FEV_1 > 80% predicted, FEV_1/FVC ratio < 70%, Mini-Mental State Score < 7, pulse rate > 100 beats/min, pH < 7.35, PaO_2 < 7.3 kPa, $PaCO_2$ > 8 kPa

Author, Year	Sample Size	Type of Service	Service Details				HaH Details (Patient Follow-up)				Reasons for Ineligibility for HaH
			Referral	Who Evaluates Patients	When are Patients Evaluated	Hours of Operation	Who	Frequency	After Hours Coverage	Types of Care Offered	
Ojoo et al, 2002 (22)	60	EDHaH	Medical wards	NR	Morning after admission during hours of operation	Monday – Thursday 9 AM – 5 PM	Respiratory outreach nurses	Daily	Telephone access through Medical Chest Unit direct line	Monitored treatment of patients and carried out patient and caregiver education and reassurance (limited information provided)	Concomitant medical conditions requiring admission, residence over 15 miles from hospital, complications of exacerbation (acidosis, cor pulmonale, acute changes on chest radiograph), newly diagnosed type 2 respiratory failure, social exclusion (discretionary and based on level of domiciliary support and performance status of pt)
Aimonino Ricauda et al, 2008 (19)	104	AA	ED†	NR	NR	7 d/wk (hrs NR)	MDs and nurses‡ HaH team mtgs daily to discuss pt needs & pt care plans	MD + nurse both visit daily in first few days, then nurse every day and MD every 2–3 days as needed	HaH staff available at all times	Blood tests, pulse oximetry, ECG, echo and Doppler US, oral and IV meds admission incl. antimicrobials and cytotoxic drugs, oxygen therapy, blood transfusion, central venous access, PT, OT, patient and caregiver education, advice on SC, nutrition, ADLs, energy conservation, meds, health maintenance, early recognition of exac., multidimensional geriatric assessment	Patients < 75 years, absence of family and social support, severe hypoxemia (PaO_2 < 50 mmHg), severe acidosis or alkalosis (pH < 7.35 or > 7.55). Suspected pulmonary embolism, suspected MI, severe comorbid illness as defined by presence of need for hemodialysis, severe renal impairment (glomerular filtration rate < 20mL/min), cancer (except skin cancer), hepatic failure or severe dementia (Mini-Mental State Examination score <14)

Author, Year	Sample Size	Type of Service	Service Details				HaH Details (Patient Follow-up)				Reasons for Ineligibility for HaH
			Referral	Who Evaluates Patients	When are Patients Evaluated	Hours of Operation	Who	Frequency	After Hours Coverage	Types of Care Offered	
Shepperd et al, 1998 (15;18)	32§	AA & EDHaH ‖	GP or hospital ward	Unclear	NR	NR	Unclear, may include nurses and GPs	NR	NR	Observation, administration of drugs (including IV meds), rehabilitation including nursing, physiotherapy, occupational therapy, pathology, and speech therapy¶ Nursing care was available 24 hrs/d if needed	Age > 60 yrs, home not suitable for hospital-at-home care (minimum requirements were hot and cold running water, indoor sanitary facilities, room for patient's bed to be moved downstairs if needed), caregiver, if applicable, consented to trial
Skwarska et al, 2000 (6)	184	EDHaH	All admitted through ED but 99% pts referred to ED by GP, 1% by self-referral	Nurses provide tests then decision for inclusion made by respirator y team (i.e., consultant and registrar)	When admitted or morning after depending on hours of operation (present on weekends excluded)	Monday – Friday, 9 AM – 5 PM	Acute respiratory assessment service nurses Weekly team mtgs with nurse & consultant in charge of trial to assess progress of pts	Day after discharge then at 2–3 day intervals	NR	Monitored the need for patient treatment. No details provided about how level of care provided differed, whether any extra services were provided, and what the nurses could do at the home	Admitted on the weekend, required obligatory admission (impaired level of consciousness, acute confusion, new acute changes on radiograph, arterial pH < 7.35, coexistence of another medical condition, poor social circumstances which preclude home supported discharge

*Abbreviations: AA, admission avoidance hospital-at-home program; ADL, activities of daily living; d, day; ECG, electrocardiogram; echo, echograph; EDHaH, early discharge hospital-at-home program; ED, emergency department; exac, exacerbation; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GP, general practitioner; HaH, hospital-at-home; hr, hour; incl., including; IV, intravenous; MD, doctor; meds, medications; MI, myocardial infarction; mtgs, meetings; NR; not reported; OT, occupational therapy; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; pt, patient; PT, physiotherapy; SC, smoking cessation; txt, treatment; US, ultrasound; wk, week.

†The hospital-at-home program in this study only recruited patients who presented to the ED, but the hospital-at-home program also receives direct GP referrals as well as hospital inpatients who are entered into early supported discharge programs.

‡The multidisciplinary team that runs the hospital-at-home program also includes a social worker, a counsellor, and 2 physiotherapists. However, it was unclear in the report whether they also visited patients.

§The total sample size in the Shepperd et al trial was 538, but only 32 were COPD patients. Only the outcomes relevant for the COPD patient group included in the study are listed. (15;18)

‖Patients included in this trial included both patients referred directly from primary care for an admission avoidance hospital-at-home program and patients admitted from hospital wards for an early discharge program. (15;18)

¶Some of the services provided to patients may not be relevant to the COPD patient population. (15;18)

Table A2: Characteristics of the Patients in the Included Studies*

	Sample Size		Mean Age (SD), years		% Male		Smoking Status											
							Current, %		Ex, %		Non, %		Pack-Years, Mean (SD)		Home Oxygen Use, %		Support at Home, %†	
Author, Year	HaH	H	HaH	H	HaH	H	HaH	H	HaH	H	HaH	H	HaH	H	HaH	H	HaH	H
Cotton et al, 2000 (21)	41	40	66 (1.6)	68 (1.2)	46	40	NR	NR	NR	NR	NR	NR	NR	NR	20	13	73	67
Davies et al, 2000 (20)	100	50	70 (8)	70 (8)	45	60	34	38	60	60	6	2	41 (31)	43 (24)	NR	NR	69‡	
Ojoo et al, 2002 (22)	30	30	70	70	53	50	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	§	§
Aimonino Ricauda et al, 2008 (19)	52	52	80 (3.2)	79 (3.1)	56	75	13	11	65	67	21	21	20 (7)‖	21 (15)‖	35	23	100	100
Shepperd et al, 1998 (15;18)	15	17	71 (7.2)	73 (10.1)	33	18	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Skwarska et al, 2000 (6)	122	62	69 (range, 39 – 84)	70 (range, 51 – 86)	52	39	41	38	58	60	NR	NR	NR	NR	7	6	74¶	61¶

*Abbreviations: Ex, indicates ex-smokers; H, inhospital care; HaH, hospital-at-home care; non, nonsmokers; SD, standard deviation.

†Support at home is defined as participants who do not live alone.

‡Results were not reported separately for the hospital-at-home and inpatient hospital groups.

§ Based on reported categories, it was not possible to determine how many patients had support at home given potentially overlapping reported categories.

‖Mean number cigarettes smoked per day ± SD.

¶The reported baseline characteristics include a category about home help. However, inadequate information is provided in the reported results to determine which categories should be included in support at home. Thus, it is possible that some of the individuals who live alone may nevertheless receive help and therefore should have been categorized as support at home.

Table A3: Further Characteristics of the Patients in the Included Studies*

	Arterial Blood Gas, Mean (SD)													
	pH		Partial Pressure O_2, kPa		Partial Pressure CO_2, kPa		Mean FEV_1 (SD), L		% of predicted FEV_1		FEV_1/FVC (SD)		Mean Respiratory. Rate (SD), B/min	
Author, Year	HaH	H	HaH	H	HaH	H	HaH	H	HaH	H	HaH	H	HaH	H
Cotton et al, 2000 (21)	39.3 (0.8) (nM)	40.0 (0.1) (nM)	8.5 (.4)	9.2 (0.4)	6.0 (0.3)	5.5 (0.2)	0.95 (0.1)	0.94 (0.1)	41 (3)	44 (3)	45 (2)	46 (2)	24.0 (0.7)	24 (0 .7)
Davies et al, 2000 (20)	7.4 (0.05)	7.39 (0.04)	9.7 (2.9)	9.0 (1.2)	5.2 (1.0)	5.2 (0.8)	0.71 (0.3)	0.65 (0.2)	36 (17)†	35 (15)†	NR	NR	24 (4)	23 (4)
Ojoo et al, 2002 (22)	NR	NR	NR	NR	NR	NR	1.00 (0.40)	0.85 (0.30)	NR	NR	NR	NR	NR	NR
Aimonino Ricauda et al, 2008 (19)	7.40 (0.10)	7.41 (0.10)	69 (19)‡	65 (14)‡	44 (12)‡	46 (12)‡	0.92 (0.40)	1.04 (0.50)	38	47	NR	NR	24 (5)	25 (7)
Shepperd et al, 1998 (15;18)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Skwarska et al, 2000 (6)	NR	NR	NR	NR	NR	NR	0.77	0.66	NR	NR	NR	NR	22.8	23.2

*Abbreviations: B, breaths; CO_2, carbon dioxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; H, inhospital care; HaH, hospital-at-home care; L, litres; NR, not reported; O_2, oxygen; Resp., respiratory; SD, standard deviation.

†Percent of predicted post-bronchodilator FEV_1.

‡The measurement unit is mmHg rather than kPa.

Appendix 3: Quality of Evidence and GRADE Tables

Table A4: Summary of Study Methodological Characteristics that Impact Study Quality*

Study	N	Adequate Randomization Methods	Adequate Allocation Concealment	Blinding	Power	Loss to FUP	Intention-to-Treat
Cotton et al, 2000 (21)	81	✓ (random numbers)	✓	NR	No a priori sample size calculation Underpowered based on post hoc sample size calculations	✓	Methods say ITT but does not account for withdrawals
Davies et al, 2000 (20)	150	Methods not reported	Unclear (opaque envelopes not specified)	NR	A priori sample size calculation Underpowered based on post hoc sample size calculations	✓	Methods say ITT but does not account for withdrawals
Ojoo et al, 2000 (22)	60	Methods not reported	Unclear (opaque envelopes not specified)	NR	No a priori sample size calculation Underpowered based on post hoc sample size calculations	20%	NR
Aimonino Ricauda et al, 2008 (19)	104	✓ (random numbers)	✓	✓ (outcome assessment blinded)	A priori sample size calculation Adequate power for readmissions Underpowered for mortality and other outcomes based on post hoc sample size calculations	✓	Methods say ITT but does not account for withdrawals
Shepperd et al, 1998, (15;18)	32†	✓ (computer-generated random numbers)	✓	NR	A priori sample size calculation (HRQOL outcome) Underpowered based on post hoc sample size calculations	NR	Methods say ITT but not clear if analysis accounts for withdrawals
Skwarska et al, 2000 (6)	184	✓ (computer-generated random numbers)	NR	NR	No a priori sample size calculation Underpowered based on post hoc sample size calculations	30%	NR

*Abbreviations: FUP, follow-up; ITT, intention-to-treat; N, sample size; NR, not reported.
†The total sample size of the Shepperd et al (15;18) study is 538, but only 32 of those are COPD patients and therefore included in this analysis.

Table A5: GRADE Quality of Evidence*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: Mortality							
6	RCT	Very serious limitations†	Serious limitations‡	No serious limitations	No serious limitations	n/a	Very Low
Outcome: Hospital Readmissions							
6	RCT	Very serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Low
Outcome: Lung Function							
3	RCT	Very serious limitations§	No serious limitations	No serious limitations	Sparse data‖	n/a	Very Low
Outcome: HRQOL							
5	RCT	Very serious limitations¶	No serious limitations#	Serious limitations**	Sparse data††	n/a	Very Low
Outcome: Mean Length of Stay							
5	RCT	Very serious limitations‡‡	Serious limitations§§	No serious limitations	No serious limitations	n/a	Very Low
Outcome: Patient Satisfaction							
3	RCT	Very serious limitations‖ ‖	No serious limitations	No serious limitations	Sparse data¶¶	n/a	Very Low
Outcome: Caregiver Satisfaction							
1	RCT	Very serious limitation##	n/a	No serious limitations	Sparse data***	n/a	Very Low
Outcome: Patient Preference							
1	RCT	Very serious limitations##	n/a	Serious limitations†††	Sparse data***	n/a	Very Low
Outcome: Caregiver Preference							
1	RCT	Very serious limitations##	n/a	Serious limitations†††	Sparse data***	n/a	Very Low

*Abbreviations: HRQOL, health-related quality of life; ITT, intention-to-treat; n/a, not applicable; RCT, randomized controlled trial.

†Study quality was downgraded for the mortality and hospital readmission outcomes because of very serious limitations in many of the studies, including unknown or inadequate allocation concealment (3 of 6 studies); unclear randomization process based on published trials (2 of 6 studies); unclear whether assessor was blinded (single blind) (5 of 6 studies); lack of a priori power calculations (4 of 6 studies) and inadequately powered studies based on post-hoc sample size calculations (mortality: 6 of 6 studies; readmissions: 5 of 6 studies), withdrawals/dropouts > 20% (1 of 6 studies) or unknown (1 of 6 studies) , and ITT analysis not used (unknown for 2 studies) or withdrawals/dropouts not considered in ITT analysis (3 of 4 studies).

‡Downgraded due to lack of consistency between the point estimates.

§Study quality was downgraded for lung function outcomes because of very serious limitations in the studies including: unknown or inadequate allocation concealment (3 of 3 studies); unclear randomization process based on published information (2 of 3 studies); unknown whether assessor was blinded (single blind) based on published information (3 of 3 studies); lack of a priori power calculations (2 of 3 studies) and likely underpowered studies but not possible to calculate post-hoc sample size calculations based on information provided (3 of 3 studies), withdrawals/dropouts > 20% (1 of 3 studies), and ITT analysis not used (unknown for 2 studies) or withdrawals/dropouts not considered in ITT analysis (1 of 3 studies).

‖Downgraded due to sparse data, as the studies each reported different measures of lung function, so there was only 1 study per lung function outcome.

¶Study quality was downgraded for HRQOL because of very serious limitations in the studies including unknown or inadequate allocation concealment (3 of 5 studies); unclear randomization process based on published information (2 of 5 studies); unknown whether assessor was blinded (single blind) based on published information (4 of 5 studies); lack of a priori power calculations (3 of 5 studies) and likely underpowered studies but not possible to calculate post-hoc sample size calculations based on information provided (5 of 5 studies), withdrawals/dropouts > 20% (1 of 5 studies), and ITT analysis not used (unknown for 2 studies) or withdrawals/dropouts not considered in ITT analysis (3 of 5 studies).

#While the GRADE for HRQOL was not downgraded due to inconsistent results because the majority of the studies (4 of 5) showed nonsignificant differences between the hospital-at-home and inpatient hospital groups, there was some inconsistency in the results as 1 study did find a significant difference between the groups for some HRQOL scales.

**Downgraded because HRQOL was measured at 2- to 6-months follow-up rather than during the exacerbation itself, and this time point may be too late to observe a change in HRQOL associated with the intervention.

††Downgraded due to sparse data because 4 of the 5 studies reported different measures of HRQOL, so there was only 1 study per HRQOL outcome.

‡‡ Study quality was downgraded for length of stay because of very serious limitations in the studies, including unknown or inadequate allocation concealment (2 of 5 studies); unclear randomization process based on published information (2 of 5 studies); unknown whether assessor was blinded (single blind) based on published information (4 of 5 studies); lack of a priori power calculations (2 of 5 studies) and likely underpowered studies but not possible to calculate post-hoc sample size calculations based on information provided (5 of 5 studies), withdrawals/dropouts > 20% (1 of 5 studies), and ITT analysis not used (unknown for 2 studies) or withdrawals/dropouts not considered in ITT analysis (3 of 5 studies).

§§Downgraded due to lack of consistency across studies: 1 study reported similar length of stay between groups, 1 study a shorter length of stay in the hospital-at-home group, and 3 studies a longer length of stay in the hospital-at-home group. Some results were significantly different and some were not.

‖‖ Study quality was downgraded for patient satisfaction with care because of very serious limitations in the studies including unknown or inadequate allocation concealment (2 of 3 studies); unclear randomization process based on published information (1 of 3 studies); unknown whether assessor was blinded (single blind) based on published information (2 of 3 studies); lack of a priori power calculations for this outcome and likely underpowered studies but not possible to calculate post-hoc sample size calculations based on information provided (3 of 3 studies), withdrawals/dropouts > 20% (1 of 3 studies), and ITT analysis not used (unknown for 2 studies) or withdrawals/dropouts not considered in ITT analysis (1 of 3 studies).

¶¶Downgraded due to sparse data as none of the studies use the same outcomes to measure satisfaction with care, so there was only 1 study for each outcome.

##Study quality was downgraded for caregiver satisfaction and for patient and caregiver preference because of very serious limitations in the study including: unknown allocation concealment (1 of 1 study); unclear randomization process based on published information (1 of 1 study); unknown whether assessor was blinded (single blind) based on published information (1 of 1 study); lack of a priori power calculations for this outcome and likely underpowered but not possible to calculate post-hoc sample size calculations based on information provided (1 of 1 study), withdrawals/dropouts > 20% (1 of 1 study), and unknown whether intention-to-treat (ITT) analysis was used (1 of 1 study).

***Downgraded due to sparse data as there was only 1 study that reported this outcome.

†††Patient and caregiver preference for hospital-at-home care was measured during the study after patients had begun their treatment either in hospital or in hospital-at-home care. Thus, patients and caregivers in the hospital-at-home group had experience with the program, whereas patients and caregivers in the inpatient hospital group did not. While this provides some information that suggests patients and caregivers become more comfortable and accepting of hospital-at-home care after they have experienced it (which may have policy implications), a comparison of patient/caregiver preferences for hospital-at-home care between the groups at baseline is needed and would be less biased.

References

(1) Braman SS, Lee DW. Primary care management of chronic obstructive pulmonary disease: an integrated goal-directed approach. Curr Opin Pulm Med. 2010 Mar;16(2):83-8.

(2) Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: updated 2009 [Internet]. [Bethesda,MD]: Medical Communications Resources, Inc.; 2009 [cited: 2010 Oct 4]. 109 p. Available from: http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003

(3) Donaldson GC, Wedzicha JA. COPD exacerbations.1: epidemiology. Thorax. 2006 Feb;61(2):164-8.

(4) Niewoehner DE. Clinical practice. Outpatient management of severe COPD. N Engl J Med. 2010 Apr 15;362(15):1407-16.

(5) Hurst JR, Donaldson GC, Quint JK, Goldring JJ, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009 Mar 1;179(5):369-74.

(6) Skwarska E, Cohen G, Skwarski KM, Lamb C, Bushell D, Parker S, et al. Randomized controlled trial of supported discharge in patients with exacerbations of chronic obstructive pulmonary disease. Thorax. 2000;55(11):907-12.

(7) Hernandez C, Casas A, Escarrabill J, Alonso J, Puig-Junoy J, Farrero E, et al. Home hospitalisation of exacerbated chronic obstructive pulmonary disease patients. Eur Respir J. 2003 Jan;21(1):58-67.

(8) Shepperd S, Doll H, Broad J, Gladman J, Iliffe S, Langhorne P, Richards S, Martin F, Harris R. Early discharge hospital at home. Cochrane Database Syst Rev 2009, Issue 1. Art. No.: CD000356. DOI: 10.1002/14651858.CD000356.pub3.

(9) Shepperd S, Doll H, Angus RM, Clarke MJ, Iliffe S, Kalra L, Ricauda NA, Wilson AD. Admission avoidance hospital at home. Cochrane Database Syst Rev 2008, Issue 4. Art. No.: CD007491. DOI: 10.1002/14651858.CD007491.

(10) Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen (DK): The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

(11) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490.

(12) Goodman, C. Literature searching and evidence interpretation for assessing health care practices. Stockholm (SE): Swedish Council on Technology Assessment in Health Care; 1996 81 p. SBU Report No. 119E.

(13) National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care [Internet]. London (UK): National Clinical Guideline Centre; 2010 [cited: 2010 Jun 24]. 673 p. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English

(14) Ram FSF,Wedzicha JA,Wright JJ,Greenstone M.Hospital at home for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2003, Issue 4. Art. No.: CD003573. DOI: 10.1002/14651858.CD003573.

(15) Shepperd S, Harwood D, Jenkinson C, Gray A, Vessey M, Morgan P. Randomised controlled trial comparing hospital at home care with inpatient hospital care. I: three month follow up of health outcomes. BMJ. 1998 Jun 13;316(7147):1786-91.

(16) Soderstrom L, Tousignant P, Kaufman T. The health and cost effects of substituting home care for inpatient acute care: a review of the evidence. CMAJ. 1999;160(8):1151-5.

(17) British Thoracic Society Guideline Development Group. Intermediate care--Hospital-at-Home in chronic obstructive pulmonary disease: British Thoracic Society guideline. Thorax. 2007 Mar;62(3):200-10.

(18) Shepperd S, Harwood D, Gray A, Vessey M, Morgan P. Randomised controlled trial comparing hospital at home care with inpatient hospital care. II: cost minimisation analysis. BMJ. 1998 Jun 13;316(7147):1791-6.

(19) Aimonino Ricauda N, Tibaldi V, Leff B, Scarafiotti C, Marinello R, Zanocchi M, et al. Substitutive "hospital at home" versus inpatient care for elderly patients with exacerbations of chronic obstructive pulmonary disease: a prospective randomized, controlled trial. J Am Geriatr Soc. 2008 Mar;56(3):493-500.

(20) Davies L, Wilkinson M, Bonner S, Calverley PMA, Angus RM. "Hospital at home" versus hospital care in patients with exacerbations of chronic obstructive pulmonary disease: prospective randomised controlled trial. BMJ. 2000;321(7271):1265-8.

(21) Cotton MM, Bucknall CE, Dagg KD, Johnson MK, MacGregor G, Stewart C, et al. Early discharge for patients with exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Thorax. 2000 Nov;55(11):902-6.

(22) Ojoo JC, Moon T, McGlone S, Martin K, Gardiner ED, Greenstone MA, et al. Patients' and carers' preferences in two models of care for acute exacerbations of COPD: results of a randomised controlled trial. Thorax. 2002 Feb;57(2):167-9.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-7016-9 (PDF)

Ontario
Health Quality Ontario
Qualité des services
de santé Ontario

Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis

J Franek

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 11, pp. 1–58, March 2012

Suggested Citation

This report should be cited as follows:

Franek J. Home telehealth for patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2012 Mar; 12(11) 1–58. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Telehealth_March.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to: MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Abbreviations

CCT	Controlled clinical trial
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CSES	Chinese Self-Efficacy Scale
ED	Emergency department
ITT	Intention-to-treat analysis
RCT	Randomized controlled trial
SGRQ	St. George's Respiratory Questionnaire

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective

The objective of this analysis was to conduct an evidence-based assessment of home telehealth technologies for patients with chronic obstructive pulmonary disease (COPD) in order to inform recommendations regarding the access and provision of these services in Ontario. This analysis was one of several analyses undertaken to evaluate interventions for COPD. The perspective of this assessment was that of the Ontario Ministry of Health and Long-Term Care, a provincial payer of medically necessary health care services.

Clinical Need: Condition and Target Population

Canada is facing an increase in chronic respiratory diseases due in part to its aging demographic. The projected increase in COPD will put a strain on health care payers and providers. There is therefore an increasing demand for telehealth services that improve access to health care services while maintaining or improving quality and equality of care. Many telehealth technologies however are in the early stages of development or diffusion and thus require study to define their application and potential harms or benefits. The Medical Advisory Secretariat (MAS) therefore sought to evaluate telehealth technologies for COPD.

Technology

Telemedicine (or telehealth) refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.

Generally there are 4 broad functions of home telehealth interventions for COPD:

- to monitor vital signs or biological health data (e.g., oxygen saturation),
- to monitor symptoms, medication, or other non-biologic endpoints (e.g., exercise adherence),
- to provide information (education) and/or other support services (such as reminders to exercise or positive reinforcement), and
- to establish a communication link between patient and provider.

These functions often require distinct technologies, although some devices can perform a number of these diverse functions. For the purposes of this review, MAS focused on home telemonitoring and telephone only support technologies.

Telemonitoring (or remote monitoring) refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.

Telephone only support refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.

Research Questions

1. What is the effectiveness, cost-effectiveness, and safety of home telemonitoring compared with usual care for patients with COPD?
2. What is the effectiveness, cost-effectiveness, and safety of telephone only support programs compared with usual care for patients with COPD?

Research Methods

Literature Search

Search Strategy

A literature search was performed on November 3, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2000 until November 3, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with unknown eligibility were reviewed with a second clinical epidemiologist, and then a group of epidemiologists until consensus was established. The quality of evidence was assessed as high, moderate, low, or very low according to GRADE methodology.

Inclusion Criteria – Question #1

- frequent transmission of a patient's physiological data collected at home and without a health care professional physically present to health care professionals for routine monitoring through the use of a communication technology;
- monitoring combined with a coordinated management and feedback system based on transmitted data;
- telemonitoring as a key component of the intervention (subjective determination);
- usual care as provided by the usual care provider for the control group;
- randomized controlled trials (RCTs), controlled clinical trials (CCTs), systematic reviews, and/or meta-analyses;
- published between January 1, 2000 and November 3, 2010.

Inclusion Criteria – Question #2

- scheduled or frequent contact between patient and a health care professional via telephone or videoconferencing technology in the absence of transmission of patient physiological data;
- monitoring combined with a coordinated management and feedback system based on transmitted data;
- telephone support as a key component of the intervention (subjective determination);
- usual care as provided by the usual care provider for the control group;
- RCTs, CCTs, systematic reviews, and/or meta-analyses;
- published between January 1, 2000 and November 3, 2010.

Exclusion Criteria

- published in a language other than English;

- intervention group (and not control) receiving some form of home visits by a medical professional, typically a nurse (i.e., telenursing) beyond initial technology set-up and education, to collect physiological data, or to somehow manage or treat the patient;
- not recording patient or health system outcomes (e.g., technical reports testing accuracy, reliability or other development-related outcomes of a device, acceptability/feasibility studies, etc.);
- not using an independent control group that received usual care (e.g., studies employing historical or periodic controls).

Outcomes of Interest

- hospitalizations (*primary outcome*)
- mortality
- emergency department visits
- length of stay
- quality of life
- other [...]

Subgroup Analyses (a priori)

- length of intervention *(primary)*
- severity of COPD *(primary)*

Quality of Evidence

The quality of evidence assigned to individual studies was determined using a modified CONSORT Statement Checklist for Randomized Controlled Trials. (1) The CONSORT Statement was adapted to include 3 additional quality measures: the adequacy of control group description, significant differential loss to follow-up between groups, and greater than or equal to 30% study attrition. Individual study quality was defined based on total scores according to the CONSORT Statement checklist: very low (0 to < 40%), low (≥ 40 to < 60%), moderate (≥ 60 to < 80%), and high (≥ 80 to 100%).

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. The following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Summary of Findings

Six publications, representing 5 independent trials, met the eligibility criteria for Research Question #1. Three trials were RCTs reported across 4 publications, whereby patients were randomized to home

telemonitoring or usual care, and 2 trials were CCTs, whereby patients or health care centers were nonrandomly assigned to intervention or usual care.

A total of 310 participants were studied across the 5 included trials. The mean age of study participants in the included trials ranged from 61.2 to 74.5 years for the intervention group and 61.1 to 74.5 years for the usual care group. The percentage of men ranged from 40% to 64% in the intervention group and 46% to 72% in the control group.

All 5 trials were performed in a moderate to severe COPD patient population. Three trials initiated the intervention following discharge from hospital. One trial initiated the intervention following a pulmonary rehabilitation program. The final trial initiated the intervention during management of patients at an outpatient clinic.

Four of the 5 trials included oxygen saturation (i.e., pulse oximetry) as one of the biological patient parameters being monitored. Additional parameters monitored included forced expiratory volume in one second, peak expiratory flow, and temperature.

There was considerable clinical heterogeneity between trials in study design, methods, and intervention/control. In relation to the telemonitoring intervention, 3 of the 5 included studies used an electronic health hub that performed multiple functions beyond the monitoring of biological parameters. One study used only a pulse oximeter device alone with modem capabilities. Finally, in 1 study, patients measured and then forwarded biological data to a nurse during a televideo consultation. Usual care varied considerably between studies.

Only one trial met the eligibility criteria for Research Question #2. The included trial was an RCT that randomized 60 patients to nurse telephone follow-up or usual care (no telephone follow-up). Participants were recruited from the medical department of an acute-care hospital in Hong Kong and began receiving follow-up after discharge from the hospital with a diagnosis of COPD (no severity restriction). The intervention itself consisted of only two 10-to 20-minute telephone calls, once between days 3 to 7 and once between days 14 to 20, involving a structured, individualized educational and supportive programme led by a nurse that focused on 3 components: assessment, management options, and evaluation.

Regarding Research Question #1:

- Low to very low quality evidence (according to GRADE) finds non-significant effects or conflicting effects (of significant or non-significant benefit) for all outcomes examined when comparing home telemonitoring to usual care.
- There is a trend towards significant increase in time free of hospitalization and use of other health care services with home telemonitoring, but these findings need to be confirmed further in randomized trials of high quality.
- There is severe clinical heterogeneity between studies that limits summary conclusions.
- The economic impact of home telemonitoring is uncertain and requires further study.
- Home telemonitoring is largely dependent on local information technologies, infrastructure, and personnel, and thus the generalizability of external findings may be low. Jurisdictions wishing to replicate home telemonitoring interventions should likely test those interventions within their jurisdictional framework before adoption, or should focus on home-grown interventions that are subjected to appropriate evaluation and proven effective.

Regarding Research Question #2:

- Low quality evidence finds significant benefit in favour of telephone-only support for self-efficacy and emergency department visits when compared to usual care, but non-significant results for hospitalizations and hospital length of stay.
- There are very serious issues with the generalizability of the evidence and thus additional research is required.

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients with Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this analysis was to conduct an evidence-based assessment of home telehealth technologies for patients with COPD in order to inform recommendations regarding the access and provision of these services in Ontario. This analysis was one of several analyses undertaken to evaluate interventions for COPD. The perspective of this assessment was that of the Ministry of Health and Long-Term Care, a provincial payer of medically necessary health care services.

Clinical Need and Target Population

Canada is facing an increase in chronic respiratory diseases due in part to its aging demographic. The projected increase in COPD will put a strain on health care payers and providers. There is therefore an increasing demand for telehealth services that improve access to health care services while maintaining or improving quality and equality of care. Many telehealth technologies however are in the early stages of development or diffusion and thus require study to define their application and potential harms or benefits. The Medical Advisory Secretariat therefore sought to evaluate telehealth technologies for COPD.

Technology

Definitions

Definitions for telehealth tend to be diverse and varied. The definitions used for the purposes of this review are described below.

Telemedicine (or telehealth) refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.

While telemedicine is often associated with direct patient clinical services, *telehealth* is often associated with a broader definition of remote health care and is perceived to be more focused on other health-related services.

Telemonitoring (or remote monitoring) refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider. Generally, there are 2 types of telemonitoring devices: i) *upload devices* which are wireless or modem-compatible devices that can measure biologic information and directly upload the data either automatically or through patient assistance via landline or wireless transmission, and ii) *entry devices* which are devices (either landline-based or wireless) or websites through which patients enter biological health data that was measured by a distinct measurement device. The monitoring of patient data by a health-care practitioner can occur either in real-time (i.e., *real-time monitoring* or *synchronous monitoring*) or can be stored and viewed at a later time (i.e., *store-and-forward monitoring* or *asynchronous monitoring*).

Telephone only support refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.

Telenursing generally refers to the in-person visit of a health care provider, typically a nurse, to a patient's home or residence, regularly, in order to provide clinical care or professional education. Because

of the resource requirements, telenursing is generally not feasible from a population perspective and is therefore not discussed further in this review.

Because of the chronic nature of COPD and the subsequent need for continuous patient management, home telehealth technologies are being increasingly used to help outpatients maintain their independence and continue living in their own homes while ensuring their symptoms, vital signs, medication, education, and other management-related factors are monitored and/or managed and/or improved.

Functions

Generally there are 4 broad functions of home telehealth interventions for COPD:

- to monitor vital signs or biological health data (e.g., oxygen saturation),
- to monitor symptoms, medication, or other non-biologic endpoints (e.g., exercise adherence),
- to provide information (education) and/or other support services (such as reminders to exercise or positive reinforcement), and
- to establish a communication link between patient and provider.

These functions often require distinct technologies, although some devices can perform a number of these diverse functions.

Evidence-Based Analysis

Research Question(s)

1. What is the effectiveness, cost-effectiveness, and safety of home telemonitoring compared with usual care for patients with COPD?
2. What is the effectiveness, cost-effectiveness, and safety of telephone only support compared with usual care for patients with COPD?

Research Methods

Literature Search

Search Strategy

A literature search was performed on November 3, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2000 until November 3, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with unknown eligibility were reviewed with a second clinical epidemiologist, and then a group of epidemiologists at the Medical Advisory Secretariat until consensus was established. The quality of evidence was assessed as high, moderate, low, or very low according to GRADE methodology. A methodological quality checklist was used to help guide the grading of the Methodological Quality domain of GRADE.

Inclusion Criteria – Question #1

- frequent transmission of a patient's physiological data collected at home and without a health care professional physically present to health care professionals for routine monitoring through the use of a communication technology;
- monitoring combined with a coordinated management and feedback system based on transmitted data;
- telemonitoring as a key component of the intervention (subjective determination);
- usual care as provided by the usual care provider in the control group;
- randomized controlled trials (RCTs), controlled clinical trials (CCTs), systematic reviews, and/or meta-analyses;
- published between January 1, 2000 and November 3, 2010.

Inclusion Criteria – Question #2

- scheduled or frequent contact between patient and a health care professional via telephone or videoconferencing technology in the absence of transmission of patient physiological data;
- monitoring combined with a coordinated management and feedback system based on transmitted data;
- telephone support as a key component of the intervention (subjective determination);
- usual care as provided by the usual care provider in the control group;
- RCTs, CCTs, systematic reviews, and/or meta-analyses;
- published between January 1, 2000 and November 3, 2010.

Exclusion Criteria

- published in a language other than English;
- intervention group (and not control) receiving some form of home visits by a medical professional, typically a nurse (i.e., telenursing), beyond initial technology set-up and education, to collect physiological data or somehow manage or treat the patient;
- not recording patient or health system outcomes (e.g., technical reports testing accuracy, reliability, or other development-related outcomes of a device, acceptability/feasibility studies, etc.);
- not using an independent control group that received usual care (e.g., studies employing historical or periodic controls such as before-after studies).

Outcomes of Interest

- hospitalizations (*primary outcome*)
- mortality
- emergeny department (ED) visits
- length of stay
- quality of life
- primary care visits
- specialist visits
- home care visits
- other [...]

Subgroup Analyses

- length of intervention *(primary)*
- severity of COPD *(primary)*
- length of follow-up
- jurisdiction
- interventional
  - modality of transmission for telemonitoring (real time or store and forward [synchronous or asynchronous])
  - service availability (with or without 24-hour/day emergency support)
  - frequency of telephone support contact
- age

Statistical Analysis

Due to excessive clinical heterogeneity in the intervention, control, study population, study methods, and outcomes, no statistical pooling was performed.

Quality of Evidence

The quality of evidence assigned to individual studies was determined using a modified CONSORT Statement Checklist for Randomized Controlled Trials. (1) The CONSORT Statement was adapted to include 3 additional quality measures: the adequacy of control group description, significant differential loss to follow-up between groups, and greater than or equal to 30% study attrition. Individual study

quality was defined based on total scores according to the CONSORT Statement checklist: very low (0 to < 40%), low (≥ 40 to < 60%), moderate (≥ 60 to < 80%), and high (≥ 80 to 100%).

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (1) as presented below:

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding, and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

The literature search returned 759 publications, published between January 1, 2000 and November 3, 2010. Of these 759 publications, 94 full texts were reviewed and 9 publications met the eligibility criteria. (2-10) Table 1 illustrates the body of evidence according to study design.

Table 1: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
Randomized Controlled Trials	
Systematic review of RCTs	2†
Large RCT	2
Small RCT	5
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	
Total	9

*Abbreviation: RCT, randomized controlled trial.

†The systematic reviews combined randomized controlled trials and observational studies.

Two publications referenced the same systematic review conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH). (9;10) This review included RCTs, CCTs, and observational trials. While the review recognized substantial clinical heterogeneity between trials, summary conclusions were generalized to all of telehealth, stating that telehealth is generally clinically effective for COPD and that more research was needed.

Methodological issues were however noted with this systematic review, pertaining primarily to its eligibility criteria, quality evaluation, and interpretation of results. The Medical Advisory Secretariat therefore sought to conduct an original systematic review to answer the above research questions.

Results are presented by Research Question.

Research Question #1 – Home Telemonitoring

Six publications, representing 5 independent trials, met the eligibility criteria for Research Question #1. (2-7)

Three trials were RCTs reported across 4 publications, (2-4;7) whereby patients were randomized to home telemonitoring or usual care, and 2 trials were CCTs, (5;6) whereby patients or centers were nonrandomly assigned to intervention or usual care. Five relevant observational trials (11-15) were identified in the literature search but were excluded because of study design, and one relevant RCT (16) was excluded because it did not include the monitoring of biological patient data (these exclusions are reported for completeness only).

Patient and study characteristics of included studies are detailed in Appendix 2. A checklist of methodological quality is provided in Appendix 3. Finally, GRADE assessments were carried out for the body of evidence pertaining to each individual outcome (as required by GRADE). Individual GRADE tables by outcome are available in Appendix 4.

A total of 310 participants were studied across the 5 included trials. The mean age of study participants in the included trials ranged from 61.2 to 74.5 years for the intervention group and 61.1 to 74.5 years for the usual care group. The percentage of men ranged from 40% to 64% in the intervention group and 46% to 72% in the usual care group. (2-7)

All 5 trials were performed in a moderate to severe COPD patient population. (2-7) Three trials initiated the intervention following discharge from hospital. (5-7) One trial initiated the intervention following a pulmonary rehabilitation program. (3;4) The final trial initiated the intervention during management of patients at an outpatient clinic. (2)

Four of the 5 trials included oxygen saturation (i.e., pulse oximetry) as one of the biological patient parameters being monitored. (2-4;6;7) Additional parameters monitored included forced expiratory volume in one second, peak expiratory flow, and temperature.

There was considerable clinical heterogeneity between trials in terms of the study design, methodological quality, the technology being used, the additional biological patient parameters being monitored, the timing of the intervention in the clinical course of disease, the number and type of co-interventions, the length of intervention/follow-up, the intensity of the intervention (i.e., the number of data transmissions or communications per day), and the number and specialties of health care practitioners involved in carrying out the intervention.

In relation to the telemonitoring technology itself, 3 of the 5 included studies used an electronic health hub (i.e., entry device) that performed numerous functions beyond the monitoring of biological parameters. (2-5) One study used only a pulse oximeter with modem capabilities (i.e., upload device). (7) Finally, in one study, patients measured and forwarded biological data to a nurse during a televideo consultation (for the purposes of this review, this was considered real-time telemonitoring using an entry device). (6) Usual care varied considerably between studies (see Appendix 2, Table A1).

Results are summarized by outcome.

Hospitalizations

All 5 trials evaluated the effect of home telemonitoring on patient hospitalizations; however, the outcome was defined differently across trials (see Table 2). (2-7) Included studies reported conflicting results, either finding non-significant benefit (i.e., a reduction in hospitalizations) in favour of home telemonitoring compared with usual care, or a significant benefit in favour of home telemonitoring. Two of the studies were powered for the outcome of hospitalizations (i.e., primary outcome), yet both found no significant difference between the groups. (3;6) The quality of the body of evidence for this outcome was very low according to GRADE (see Appendices 3 and 4). All hospitalizations were assumed to be all-cause hospitalizations unless otherwise reported.

Table 2: The Effect of Home Telemonitoring on Hospitalizations When Compared to Usual Care Across Included Studies*†

Author, Year	n	Design	Outcome	Telemonitoring	Usual Care	*P* value
Mean number of hospitalizations per patient over 6 months of follow-up						
Lewis et al, 2010 (3)	40	RCT	COPD-related	0.20	0.35	0.16
Pare et al, 2006 (5)	**29**	**CCT**	**All-cause**	**0.10**	**0.60**	**< 0.05**
Mean hospitalizations per patient-month of follow-up (mean ± SD)						
Vitacca et al, 2006 (7)	**101**	**RCT**	**All-cause**	**0.17 ± 0.23**	**0.30 ± 0.30**	**< 0.019**
Proportion of patients with at least one hospitalization during follow-up						
Koff et al, 2008 (2)	40	RCT	All-cause	1/19 (5.3)	3/19 (15.8)	> 0.05
Pare et al, 2006 (5)	29	CCT	All-cause	1/19 (5.3)	4/10 (40.0)	> 0.05
Sorknaes et al, 2010 (6)	100	CCT	All-cause	8/50 (16.0)	15/50 (30.0)	> 0.05

*Abbreviations: CCT, controlled clinical trial (non-randomized); n, sample size; RCT, randomized controlled trial.
†Bolding denotes significance at *P* value < 0.05.

Time Free of Hospitalization

Two trials evaluated the effect of home telemonitoring on time free of hospitalization as a secondary outcome in a population with severe COPD. (6;7) In an RCT by Vitacca et al, (7) Kaplan-Meier survival analysis adjusting for the use of home mechanical ventilation found that patients in the home telemonitoring group were more likely to have a longer time until first hospitalization than those in the usual care group ($P < 0.0012$). In a CCT by Sorknaes et al, (6) multivariate Cox regression model adjusting for a number of different factors (including age and current smoking status) found that home telemonitoring was protective of early hospitalization (hazard ratio [HR], 0.25; 95% confidence interval [CI], 0.09–0.60; $P < 0.05$). The quality of the body of evidence for this outcome was low according to GRADE (see Appendices 3 and 4).

Mortality

Only 1 trial evaluated the effect of home telemonitoring on mortality (undefined) as a secondary outcome. (7) The RCT, by Vitacca et al, reported no significant difference in the mortality rate between the home telemonitoring group and the usual care group ($P = 0.148$), but no data were provided. The quality of the body of evidence for this outcome was low according to GRADE (see Appendices 3 and 4).

Quality of Life

Two trials evaluated the effect of home telemonitoring on quality of life (see Table 3). (2;4) In an RCT by Koff et al, (2) the home telemonitoring group showed a significant improvement in the mean change from baseline in the St. George's Respiratory Questionnaire (SGRQ) score when compared with the usual care group (see Table 3). This study was powered for this specific outcome (i.e., this was the primary outcome). The home telemonitoring group also showed improvement in the individual domains of the SGRQ, although the benefit did not reach statistical significance. In an RCT by Lewis et al, there was no significant difference noted between study groups across 3 different measures: change in SGRQ, hospital anxiety score, and EuroQol 5-D (EQ-5D). (4) This study however was not powered for these outcomes (i.e., these were secondary outcomes). The quality of the body of evidence for this outcome was low according to GRADE (see Appendices 3 and 4).

Table 3: The Effect of Home Telemonitoring on Quality of Life When Compared to Usual Care Across Included Studies*†

Author, Year	n	Design	Measurement	Telemonitoring	Usual Care	*P*
Mean number of hospitalizations per patient over 6 months follow-up						
Koff et al, 2008 (2)	40	RCT	**∆SGRQ score mean (95% CI)**	**-10.3 (-17.1,-3.1)**	**-0.6 (-6.5, 5.3)**	**.018**
			Symptoms	-12.8 (-24.4, -1.1)	-3.3 (-14.0, 7.4)	.27
			Activity	-8.8 (-18.8, 1.1)	-0.5 (-8.9, 7.9)	.16
			Impact	-6.6 (-15.3, 2.2)	-0.6 (-7.2, 6.0)	.20
Lewis et al, 2010 (4)	40	RCT	∆SGRQ score	NR	NR	.83
			Hospital depression			.70
			Hospital anxiety			.83
			EQ-5D			.64

*Abbreviations: CI, confidence interval; EQ-5D, EuroQol-5D; n, sample size; RCT, randomized controlled trial, SGRQ, St. George's Respiratory Questionnaire.

†Bolding denotes significance at *P* value < 0.05.

Length of Stay

Two trials evaluated the effect of home telemonitoring on hospital length of stay as a secondary outcome. (3;5) No significant differences between arms were identified in an RCT by Lewis et al ($P = 0.66$) (3) or in a CCT by Pare et al ($P > 0.05$) (5) when comparing median days in hospital between study groups. The quality of the body of evidence for this outcome was low according to GRADE (see Appendices 3 and 4).

Exacerbations

One trial evaluated the effect of home telemonitoring on exacerbations as a secondary outcome. (6) In a CCT by Sorknaes et al, (6) there was no significant difference in the number of exacerbations ($P > 0.05$) between study groups. The quality of the body of evidence for this outcome was low according to GRADE (see Appendices 3 and 4).

Emergency Department Visits

Two trials evaluated the effect of home telemonitoring on emergency department (ED) visits as a secondary outcome. (2;3) There was no significant difference between study groups in an RCT by Lewis et al (3) that evaluated median ED visits per patient during the study period ($P = 0.24$), and similarly, there appeared to be no significant difference in an RCT by Koff et al (2) that evaluated total ED visits over the study period (*P* value not reported). The quality of the body of evidence for this outcome was very low according to GRADE (see Appendices 3 and 4).

Patient Satisfaction

Patient satisfaction was evaluated across 4 trials. (2;3;5;6) Study participants generally felt safer or more secure when using home telemonitoring, (5;6) participants perceived that the intervention was beneficial, (3;5;6) and lastly, participants reported being satisfied with the equipment. (2)

Time Free of Other Health Care Services

In an RCT by Vitacca et al, (7) Kaplan-Meier survival analysis adjusting for the use of home mechanical ventilation found that patients in the home telemonitoring group were more likely to have a longer time until first ED visit ($P = 0.0003$), first exacerbation ($P < 0.001$), and first urgent generalized practitioner call ($P = 0.013$). The quality of the body of evidence for these outcomes was low according to GRADE (see Appendices 3 and 4).

Safety
No trials reported safety-related outcomes (i.e., adverse events caused by home telemonitoring).

Research Question #2 – Telephone Only Support

Only 1 trial met the eligibility criteria for Research Question #2. (8)

Four relevant RCTs (17-20) were excluded because the intervention included home visits by a nurse, 1 relevant RCT (21) was excluded because there was no coordinated feedback/patient management based on the telephone communication (i.e., the telephone calls provided encouragement only), 2 relevant RCTs (22;23) were excluded because telephone support was not a focus of the intervention, and lastly, 2 relevant observational trials (24;25) were excluded because of study design (these exclusions are reported for completeness only).

Patient and study characteristics of the included study are detailed in Appendix 2. A checklist of methodological quality is provided in Appendix 3. Finally, GRADE assessments were carried out for the body of evidence pertaining to each individual outcome (as required by GRADE). Individual GRADE tables by outcome are available in Appendix 4.

The included trial, by Wong et al, (8) was an RCT that randomized 60 patients to nurse telephone follow-up or usual care (no telephone follow-up). Participants were recruited from the medical department of an acute-care hospital in Hong Kong and began receiving follow-up after discharge from hospital with a diagnosis of COPD (no severity restriction). The intervention itself consisted of only two 10-to 20-minute telephone calls, once between days 3 to 7 and once between days 14 to 20, involving a structured, individualized educational and supportive programme led by a nurse that focused on 3 components: assessment, management options, and evaluation. The trial originally aimed for 196 participants but managed to only recruit 72 (60 of which participated in the trial). The primary outcome of the trial was the change in score on the Chinese Self Efficacy Scale (CSES).

Quality of Life
Participants in the telephone follow-up group significantly improved in the change in CSES (see Table 4). Of the 5 domains of the CSES, significant improvements were also noted in Physical Exertion and in Weather or Environment in favour of the telephone follow-up group. In a multiple regression model, telephone follow-up (β = 0.33; 95% CI, 0.19–0.48; P = 0 .001), having attended a pulmonary rehabilitation programme (β = 0.44; 95% CI, 0.6–0.72; P = 0 .003), smoking (β = 0.34; 95% CI, 0.09–0.57; P = 0.009), and health care use (β = 0.27; 95% CI, 0.47 to -0.07; P = 0.008) were significant factors in predicting patient self-efficacy. (8) The quality of the body of evidence for this outcome was low according to GRADE (see Appendices 3 and 4).

Table 4: The Effect of Telephone Only Support on Quality of Life When Compared to Usual Care in a Study by Wong et al*†

Author, Year	n	Design	Measurement	Telemonitoring	Usual Care	*P value*
Wong et al, 2005 (8)	60	RCT	**ΔCSES score median (IQR)**	**0.5 (0.7)**	**0.3 (0.6)**	**0.009**
			Negative Affect	0.4 (0.7)	0.3 (0.6)	0.260
			Emotional Arousal	0.5 (0.9)	0.1 (0.6)	0.342
			Physical Exertion	**0.6 (1.0)**	**-0.2 (1.1)**	**0.001**
			Weather or Environment	**0.5 (0.8)**	**0.0 (0.9)**	**0.009**
			Behavioural Risk Factors	0.0 (0.5)	0.0 (1.1)	0.901

*Abbreviations: CSES, Chinese Self-Efficacy Scale; IQR, interquartile range; n, sample size; RCT, randomized controlled trial.

†Bolding denotes significance at P value < 0.05.

Hospitalization
There was no significant difference between study groups when comparing mean hospitalizations per patient during the study and follow-up period ($P = 0.182$). (8) The quality of the body of evidence for this outcome was low according to GRADE (see Appendices 3 and 4).

Length of Stay
There was no significant difference between study groups when comparing mean days of readmission during the study and follow-up period ($P = 0.354$). (8) The quality of the body of evidence for this outcome was low according to GRADE (see Appendices 3 and 4).

Emergency Department Visits
The telephone follow-up group had significantly ($P = 0.034$) fewer ED visits (mean 0.1 ± 0.3) compared with the usual care group (mean 0.4 ± 0.7). (8) The quality of the body of evidence for this outcome was low according to GRADE (see Appendices 3 and 4).

Safety
No trials reported safety-related outcomes (i.e., adverse events caused by home telemonitoring).

Quality of the Evidence

GRADE evaluations were performed to summarize the quality of the body of evidence pertaining to each individual outcome (see Appendix 4). A methodological checklist (see Appendix 3) was used to help inform the Methodological Quality component of GRADE (see Appendix 4). The quality of evidence according to GRADE was low to very low quality across all outcomes. Serious to very serious limitations were noted in the methodological quality of studies owing to a lack of blinding, lack of randomization (with the inclusion of controlled clinical trials), significant differences in baseline comparisons (see Appendix 3, Table A3), a lack of baseline comparison, lack of power due to small sample sizes, unplanned subgroup analysis, and a lack of intention-to-treat analysis. Inconsistencies in the magnitude of effect and statistical significance were also noted and contributed to downgrading. Lastly, issues of generalizability, primarily in the intervention, were noted throughout but did not always contribute to downgrading (unless serious issues were noted). Serious issues with generalizability were noted in the telephone only study by Wong et al; (8) specifically, there were issues with the population (Chinese population with limited comorbidities) and with the outcome/intervention (an adapted CSES was used both as a tool to measure self efficacy (i.e., quality of life) and to help guide the intervention).

Economic Analysis

The results of the economic analysis are summarized in issue 12 of the COPD series entitled *Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model*. This report can be accessed at: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Economic_March.pdf.

The results from the systematic review of the clinical evidence for home telemonitoring and telephone only support for COPD were not included in the economic model because of the low to very low quality of evidence and the lack of significant findings for the model inputs.

Conclusions

Regarding Research Question #1:

- Low to very low quality evidence (according to GRADE) shows non-significant effects or conflicting effects (of significant or non-significant benefit) for all outcomes examined when comparing home telemonitoring to usual care.
- There is a trend towards a significant increase in time free of hospitalization and use of other health care services with home telemonitoring, but these findings need to be confirmed further in randomized trials of high quality.
- There is severe clinical heterogeneity between studies that limits summary conclusions.
- The economic impact of home telemonitoring is uncertain and requires further study.
- Home telemonitoring is largely dependent on local information technologies, infrastructure, and personnel, and thus the generalizability of external findings may be low. Jurisdictions wishing to replicate home telemonitoring interventions should likely test those interventions within their jurisdictional framework before adoption, or should focus on home-grown interventions that are subjected to appropriate evaluation and proven effective.

Regarding Research Question #2:

- Low quality evidence shows significant benefit in favour of telephone only support for self-efficacy and ED visits when compared to usual care, but non-significant results for hospitalizations and hospital length of stay.
- There are very serious issues with the generalizability of this evidence and thus additional study is required.

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity (FVC)	The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.
Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.

Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[1]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.
Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.
Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.

[1] The mild-to-moderate classification was created for the purposes of the report.

Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Medical Information Officer

Kellee Kaulback

Editorial Staff

Irina Alecu

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

Appendices

Appendix 1: Literature Search Strategies

Search date: November 3, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to October Week 3 2010>
Search Strategy:
---
1 exp Pulmonary Disease, Chronic Obstructive/ (14736)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (21651)
3 (copd or coad).ti,ab. (16560)
4 chronic airflow obstruction.ti,ab. (492)
5 exp Emphysema/ (7011)
6 ((chronic adj2 bronchitis) or emphysema).ti,ab. (22852)
7 or/1-6 (54191)
8 exp telecommunications/ (41357)
9 exp Computer Communication Networks/ (46975)
10 (tele* or ehealth or e-health or mhealth or m-health).mp. [mP = title, original title, abstract, name of substance word, subject heading word, unique identifier] (105201)
11 ((remote or wireless or mobile) adj2 (monitor* or consult*)).mp. [mP = title, original title, abstract, name of substance word, subject heading word, unique identifier] (3661)
12 (Aerotel Medical or Aivea or AMD Global Telemedicine or American TeleCare or AvidCare or Carematix or Care2Wear or CareVoyant or Centura or Cifra or Clinidata or CyberCare or Cybernet or DexCom or ExceliCare or FireLogic or FONEMED or Health Buddy or Health Hero or HealthEngage or Health@nywhere or HomMed or Homecare Homebase or iCare Desktop or IEM GmbHOR or iMetrikus or InforMedix or INRange or Intelsis or Lifewatch or Lifelink or March Networks or McKesson or MDHome or Medic4All or MediCompass or MedNovations or MedShare or Morepress or Neptec or NewIt or Patient Care Technologies or PERS Buddy or Pharos or RemoteAccess or RemoteNurse or Senior Health Advantage Network or Spirotel or TCARE or Teledoctor or Telehealth Solutions or TeleMedic or Telescale or TouchPointCare or (Tunstall adj3 Genesis) or ViTel Net or VitalNet or Viterion or Well@home or WiPaM).mp. [mP = title, original title, abstract, name of substance word, subject heading word, unique identifier] (188)
13 or/8-12 (156487)
14 7 and 13 (348)
15 limit 14 to (english language and humans and yr="2000 -Current") (251)

****

Database: EMBASE <1980 to 2010 Week 43>
Search Strategy:
---
1 exp chronic obstructive lung disease/ (48442)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (26232)
3 (copd or coad).ti,ab. (21514)
4 chronic airflow obstruction.ti,ab. (549)
5 exp emphysema/ (25645)
6 exp chronic bronchitis/ (6583)
7 ((chronic adj2 bronchitis) or emphysema).ti,ab. (25526)
8 or/1-7 (88664)
9 exp telecommunication/ (22728)
10 exp mass communication/ (274378)
11 (tele* or ehealth or e-health or mhealth or m-health).mp. [mP = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] (121632)
12 ((remote or wireless or mobile) adj2 (monitor* or consult*)).mp. [mP = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] (1182)
13 (Aerotel Medical or Aivea or AMD Global Telemedicine or American TeleCare or AvidCare or Carematix or Care2Wear or CareVoyant or Centura or Cifra or Clinidata or CyberCare or Cybernet or DexCom or ExceliCare or FireLogic or FONEMED or Health Buddy or Health Hero or HealthEngage or Health@nywhere or HomMed or Homecare Homebase or iCare Desktop or IEM GmbHOR or iMetrikus or InforMedix or INRange or Intelsis or Lifewatch or Lifelink or March Networks or McKesson or MDHome or Medic4All or MediCompass or MedNovations or MedShare or Morepress or Neptec or NewIt or Patient Care Technologies or PERS Buddy or Pharos or RemoteAccess or RemoteNurse or Senior Health Advantage Network or Spirotel or TCARE or Teledoctor or Telehealth Solutions or TeleMedic or Telescale or TouchPointCare or (Tunstall adj3 Genesis) or ViTel Net or VitalNet or Viterion or Well@home or WiPaM).mp. [mP = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] (381)
14 or/9-13 (345125)
15 8 and 14 (954)
16 limit 15 to (human and english language and yr="2000 -Current") (584)

Appendix 2: Study Design and Participant Characteristics

Table A1: Design and Participant Characteristics of Included Studies of Home Telemonitoring*

Author, Year	Country	Outcomes	Recruit. Period/ Study Period	Length of Intervention/ Follow-up (months)	Patient Eligibility Criteria	Arms (n)	Intervention/Control
Randomized Controlled Trials (N = 3)							
Vitacca et al, 2009 (7)	Italy	• hospitalizations • time free of hospitalization • time free of exacerbation • time free of urgent GP call • time free of ED visit • mortality • cost	*Study period:* April 2004 – March 2007	12-month intervention with no additional follow-up	*Eligible participants:* All CRF patients discharged from a single hospital *Inclusion criteria*: 1) need for HMV, and/or need for LTOT and 2) ≥ 1 hospitalization for respiratory illness *Exclusion criteria*: 1) illiteracy, no home telephone, 2) nursing home resident, 3) no caregiver to facilitate telephone, or 4) refusal	Total (240) ---------- Total COPD (101) Intervention (57) Usual care (44)	Intervention *Timing:* Post discharge *Technology:* • pulse oximeter (Nonin 9500) • oximeter; Nonin, Plymouth, MN, USA) • pulse oximeter (Nonin 2500 oximeter; Nonin) plus modem (30 EM model Medical Botticelli web; Digicom, Cardano al Campo, Italy) *Components:* 1) No usual care 2) Home telemonitoring of oximetry data • real-time • nurse 3) Telephone support • scheduled • symptoms assessment • outcomes assessment • nurse 4) Telephone support • unscheduled • symptoms assessment • outcomes assessment • additional needs/questions • specialized physician 5) Coordinated feedback/management

Author, Year	Country	Outcomes	Recruit. Period/ Study Period	Length of Intervention/ Follow-up (months)	Patient Eligibility Criteria	Arms (n)	Intervention/Control
							• via telephone/email/visits • nurse • specialized physician • external contacts: GP <u>Usual care</u> Follow-up outpatient visits were scheduled every 3 months to assess compliance, HMV, and/or LTOT
Lewis et al, 2010a/b (3;4)	United Kingdom.	*Primary*: • hospitalizations *Secondary*: • COPD admissions • ED attendances • GP visits • length of stay • usage • SGRQ • hospital anxiety • hospital depression • EQ-5D • communication	NR	6-month intervention with additional 6 months of observational follow-up during which interventional arm received usual care	*Eligible participants:* Identified from a PR database *Inclusion*: 1) a primary diagnosis of moderate to severe COPD <u>and</u> 2) prescribed optimal medication <u>and</u> 3) at least 12 of 18 sessions in researcher's pulmonary rehabilitation program *Exclusion:* 1) chronic asthma and ILD, 2) no longer living at home, <u>or</u> 3) attended <12 PR sessions	Total (40) Intervention (20) Control (20)	<u>Intervention:</u> *Timing:* Median of 8 months after completion of PR *Technology*: • landline-connected care management system (doc@HOME Docobo Ltd, Bookham, UK) • handheld telemonitor (Docobo Health Hub, Docobo Ltd, Bookham, UK) • manual thermometer (model FT04-1, Beurer, Ulm, Germany) • pulse oximeter (Nonin Inc, Minnesota, USA) *Components:* 1) Usual care, plus: 2) Home telemonitoring of oximetry and temperature data • store-and-forward • chronic disease management team

Author, Year	Country	Outcomes	Recruit. Period/ Study Period	Length of Intervention/ Follow-up (months)	Patient Eligibility Criteria	Arms (n)	Intervention/Control
							3) Home monitoring • store-and-forward • symptoms assessment • medication assessment 4) Coordinated feedback/management • via telephone/visits • chronic disease management team: – specialized nurse – nurse case manager – respiratory physiotherapist <u>Usual care:</u> Continued chronic disease management by the chronic disease management team and hospital/primary care support at the discretion of the team
Koff et al, 2008 (2)	United States	*Primary:* • SGRQ *Secondary:* • Hospitalizations • ED visits • costs • satisfaction • communication	*Recruitment period:* November 2004 – June 2005	3-month intervention with no additional follow-up	*Eligible participants:* Recruited from 2 outpatient clinics at a single hospital *Inclusion*: 1) GOLD stage 3 or 4 COPD <u>and</u> 2) home telephone landline *Exclusion*: 1) active treatment for lung cancer, 2) illiteracy, 3) non-English speaking, or 4) inability to complete a 6-min walking test	Total (40) Intervention (20) Control (20)	<u>Intervention:</u> *Timing*: During management at an outpatient clinic *Technology:* • landline-connected care management system (Health Buddy System HealthHero Network, Palo Alto, CA, USA) • pulse oximeter (Tuffsat, GE Healthcare, Chalfont St Giles, UK) • FEV1 monitor (Microlife PF100, iCare Health Monitoring, Golden, CO, USA) • pedometer (Omron, Omron

Author, Year	Country	Outcomes	Recruit. Period/ Study Period	Length of Intervention/ Follow-up (months)	Patient Eligibility Criteria	Arms (n)	Intervention/Control
							Healthcare Inc., Bannockburn, IL, USA) *Components:* 1) No usual care 2) Self-management education • at enrolment by case manager (respiratory therapist) • reinforced through the landline-connected care management system 2) Disease-specific education • at enrolment by case manager 3) Home telemonitoring of oximetry, FEV1, and 6MWD • store-and-forward • case manager 4) Home monitoring • store-and-forward • symptoms assessment • medications assessment • case manager 5) Telephone support • unscheduled • additional needs/questions • case manager 6) Coordinated feedback/management • case manager • external contacts: GP <u>Usual care:</u> Continued on treatment regimen prescribed by their healthcare provider. The care coordinator made no attempt to change any aspect of the patient's treatment regimen at enrolment.

Author, Year	Country	Outcomes	Recruit. Period/ Study Period	Length of Intervention/ Follow-up (months)	Patient Eligibility Criteria	Arms (n)	Intervention/Control
Controlled Clinical Trials (N = 2)							
Pare et al, 2006 (5)	Canada	*Primary:* • costs *Secondary:* • hospitalizations • home visits • communication	*Recruitment period*: December 2003 – June 2004	6-month intervention with no additional follow-up	*Eligible participants*: Newly admitted patients with severe COPD at a single hospital *Inclusion*: 1) newly admitted, and 2) severe COPD, and 3) required frequent home visits *Exclusion*: 1) psychological or psychiatric disorders, 2) cognitive deficiency that prevented self-treatment, or 3) visual or motor deficiency that prevented use of telemonitoring technology (unless caregiver was able to help)	Total (29) Intervention (19) Control (10)	Intervention: *Timing:* Post-discharge *Technology:* Landline-connected care management system (New IT Technologies Inc., Montreal, Quebec) *Components:* 1) No usual care 2) Home telemonitoring of peak flow • store-and-forward • real-time alerts • nurse 3) Home monitoring • store-and-forward • real-time alerts • symptoms assessment • medications assessment • nurse 4) Coordinated feedback/management • via telephone • nurse • external contacts: GP Usual care: Traditional system of home visits
Sorknaes et al, 2011 (6)	Denmark	Primary: • hospitalizations Secondary: • length of Stay • hospitalizations	*Recruitment period:* June 2007 – March 2008 & August 2008 – January	1-month intervention with no additional follow-up	*Eligible participants:* All patients admitted due to acute exacerbation from COPD to a single hospital	Total (100) Intervention (50) Control (50)	Intervention *Timing:* Within 24 hours after patient discharge *Technology:* Computer with web camera, microphone, physiological measurement

Author, Year	Country	Outcomes	Recruit. Period/ Study Period	Length of Intervention/ Follow-up (months)	Patient Eligibility Criteria	Arms (n)	Intervention/Control
		due to exacerbation • time free from hospitalization	2009		*Inclusion criteria*: 1) COPD, and 2) acute exacerbation, and 3) ≥ 40 years of age, and 4) ≥ 10 pack years, and 5) able to use a phone *Exclusion criteria*: 1) communication problems, 2) previous participation in scientific study, 3) systolic blood pressure < 100 mmHg, 4) pH < 7.35 or pO_2 < 7.3 or saturation < 90%, 5) X-ray with lobar pneumonia or tumour or no X-ray taken, 6) other serious diseases, 7) cancer or severe heart failure (EF < 30%), 8) refused to participate, 9) nurse strike, holiday, not possible to get a suitcase, or 10) death before discharge		equipment, nurse call button and alarm button *Components:* 1) Home telemonitoring of pulse oximetry and lung function • real-time • video consultation • nurse 2) Home monitoring • real-time • symptoms assessment 3) Disease-specific education • by nurse during video monitoring sessions Usual care*:* NR

*Abbreviations: COPD, chronic obstructive pulmonary disease; CRF, chronic respiratory failure; ED, emergency department; EF, ejection fraction; EQ-5D, EuroQol-5D; FEV1, forced expiratory volume in 1 second; h, hour(s); GOLD, the Global Initiative for Chronic Obstructive Lung Disease; GP, general practitioner; HMV, home mechanical ventilation; ILD, interstitial lung disease; LTOT, long-term oxygen therapy; n, sample size; NR, not reported; Recruit., recruitment; SGRQ, St. George's Respiratory Questionnaire.

Table A2: Design and Participant Characteristics of Included Studies of Telephone Only Support*

Author, Year	Outcomes	Recruit. Period / Study Period	Length of Intervention / Follow-up (months)	Patient Eligibility Criteria	Arms (n)	Intervention/Control
Randomized Controlled Trials (N = 1)						
Wong et al, 2005 (8)	Primary: • CSES Secondary: • hospitalizations • length of stay • ED visits	NR	18-day intervention with additional 15- day follow-up	*Eligible participants:* All patients discharged from a single hospital *Inclusion criteria:* 1) diagnosis of COPD, and 2) no ischaemic heart disease, musculoskeletal disorders, or other diseases that might limit rehabilitation, and 3) able to speak Cantonese, and 4) alert and oriented, and 5) contactable by phone/mobile phone *Exclusion criteria:* 1) discharged to an old-age home, 2) serious abuse of alcohol or drugs, or suffering from a psychiatric disease, or 3) dying and/or unable to provide informed consent	Total (60) Intervention (30) Control (30)	Intervention: *Timing:* Post-discharge *Components:* Nurse-led post-discharge telephone support *Description:* A structured, individualized educational and supportive programme, which consisted of 2 telephone contacts on days 3–7 and days 14–20, lasting 10–20 minutes. The protocol consisted of 3 parts: assessment, management options, and evaluation. Usual care: Routine care without follow-up

*Abbreviations: COPD, chronic obstructive pulmonary disease; CSES, Chinese Self-Efficacy Scale; ED, emergency department; n, sample size; NR, not reported; Recruit., recruitment.

Appendix 3: Quality Characteristics

Table A3: Methodological Quality Characteristics of Included Trials of Home Telemonitoring*

Author, Year	n	Adequate Randomization	Adequate Allocation Concealment	Blinding	Baseline Measures Comparable	Sample Size/Power Calculation	Met Sample Size	Lost to Follow-Up	ITT
Vitacca et al, 2009 (7)	101	✓	?	X	X†	X*	?	?	X
Lewis et al, 2010a/b (3;4)	40	✓	✓	Single (some treating physicians and nurses and outcome assessors)	X‡	X	?	Intervention 2/20 (10%) Control 0/20 (0%)	?
Koff et al, 2008 (2)	40	✓	?	X	✓	✓	✓	Intervention 1/20 (5%) Control 1/20 (5%)	X
Pare et al, 2006 (5)	29	X	X	X	✓	X	X	0	✓
Sorknaes et al, 2011 (6)	100	X	X	X	X§	✓	✓	Intervention 2/50 (4%) Control 1/50 (2%)	✓

*Abbreviations: ITT, intention-to-treat analysis; n, sample size.

† Sample size/power calculation and baseline comparisons were estimated for full patient population (N = 240) and not for the unplanned COPD-only subgroup (n = 101).

‡ Intervention and control significantly differed in Body Mass Index (BMI), months since finishing pulmonary rehabilitation, and the Medical Research Council (MRC) dyspnoea score.

§ Intervention and control significantly differed in current smoking status.

Table A4: Methodological Quality Characteristics of Included Trials of Telephone Only Support*

Study	n	Adequate Randomization	Adequate Allocation Concealment	Blinding	Baseline Measures Comparable	Sample Size/Power Calculation	Met Sample Size	Lost to Follow-Up	ITT
Wong et al, 2005 (8)	60	✓	?	Single (outcome assessors only)	✓	✓	X	Intervention 2/30 (7%) Control 2/30 (7%)	✓

*Abbreviations: ITT, intention-to-treat analysis; n, sample size.

Appendix 4: GRADE evaluation

Table A5: GRADE Assessment of Quality of Evidence for Home Telemonitoring for the Outcome of Hospitalizations*

Studies	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Lewis et al, 2010 (3;4) Pare et al, 2006 (5) Vitacca et al, 2006 (7) Koff et al, 2008 (2) Sorknaes et al, 2010 (6)	RCTs / CCTs	Very serious limitations • included non-randomized trials • lack of blinding • unplanned subgroup analysis • important baseline variables differed significantly in some trials • potential power concerns • other issues	Inconsistency	Potential issues with generalizability of intervention	No serious limitations	N/A	
	HIGH	-2 (LOW)	-1 (VERY LOW)	VERY LOW	VERY LOW	VERY LOW	**VERY LOW**

*Abbreviations: CCT, controlled clinical trial; N/A, not applicable; RCT, randomized controlled trial.

Table A6: GRADE Assessment of Quality of Evidence for Home Telemonitoring for the Outcome of Time Free of Hospitalization*

Studies	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Vitacca et al, 2006 (7) Sorknaes et al, 2010 (6)	RCTs / CCTs	Very serious limitations • included non-randomized trials • unplanned subgroup analysis • lack of blinding • important baseline variables differed significantly or no comparison of baseline variables	No serious limitations	Potential issues with generalizability of intervention	No serious limitations	N/A	
	HIGH	-2 (LOW)	LOW	LOW	LOW	LOW	**LOW**

*Abbreviations: CCT, controlled clinical trial; N/A, not applicable; RCT, randomized controlled trial.

Table A7: GRADE Assessment of Quality of Evidence for Home Telemonitoring for the Outcome of Mortality*

Studies	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Vitacca et al, 2006 (7)	RCTs HIGH	Very serious limitations • unplanned COPD subgroup analysis • lack of blinding • no comparison of baseline values for COPD subgroup • sample size and power calculations targeted to whole population not COPD subgroup • no ITT -2 (LOW)	No inconsistency LOW	Potential issues with generalizability of intervention LOW	No serious limitations LOW	N/A LOW	**LOW**

*Abbreviations: COPD, chronic obstructive pulmonary disease; ITT, intention-to-treat analysis; N/A, not applicable; RCT, randomized controlled trial.

Table A8: GRADE Assessment of Quality of Evidence for Home Telemonitoring for the Outcome of Quality of Life*

Studies	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Koff et al, 2008 (2) Lewis et al, 2010 (3;4)	RCTs	Serious limitations • important differences in baseline variables • no ITT	Inconsistency	Potential issues with generalizability of intervention	No serious limitations	N/A	
	HIGH	-1 (MODERATE)	-1 (LOW)	LOW	LOW	LOW	**LOW**

*Abbreviations: ITT, intention-to-treat analysis; N/A, not applicable; RCT, randomized controlled trial.

Table A9: GRADE Assessment of Quality of Evidence for Home Telemonitoring for the Outcome of Length of Stay*

Studies	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Lewis et al, 2010 (3;4) Pare et al, 2006 (5)	RCT / CCT	Very serious limitations • included non-randomized study • important differences in baseline variables • potential lack of power	No serious limitations	Potential issues with generalizability of intervention	No serious limitations	N/A	
	HIGH	-2 (LOW)	LOW	LOW	LOW	LOW	**LOW**

*Abbreviations: CCT, controlled clinical trial; N/A, not applicable; RCT, randomized controlled trial.

Table A10: GRADE Assessment of Quality of Evidence for Home Telemonitoring for the Outcome of Exacerbation*

Studies	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Sorknaes et al, 2010 (6)	CCT HIGH	Very serious limitations • non-randomized • lack of blinding • intervention and usual care differed in current smoker status at baseline -2 (LOW)	No serious limitations LOW	Potential issues with generalizability of intervention LOW	No serious limitations LOW	N/A LOW	**LOW**

*Abbreviations: CCT, controlled clinical trial; N/A, not applicable.

Table A11: GRADE Assessment of Quality of Evidence for Home Telemonitoring for the Outcome of Emergency Department Visits*

Studies	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Koff et al, 2008 (2) Lewis et al, 2010 (3;4)	RCTs / CCTs	Very serious limitations • included non-randomized trials • lack of blinding • important baseline variables differed significantly • no ITT	Inconsistency	Potential issues with generalizability of intervention	No serious limitations	N/A	
	HIGH	-2 (LOW)	(-1) VERY LOW	VERY LOW	VERY LOW	VERY LOW	**VERY LOW**

*Abbreviations: CCT, controlled clinical trial; ITT, intention-to-treat analysis; N/A, not applicable; RCT, randomized controlled trial.

Table A12: GRADE Assessment of Quality of Evidence for Home Telemonitoring for Time to Other Health Care Services*

Studies	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Vitacca et al, 2006 (7)	RCTs HIGH	Very serious limitations • unplanned COPD subgroup analysis • lack of blinding • no comparison of baseline values for COPD subgroup • sample size and power calculations targeted to whole population not COPD subgroup • no ITT -2 (LOW)	No inconsistency LOW	Potential issues with generalizability of intervention LOW	No serious limitations LOW	N/A LOW	**LOW**

*Abbreviations: COPD, chronic obstructive pulmonary disease; ITT, intention-to-treat analysis; N/A, not applicable; RCT, randomized controlled trial.

Table A13: GRADE Assessment of Quality of Evidence for Telephone Only Support for the Outcome of Hospitalization*

Studies	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Wong et al, 2005 (8)	RCT HIGH	No serious limitations HIGH	N/A HIGH	Very serious issues with generalizability • Chinese population • no comorbidities that may have limited pulmonary rehabilitation • intervention (adapted Chinese Self Efficacy Scale used to guide telephone follow-up) -2 (LOW)	No serious limitations LOW	N/A LOW	**LOW**

*Abbreviations: N/A, not applicable; RCT, randomized controlled trial.

Table A14: GRADE Assessment of Quality of Evidence for Telephone Only Support for the Outcome of Quality of Life*

Studies	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Wong et al, 2005 (8)	RCT	No serious limitations	N/A	Very serious issues with generalizability • Chinese population • no comorbidities that may have limited pulmonary rehabilitation • intervention (adapted Chinese Self-Efficacy Scale used to guide telephone follow-up)	No serious limitations	N/A	
	HIGH	HIGH	HIGH	-2 (LOW)	LOW	LOW	**LOW**

*Abbreviations: N/A, not applicable; RCT, randomized controlled trial.

Table A15: GRADE Assessment of Quality of Evidence for Telephone Only Support for the Outcome of Length of Stay*

Studies	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Wong et al, 2005 (8)	RCT	No serious limitations	N/A	Very serious issues with generalizability • Chinese population • no comorbidities that may have limited pulmonary rehabilitation • intervention (adapted Chinese Self Efficacy Scale used to guide telephone follow-up)	No serious limitations	N/A	
	HIGH	HIGH	HIGH	-2 (LOW)	LOW	LOW	**LOW**

*Abbreviations: N/A, not applicable; RCT, randomized controlled trial.

Table A16: GRADE Assessment of Quality of Evidence for Telephone Only Support for the Outcome of Emergency Department Visits*

Studies	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Wong et al, 2005 (8)	RCT	No serious limitations	N/A	Very serious issues with generalizability • Chinese population • no comorbidities that may have limited pulmonary rehabilitation • intervention (adapted Chinese Self Efficacy Scale used to guide telephone follow-up)	No serious limitations	N/A	
	HIGH	HIGH	HIGH	-2 (LOW)	LOW	LOW	**LOW**

*Abbreviations: N/A, not applicable; RCT, randomized controlled trial.

References

(1) Report from the Swedish Council on Technology Assessment in Health Care (SBU). Literature searching and evidence interpretation for assessing health care practices. Int J Technol Assess Health Care. 1994;10(4):714-5.

(2) Koff PB, Jones RH, Cashman JM, Voelkel NF, Vandivier RW. Proactive integrated care improves quality of life in patients with COPD. Eur Respir J. 2009 May;33(5):1031-8.

(3) Lewis KE, Annandale JA, Warm DL, Rees SE, Hurlin C, Blyth H, et al. Does home telemonitoring after pulmonary rehabilitation reduce healthcare use in optimized COPD? A pilot randomized trial. COPD. 2010 Feb;7(1):44-50.

(4) Lewis KE, Annandale JA, Warm DL, Hurlin C, Lewis MJ, Lewis L. Home telemonitoring and quality of life in stable, optimised chronic obstructive pulmonary disease. J Telemed Telecare. 2010 Jul;16(5):253-9.

(5) Pare, G, Sicotte C, St-Jules D, Gauthier R. Cost-minimization analysis of a telehomecare program for patients with chronic obstructive pulmonary disease. Telemed J E Health. 2006 Apr;12(2):114-21.

(6) Sorknaes AD, Madsen H, Hallas J, Jest P, Hansen-Nord M. Nurse tele-consultations with discharged COPD patients reduce early readmissions--an interventional study. Clin Respir J. 2011 Jan;5(1):26-34.

(7) Vitacca M, Bianchi L, Guerra A, Fracchia C, Spanevello A, Balbi B, et al. Tele-assistance in chronic respiratory failure patients: a randomised clinical trial. Eur Respir J. 2009 Feb;33(2):411-8.

(8) Wong KW, Wong FK, Chan MF. Effects of nurse-initiated telephone follow-up on self-efficacy among patients with chronic obstructive pulmonary disease.[Erratum appears in J Adv Nurs. 2005 Mar;49(5):561]. J Adv Nurs. 2005 Jan;49(2):210-22.

(9) Polisena J, Tran K, Cimon K, Hutton B, McGill S, Palmer K, et al. Home telehealth for chronic obstructive pulmonary disease: a systematic review and meta-analysis. J Telemed Telecare. 2010;16(3):120-7.

(10) Polisena J, Coyle D, Coyle K, McGill S. Home telehealth for chronic disease management: a systematic review and an analysis of economic evaluations. Int J Technol Assess Health Care. 2009 Jul;25(3):339-49.

(11) Dang S, Ma F, Nedd N, Aguilar EJ, Roos BA. Differential resource utilization benefits with Internet-based care coordination in elderly veterans with chronic diseases associated with high resource utilization. Telemed J E Health. 2006 Feb;12(1):14-23.

(12) Nguyen HQ, Carrieri-Kohlman V, Rankin SH, Slaughter R, Stulbarg MS. Is Internet-based support for dyspnea self-management in patients with chronic obstructive pulmonary disease possible? Results of a pilot study. Heart Lung. 2005 Jan;34(1):51-62.

(13) Sund ZM, Powell T, Greenwood R, Jarad NA. Remote daily real-time monitoring in patients with COPD --a feasibility study using a novel device. Respir Med. 2009 Sep;103(9):1320-8.

(14) Vontetsianos T, Giovas P, Katsaras T, Rigopoulou A, Mpirmpa G, Giaboudakis P, et al. Telemedicine-assisted home support for patients with advanced chronic obstructive pulmonary disease: Preliminary results after nine-month follow-up. J Telemed Telecare. 2005;11(SUPPL. 1):86-8.

(15) Maiolo C, Mohamed EI, Fiorani CM, De LA. Home telemonitoring for patients with severe respiratory illness: the Italian experience. J Telemed Telecare. 2003;9(2):67-71.

(16) Trappenburg JCA, Niesink A, De Weert-Van Oene GH, van der ZH, van SR, Peters A, et al. Effects of telemonitoring in patients with chronic obstructive pulmonary disease. Telemed J E Health. 2008;14(2):138-46.

(17) Farrero E, Escarrabill J, Prats E, Maderal M, Manresa F. Impact of a hospital-based home-care program on the management of COPD patients receiving long-term oxygen therapy. Chest. 2001 Feb;119(2):364-9.

(18) de Toledo P, Nez S, del PF, Roca J, Alonso A, Hernandez C. Telemedicine experience for chronic care in COPD. IEEE Trans Inf Technol Biomed. 2006 Jul;10(3):567-73.

(19) Casas A, Troosters T, Garcia-Aymerich J, Roca J, Hernandez C, Alonso A, et al. Integrated care prevents hospitalisations for exacerbations in COPD patients. Eur Respir J. 2006;28(1):123-30.

(20) Sridhar M, Taylor R, Dawson S, Roberts NJ, Partridge MR. A nurse led intermediate care package in patients who have been hospitalised with an acute exacerbation of chronic obstructive pulmonary disease. Thorax. 2008 Mar;63(3):194-200.

(21) Waterhouse JC, Walters SJ, Oluboyede Y, Lawson RA. A randomised 2 x 2 trial of community versus hospital pulmonary rehabilitation for chronic obstructive pulmonary disease followed by telephone or conventional follow-up. Health Technol Assess. 2010;14(6):1-164.

(22) Bourbeau J, Julien M, Maltais F, Rouleau M, Beaupré A, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. Arch Intern Med. 2003 Mar 10;163(5):585-91.

(23) Egan E, Clavarino A, Burridge L, Teuwen M, White E. A randomized control trial of nursing-based case management for patients with chronic obstructive pulmonary disease. Lippincotts Case Manag. 2002 Sep;7(5):170-9.

(24) Hurst JR, Fitzgerald-Khan F, Quint JK, Goldring JJ, Mikelsons C, Dilworth JP, et al. Use and utility of a 24-hour Telephone Support Service for 'high risk' patients with COPD. Prim Care Respir J. 2010 Sep;19(3):260-5.

(25) Lawlor M, Kealy S, Agnew M, Korn B, Quinn J, Cassidy C, et al. Early discharge care with ongoing follow-up support may reduce hospital readmissions in COPD. Int J Chron Obstruct Pulmon Dis. 2009;4:55-60.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-7017-6 (PDF)

Ontario
Health Quality Ontario
Qualité des services de santé Ontario

Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease (COPD) Using an Ontario Policy Model

K Chandra, G Blackhouse, BR McCurdy, M Bornstein, K Campbell, V Costa, J Franek, K Kaulback, L Levin, S Sehatzadeh, N Sikich, M Thabane, R Goeree

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 12, pp. 1–61, March 2012

Suggested Citation

This report should be cited as follows: Chandra K, Blackhouse G, McCurdy BR, Bornstein M, Campbell K, Costa V, Franek J, Kaulback K, Levin L, Sehatzadeh S, Thabane M, Sikich N, Goeree R. Cost-effectiveness of interventions for chronic obstructive pulmonary disease using an Ontario policy model. Ont Health Technol Assess Ser [Internet]. 2012 Mar; 12(12):1-61. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Economic_March.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

CCI	Canadian Classification of Health Interventions
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPS	*Compendium of Pharmaceuticals and Specialties*
CUA	Cost-utility analysis
EBA	Evidence-based analysis
FEV_1	Forced expiratory volume in 1 second
FHT	Family Health Team
FVC	Forced vital capacity
FY	Fiscal year
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
IC	Intensive counselling
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
LOS	Length of stay
LTOT	Long-term oxygen therapy
MAS	Medical Advisory Secretariat
MDC	Multidisciplinary care
NPPV	Noninvasive positive pressure ventilation
NRT	Nicotine replacement therapy
OCCI	Ontario Case Costing Initiative
ODB	Ontario Drug Benefit
OSB	Ontario Schedule of Physician Benefits
PR	Pulmonary rehabilitation
QALY	Quality-adjusted life-year
QOL	Quality of life
RN	Registered nurse
RR	Relative risk
UC	Usual care
UMC	Usual medical care
WTP	Willingness to pay

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-Term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Background

Chronic obstructive pulmonary disease (COPD) is characterized by chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature. The inflammation causes repeated cycles of injury and repair in the airway wall—inflammatory cells release a variety of chemicals and lead to cellular damage. The inflammation process also contributes to the loss of elastic recoil pressure in the lung, thereby reducing the driving pressure for expiratory flow through narrowed and poorly supported airways, in which airflow resistance is significantly increased. Expiratory flow limitation is the pathophysiological hallmark of COPD.

Exacerbations of COPD contribute considerably to morbidity and mortality, and impose a burden on the health care system. They are a leading cause of emergency room visits and hospitalizations, particularly in the winter. In Canada, the reported average cost for treating a moderate exacerbation is $641; for a major exacerbation, the cost is $10,086.

Objective

The objective of this study was to evaluate the cost-effectiveness and budget impact of the following interventions in moderate to very severe COPD, investigated in the Medical Advisory Secretariat Chronic Obstructive Pulmonary Disease Mega-Analysis Series:

- smoking cessation programs in moderate COPD in an outpatient setting:
  - intensive counselling (IC) versus usual care (UC)
  - nicotine replacement therapy (NRT) versus UC
  - IC + NRT versus placebo
  - bupropion versus placebo
- multidisciplinary care (MDC) teams versus UC in moderate to severe COPD in an outpatient setting
- pulmonary rehabilitation (PR) versus UC following acute exacerbations in moderate to severe COPD
- long-term oxygen therapy (LTOT) versus UC in severe hypoxemia in COPD in an outpatient setting
- ventilation:
  - noninvasive positive pressure ventilation (NPPV) + usual medical care versus usual medical care in acute respiratory failure due to an acute exacerbation in severe COPD in an inpatient setting
  - weaning with NPPV versus weaning with invasive mechanical ventilation in acute respiratory failure due to an acute exacerbation in very severe COPD in an inpatient setting

Methods

A cost-utility analysis was conducted using a Markov probabilistic model. The model consists of different health states based on the Global Initiative for Chronic Obstructive Lung Disease COPD severity classification. Patients were assigned different costs and utilities depending on their severity health state during each model cycle. In addition to moving between health states, patients were at risk of acute exacerbations of COPD in each model cycle. During each cycle, patients could have no acute exacerbation, a minor acute exacerbation, or a major exacerbation. For the purposes of the model, a major

exacerbation was defined as one that required hospitalization. Patients were assigned different costs and utilities in each model cycle, depending on whether they experienced an exacerbation, and its severity.

Starting cohorts reflected the various patient populations from the trials analyzed. Incremental cost-effectiveness ratios (ICERs)—that is, costs per quality-adjusted life-year (QALY)—were estimated for each intervention using clinical parameters and summary estimates of relative risks of (re)hospitalization, as well as mortality and abstinence rates, from the COPD mega-analysis evidence-based analyses.

A budget impact analysis was also conducted to project incremental costs already being incurred or resources already in use in Ontario. Using provincial data, medical literature, and expert opinion, health system impacts were calculated for the strategies investigated.

All costs are reported in Canadian dollars.

Results

All smoking cessation programs were dominant (i.e., less expensive and more effective overall). Assuming a base case cost of $1,041 and $1,527 per patient for MDC and PR, the ICER was calculated to be $14,123 per QALY and $17,938 per QALY, respectively. When the costs of MDC and PR were varied in a 1-way sensitivity analysis to reflect variation in resource utilization reported in the literature, the ICER increased to $55,322 per QALY and $56,270 per QALY, respectively. Assuming a base case cost of $2,261 per year per patient for LTOT as reported by data from the Ontario provincial program, the ICER was calculated to be $38,993 per QALY. Ventilation strategies were dominant (i.e., cheaper and more effective), as reflected by the clinical evidence of significant in-hospital days avoided in the study group.

Ontario currently pays for IC through physician billing (translating to a current burden of $8 million) and bupropion through the Ontario Drug Benefit program (translating to a current burden of almost $2 million). The burden of NRT was projected to be $10 million, with future expenditures of up to $1 million in Years 1 to 3 for incident cases.

Ontario currently pays for some chronic disease management programs. Based on the most recent Family Health Team data, the costs of MDC programs to manage COPD were estimated at $85 million in fiscal year 2010, with projected future expenditures of up to $51 million for incident cases, assuming the base case cost of the program. However, this estimate does not accurately reflect the current costs to the province because of lack of report by Family Health Teams, lack of capture of programs outside this model of care by any data set in the province, and because the resource utilization and frequency of visits/follow-up phone calls were based on the findings in the literature rather than the actual Family Health Team COPD management programs in place in Ontario. Therefore, MDC resources being utilized in the province are unknown and difficult to measure.

Data on COPD-related hospitalizations were pulled from Ontario administrative data sets and based on consultation with experts. Half of hospitalized patients will access PR resources at least once, and half of these will repeat the therapy, translating to a potential burden of $17 million to $32 million, depending on the cost of the program. These resources are currently being absorbed, but since utilization is not being captured by any data set in the province, it is difficult to quantify and estimate. Provincial programs may be under-resourced, and patients may not be accessing these services effectively.

Data from the LTOT provincial program (based on fiscal year 2006 information) suggested that the burden was $65 million, with potential expenditures of up to $0.2 million in Years 1 to 3 for incident cases.

From the clinical evidence on ventilation (i.e., reduction in length of stay in hospital), there were potential cost savings to the hospitals of $42 million and $12 million for NPPV and weaning with NPPV, respectively, if the study intervention were adopted. Future cost savings were projected to be up to $4 million and $1 million, respectively, for incident cases.

Conclusions

Currently, costs for most of these interventions are being absorbed by provider services, the Ontario Drug Benefit Program, the Assistive Devices Program, and the hospital global budget. The most cost-effective intervention for COPD will depend on decision-makers' willingness to pay. Lack of provincial data sets capturing resource utilization for the various interventions poses a challenge for estimating current burden and future expenditures.

Purpose

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-Term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

DISCLAIMER: The Medical Advisory Secretariat (MAS) uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative (OCCI) cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions (CCI) procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the Secretariat normally defaults to considering direct treatment costs only.

Non-hospital: These include physician services costs obtained from the Ontario Schedule of Benefits (OSB), laboratory fees from the Ontario Schedule of Laboratory Fees (OSLF), drug costs from the Ontario Drug Benefit Formulary (ODB), and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

Downstream costs: All numbers reported are based on assumptions on population trends (i.e., incidence, prevalence, and mortality rates), time horizon, resource utilization, patient compliance, health care patterns, market trends (i.e., rates of intervention uptake or trends in current programs in place in the province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references, provincial data sets, and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents ***an estimate only***, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

NOTE: Numbers are rounded to the nearest decimal and are reported from an Excel spreadsheet.

The Programs for Assessment of Technology in Health Research Institute was commissioned by the Medical Advisory Secretariat (MAS) of Health Quality Ontario to predict the long-term costs and effects, along with the cost-effectiveness, of interventions for the management and treatment of chronic obstructive pulmonary disease (COPD). This report summarizes the structure and inputs for the COPD economic model used to estimate the cost-effectiveness of the various treatment strategies, and it presents the results of the economic analyses for the following interventions: smoking cessation programs, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, and ventilation. Additionally, this report reviews published economic evaluations of these COPD interventions and presents estimates of the budget impact of implementing them.

MAS conducts full evidence-based analyses (EBAs) of health technologies being considered for use in Ontario. These analyses are then presented to the Ontario Health Technology Advisory Committee, whose mandate is to provide evidence-based examination of proposed health technologies in the context of existing clinical practice and provide advice and recommendations to Ontario practitioners, the broader health care system, and the Ministry of Health and Long-Term Care.

Background

COPD is characterized by chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature. This inflammation causes repeated cycles of injury and repair in the airway wall—inflammatory cells release a variety of chemicals and lead to cellular damage. (1;2) The inflammation process also contributes to the loss of elastic recoil pressure in the lung, thereby reducing the driving pressure for expiratory flow through narrowed and poorly supported airways, in which airflow resistance is significantly increased. (3) Expiratory flow limitation is the pathophysiological hallmark of COPD.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a preventable and treatable disease with numerous extrapulmonary effects that may contribute to the severity of disease in individual patients. (4) Its pulmonary component is characterized by airflow limitation that is not fully reversible. The GOLD criteria outline 4 stages of COPD severity, defined by postbronchodilator spirometry measures. These are shown in Table 1, along with a description of the symptoms a patient might experience.

Table 1: The Four Stages of COPD Severity*

Stage	FEV_1 Value	FEV_1/FVC Value	Description
I: Mild	≥ 80% predicted	< 0.70	The patient is probably unaware that lung function is starting to decline
II: Moderate	50% ≤ FEV_1 < 80% predicted	< 0.70	Symptoms during this stage progress, with shortness of breath developing upon exertion
III: Severe	30% ≤ FEV_1 < 50% predicted	< 0.70	Shortness of breath becomes worse at this stage, and COPD exacerbations are common
IV: Very severe	< 30% predicted or < 50% predicted plus chronic respiratory failure	< 0.70	Quality of life at this stage is considerably impaired; COPD exacerbations can be life-threatening

*Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
Source: Global Initiative for Chronic Obstructive Lung Disease, 2010 (4)

Exacerbations of COPD contribute considerably to morbidity and mortality, and impose a burden on the health care system. They are a leading cause of emergency room visits and hospitalizations, particularly in the winter. In Canada, the reported average cost for treating a moderate exacerbation is $641; for a major exacerbation, the cost is $10,086. (5)

Objective

The objective of this study was to evaluate the cost-effectiveness and budget impact of the following interventions in moderate to very severe COPD, investigated in the MAS Chronic Obstructive Pulmonary Disease Mega-Analysis series:

- smoking cessation programs in moderate COPD in an outpatient setting:
  - intensive counselling (IC) versus usual care (UC)
  - nicotine replacement therapy (NRT) versus UC
  - IC + NRT versus placebo
  - bupropion versus placebo
- multidisciplinary care (MDC) teams versus UC in moderate to severe COPD in an outpatient setting
- pulmonary rehabilitation (PR) versus UC following acute exacerbations in moderate to severe COPD
- long-term oxygen therapy (LTOT) versus UC in severe hypoxemia in COPD in an outpatient setting
- ventilation:
  - noninvasive positive pressure ventilation (NPPV) + usual medical care (UMC)[1] versus UMC in acute respiratory failure due to an acute exacerbation in severe COPD in an inpatient setting
  - weaning with NPPV versus weaning with invasive mechanical ventilation (IMV) in acute respiratory failure due to an acute exacerbation in very severe COPD in an inpatient setting

Only interventions that had high, moderate, or low quality evidence (based on the GRADE criteria (6)) with statistically significant differences in outcomes were evaluated in the economic model. COPD interventions that had very low quality evidence were excluded (i.e., vaccinations, hospital at home, home telehealth); the estimates of effect for these investigations were judged to be too uncertain to provide meaningful results. Technologies that were not effective or did not reach statistical significance based on the clinical evidence were also excluded from evaluation in the economic model.

[1] Usual medical care is the term used for the medical treatment of patients with acute respiratory failure as an alternative to NPPV. Usual care is the generic term for the comparison group in other analyses.

Economic Literature Review

Literature Search

Economic literature searches were conducted for each intervention investigated in the COPD mega-analysis, and the following databases were searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment, and EconLit. The following criteria were considered when reviewing abstracts and extracting economic evaluations:

- full economic evaluations (i.e., cost-utility analysis [CUA], cost-effectiveness analysis, cost-benefit analysis)
- economic evaluations reporting total costs and benefits, or incremental cost-effectiveness ratios (ICERs) (i.e., cost per quality-adjusted life-year [QALY] per life years gained or cost per event avoided)
- studies in patients with COPD
- studies reporting on smoking cessation programs, MDC, PR, LTOT, or ventilation
- studies in the English language

There was a large volume of cost analyses in the economic literature; therefore, a second literature search was conducted in July 2011 to investigate only CUAs, since the primary economic evaluation was a CUA. This second literature search is described in the appendix.

Economic Literature Review Results

CUAs in COPD, published since 2009, were reviewed. Two articles were identified that described assessments of smoking cessation programs and MDC using the same COPD model.

Hoogendoorn et al (7) estimated the long-term cost-effectiveness of smoking cessation interventions for patients with COPD. The 4 interventions assessed were UC, minimal counselling, IC, and IC + pharmacotherapy. A population model for COPD was used to predict the costs and benefits of these strategies compared to UC (for policy-making decisions). Abstinence rates were estimated to be 1.4% for UC, 2.6% for minimal counselling, 6.0% for IC, and 12.3% for IC + pharmacotherapy. Compared with UC, the costs per QALY gained for minimal counselling, IC, and IC + pharmacotherapy were €16,900, €8,200, and €2,400, respectively, over a 25-year time horizon. The authors concluded that IC + pharmacotherapy resulted in low costs per QALY gained, was cost-saving, and dominated the other interventions.

The same group used the same policy model to assess MDC in COPD management. (8) The authors conducted the analysis alongside a 2 year randomized controlled trial, in which 199 patients were assigned to either the Interdisciplinary Community-Based COPD Management (INTERCOM) program or UC. The INTERCOM program consisted of exercise training, education, nutrition therapy, and smoking cessation counselling offered by community-based physiotherapists, dietitians, and hospital-based respiratory nurses. The authors found that the INTERCOM program significantly improved disease-specific quality of life (QOL), but did not affect exacerbation rates. The cost per QALY was estimated to be €32,425, and the authors concluded that this estimate was within the acceptable range.

Primary Economic Evaluation

The published economic evaluations identified in the literature review addressed only 2 of the interventions of interest (smoking cessation programs and MDC). Neither of these published studies took a Canadian perspective. Due to these limitations, primary economic evaluations of the COPD interventions of interest were conducted.

Cost-Effectiveness Analysis Method

A CUA was conducted using a Markov probabilistic model for patients with COPD, based on the GOLD classification of disease severity. Cost per QALY allows the QOL impact of the COPD treatment interventions to be incorporated.

The QALY is a measure of disease burden, including both the quality and quantity of life lived. (9) Perfect health is assigned a value of 1.0, and death is assigned a value of 0. Negative scores can be reported, indicating a situation considered to be worse than death. Health states not lived in full health are given a score/utility depending on how patients perceive their state. For example, if the patient would be blind or have to use a wheelchair, extra life-years are given a value to account for this. The weight values can be determined using time trade-off and standard gamble methods, visual analogue scales, and/or pre-existing indices (i.e., Health Utilities Index, EQ-5D). (9) The EQ-5D questionnaire, for example, categorizes health states according to the following dimensions: mobility, self-care, usual activities (e.g., work, study, homework, or leisure activities), pain/discomfort, and anxiety/depression. (9) The QALY is used in assessing the value for money of a medical intervention.

The use of a common metric such as the cost per QALY outcome also allows for comparison with evaluations of different interventions (given similar population characteristics) and may be used to infer from other disease areas that report this standard outcome.

The cost-effectiveness acceptability curve (CEAC) is a method for summarizing uncertainty in estimates of cost-effectiveness. Distributions are assigned to the summary estimates from the clinical evidence reviews, and CEACs are derived from the joint distribution of costs and effects, illustrating the Bayesian probability that the data may or may not be cost-effective, depending on a specified ceiling ratio that a decision-maker is willing to invest to achieve 1 unit of effectiveness.

Interventions Evaluated

Separate evaluations were conducted for the various COPD interventions, compared to UC or placebo. UC was defined according to the trials investigated in the COPD mega-analysis. Table 2 summarizes the interventions evaluated by the economic model, along with the comparator for each intervention.

Table 2: COPD Interventions and Comparators Evaluated in the Primary Economic Model*

Intervention	Comparator
Smoking cessation programs	
Intensive counselling	Usual care
Nicotine replacement therapy	Usual care
Intensive counselling + nicotine replacement therapy	Placebo
Bupropion	Placebo
Multidisciplinary care teams	Usual care
Pulmonary rehabilitation	Usual care
Long-term oxygen therapy	Usual care
Ventilation strategies	
Noninvasive positive pressure ventilation + usual medical care	Usual medical care
Weaning with noninvasive positive pressure ventilation	Weaning with invasive mechanical ventilation

*Abbreviation: COPD, chronic obstructive pulmonary disease.

Target Population

The target population for the economic analyses was patients with moderate to very severe COPD. Cohorts differed in terms of sex, starting age, and starting COPD severity level. Cohort demographics were based on average characteristics described in the trials for each intervention. For further description on trial characteristics, please see individual EBAs from the COPD mega-analysis. Table 3 describes the starting cohorts for the COPD economic model.

Table 3: Starting Cohort Demographics Used in the COPD Model*

Intervention	Age, years	Female, %	Mild, %	Moderate, %	Severe, %	Very severe, %
Smoking cessation programs						
IC vs. UC	48	37	0	100	0	0
NRT vs. UC	48	37	0	100	0	0
IC + NRT vs. placebo	48	37	0	100	0	0
Bupropion vs. placebo	48	37	0	100	0	0
Multidisciplinary care teams						
MDC vs. UC	68	12	0	50	50	0
Pulmonary rehabilitation						
PR vs. UC	68	46	0	40	60	0
Long-term oxygen therapy						
LTOT vs. UC	58	24	0	0	0	100
Ventilation strategies						
NPPV + UMC vs. UMC	65	33	0	0	100	0
Weaning with NPPV versus weaning with IMV	64	30	0	0	0	100

*Abbreviations: COPD, chronic obstructive pulmonary disease; IC, intensive counselling; IMV, invasive mechanical ventilation; LTOT, long-term oxygen therapy; MDC, multidisciplinary care; NPPV, noninvasive positive pressure ventilation; NRT, nicotine replacement therapy; PR, pulmonary rehabilitation; UC, usual care; UMC, usual medical care.

Populations varied with respect to disease severity and distribution of age and sex. Except for the smoking cessation interventions, trials largely reflected an elderly patient population (over 65 years of age) and a skewed distribution (higher proportion of males).

Perspective

The analysis was taken from the perspective of a publicly funded health care system. Costs from this perspective included drugs covered by provincial formularies, inpatient costs described by the Ontario Case Costing Initiative (OCCI), (10) and physician fees and laboratory fees for services covered by provincial fee schedules. Indirect costs, such as productivity losses, were not considered in the analysis; the base case starting age was 65 years for most interventions, so productivity costs were assumed to be minimal. Costs to family members were beyond the scope of this analysis.

All costs are reported in Canadian dollars.

Discounting and Time Horizon

An annual discount rate of 5% was applied to both costs and QALYs as recommended by economic guidelines. (11) A lifelong time horizon was used in all analyses.

Variability and Uncertainty

Variability and uncertainty were assessed using a probabilistic model and 1-way sensitivity analyses. The program costs of MDC and PR were varied in 1-way analyses. Model parameter uncertainty was assessed using probabilistic sensitivity analysis by assigning distributions around the point estimate. Results were presented in the form of CEACs showing the probability that the intervention would be cost-effective by ceiling ratio (i.e., willingness to pay [WTP] values).

Generalizability

The findings of this economic analysis cannot be generalized to all patients with COPD. They may, however, be used to guide decision-making about the specific patient populations addressed in the trials investigated at MAS.

Model Structure

Because COPD is a chronic progressive disease, a Markov model was used for the analyses. The overall structure of the model, including the transitions between health states, is presented in Figure 1. The circles in the diagram represent different health states based on the GOLD COPD severity classification, and the arrows show the possible patient transitions in a given model cycle. The circular arrows represent cycling within a health state until transition to the next state. Severity is defined by forced expiratory volume in 1 second (FEV_1) as a percentage of predicted FEV_1. The 4 severity-based health states in the model are mild ($FEV_1 \geq 80\%$), moderate ($50\% \leq FEV_1 < 80\%$), severe ($30\% \leq FEV_1 < 50\%$), and very severe ($FEV_1 < 30\%$). Patients were assigned different costs and utilities depending on their severity health state during each model cycle.

In addition to moving between health states, patients were at risk of acute exacerbations of COPD in each model cycle: they could have no acute exacerbation, a minor acute exacerbation, or a major exacerbation. For the purposes of the model, a major exacerbation was defined as one that required hospitalization. Patients suffering a major exacerbation were at risk of inpatient death. Patients were assigned different

costs and utilities in each model cycle, depending on whether they experienced an exacerbation, and its severity.

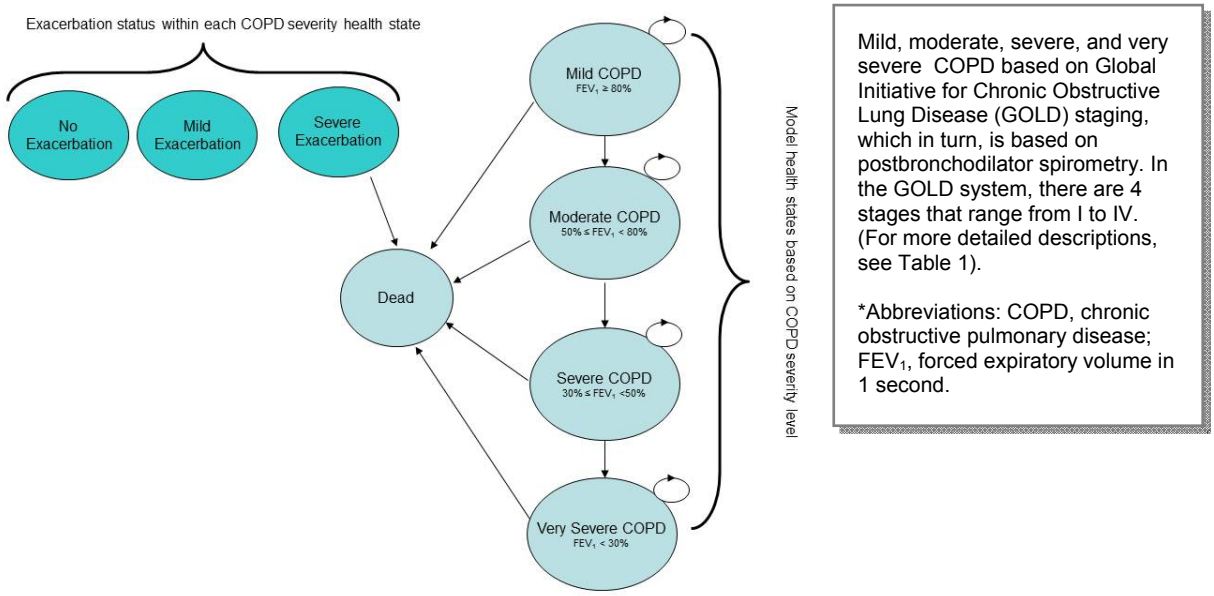


Figure 1: Structure of COPD Model*

Figure 2 describes up-front modifications to the model structure made for the analyses of smoking cessation interventions. These modifications were made because the original model structure could not accommodate smoking abstinence rates—the primary outcome evaluated in the literature review for the smoking cessation EBA. As shown in Figure 2, a proportion of the cohort was assumed to have successfully quit smoking (quitters), while a proportion of patients continued to smoke (non-quitters). The proportion of quitters was based on abstinence rates reported in the smoking cessation trials. Quitters and non-quitters were treated differently in the model in 2 ways. First, quitters were assigned a reduction in overall mortality throughout the lifetime model, while non-quitters are assumed to have the same background mortality as the unmodified COPD model. Second, quitters were assumed to have different annual reductions in FEV_1 throughout the model. These differences in FEV_1 change affected the progress of patients to worse COPD health states.

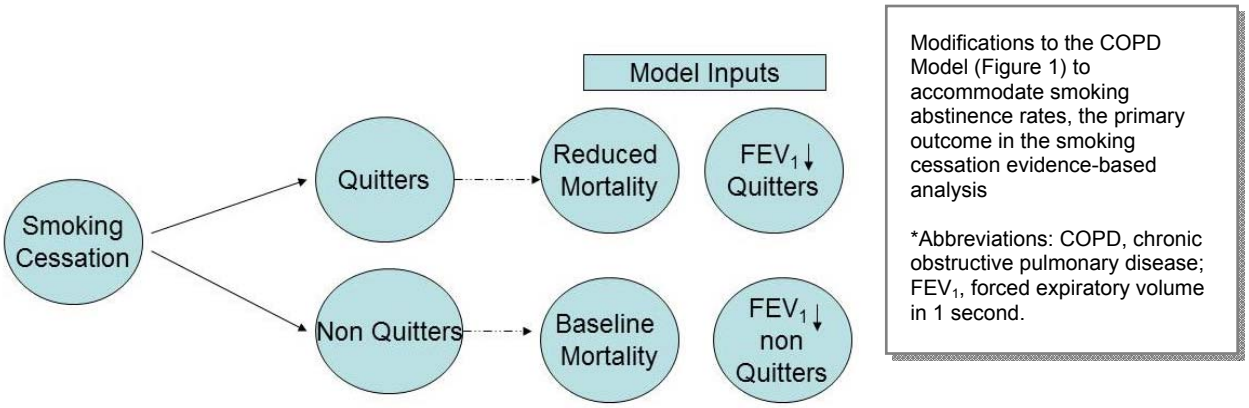


Figure 2: Structure of COPD Model—Modifications for Smoking Cessation Intervention Analyses*

Model Input Parameters

A number of different input parameters were used to populate the model. These include variables used to model the natural history of the disease and variables that modify the natural history model to account for treatment effects and costs of the COPD interventions being evaluated.

Natural History Model Input Parameters

Several input parameters were used to model the natural history of COPD: the annual probability of minor and major exacerbations by COPD severity; QOL utility values by COPD severity; and annual maintenance costs (i.e., clinical visits and drugs) (Table 4). The disutilities from major and minor exacerbations were assumed to be 0.042 (12) and 0.010, (12) respectively. The relative risk of mortality for COPD patients compared to the general population was assumed to be 3.3 (95% confidence interval [CI] 3.1–3.6), (13) and the costs of a major and minor exacerbation were assumed to be $10,086 and $212, respectively. (5) Costs and QALYs derived using the natural history model input parameters were also used for the UC/placebo comparators.

Table 4: Natural History Model Input Parameters by COPD Severity*

Model Parameter	Mild	Moderate	Severe	Very Severe
Annual total exacerbation rate (95% CI) (14)	0.82 (0.46–1.49)	1.17 (0.93–1.50)	1.61 (1.51–1.74)	2.1 (1.51–2.94)
Annual major exacerbation rate (95% CI) (14)	0.11 (0.02–1.49)	0.16 (0.07–0.33)	0.22 (0.20–0.23)	0.28 (0.14–0.63)
No exacerbation–utility value (12;15)	0.85	0.81	0.76	0.66
Annual maintenance cost (16)	$500	$500	$1,488	$2,176

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Treatment Effect Model Input Parameters

Treatment effect model input parameters were derived from the EBAs in the COPD mega-analysis. The treatment effect varied by COPD intervention. For smoking cessation interventions, abstinence rate was the treatment effect implemented in the model, and pooled abstinence rates for UC and placebo were 5.6% and 7.2%, respectively. The long-term benefits of smoking cessation were extracted from the Lung Health Study, (17) a long-term randomized controlled trial in which COPD smokers were randomized to receive UC, IC, or pharmacotherapy. The trial compared those who remained sustained quitters to those who were continuing smokers after 11 years of follow-up. The significant mortality benefit of quitting smoking was reported to be 0.54. The significant improvement in lung function was reported as a change in FEV_1, as described below:

- first year: quitters = +4.87 mL; non-quitters = −6.81 mL
- second year and beyond: quitters = −2.86 mL; non-quitters = −6.19 mL

These inputs, along with the abstinence rates derived from the MAS EBA, were used in the model to predict the long-term benefits of smoking cessation.

The relative risk (RR) of major exacerbation (rehospitalization) was used in the analyses of MDC and PR. The RR of all-cause mortality was used to model LTOT. The RR of inpatient mortality was used to model ventilation. Table 5 provides a summary of the clinical treatment effects by intervention, derived from the individual EBAs.

Table 5: Summary Estimates Used in the COPD Model*

Intervention	Population	Outcome	Relative Risk (95% CI)	Quality of Evidence	Effect Duration
Smoking cessation programs					
IC vs. UC	Stable COPD	Abstinence	7.70 (4.64–12.79)	Moderate	Lifetime
NRT vs. UC	Stable COPD	Abstinence	3.01 (1.02–8.89)	Moderate	Lifetime
IC + NRT vs. placebo	Stable COPD	Abstinence	4.41 (3.60–5.39)	Moderate	Lifetime
Bupropion vs. placebo	Stable COPD	Abstinence	2.01 (1.24–3.24)	Moderate	Lifetime
Multidisciplinary care teams					
MDC vs. UC	Stable COPD	Rehospitalization	0.67 (0.52–0.87)	Moderate	1 year
Pulmonary rehabilitation					
PR vs. UC	Acute COPD	Rehospitalization	0.41 (0.18–0.93)	Moderate	1 year
Long-term oxygen therapy					
LTOT vs. UC	Stable COPD	All-cause mortality	0.68 (0.46–1.0)	Low	Lifetime
Ventilation strategies					
NPPV + UMC vs. UMC	Acute COPD	Inpatient mortality	0.53 (0.35–0.81)	Moderate	1 episode
Weaning with NPPV vs. weaning with IMV	Acute COPD	Inpatient mortality	0.47 (0.23–0.97)	Moderate	1 episode

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; IC, intensive counselling; IMV, invasive mechanical ventilation; LTOT, long-term oxygen therapy; MDC, multidisciplinary care; NPPV, noninvasive positive pressure ventilation; NRT, nicotine replacement therapy; PR, pulmonary rehabilitation; UC, usual care; usual medical care.

Individual RRs were compared to different control groups (i.e., UC or placebo), depending on the inclusion criteria of the individual EBA. For further details on the comparisons, please see the individual EBAs.

Intervention Cost Model Input Parameters

All intervention costs were based on resources reported in the medical literature, consultation with an expert panel, and consultation with Ministry of Health and Long-Term Care whenever an existing program was available in Ontario. Baseline costs in the model were assumed to be UC or placebo for all interventions, except for smoking cessation programs, in which UC was assumed to be a family physician visit.

Ventilation strategies (both intervention and comparator) were costed based on average length of stay (LOS) in hospital, since hospital costs are reported per diem based on the case costing for the ventilation episode in acute COPD. Total costs included all costs directly related to the provision of care: nursing (operating room and intensive care unit), diagnostic imaging, pharmacy, and laboratory tests. Ventilator acquisition costs were not included as an amortized portion, and assumptions were not made regarding clinical visits by specialists.

Smoking Cessation Programs

Resources for smoking cessation programs were identified from the trials investigated in the smoking cessation EBA, and included pharmacotherapy and health care professional counselling. Bupropion was costed from the Ontario Drug Benefit (ODB) formulary (18) based on a typical regimen for smoking cessation (maximum of 12 weeks) as per the product monograph in the 2009 *Compendium of Pharmaceuticals and Specialties* (CPS). (19) NRT costs were also based on a typical regimen (maximum of 6 months) from the CPS, and the cost of NRT was obtained from the manufacturer pricing list from an Internet source. (20)

Counselling was costed based on physician billing in the Ontario Schedule of Physician Benefits (OSB). (21) IC was defined in the smoking cessation EBA as ≥ 90 minutes of counselling with a health care professional (MAS EBA), such as a general practitioner (GP). Nurses could also conduct the counselling. Based on expert opinion (Personal communication, Expert Panel, March 2011), IC was assumed to be 3 GP counselling sessions of 30 minutes each, with costing based on the OSB. UC was defined as a single physician visit (based on trial data) and was also costed based on the OSB. The program costs per patient and the assumptions used to calculate these costs are presented in Table 6.

Table 6: Cost per Patient of Smoking Cessation Programs*†

Intervention	Cost per Patient	Assumptions	Sources
UC	$35.40	UC = 1 GP visit at $33.50; pamphlets/ manuals included in the visit cost	Program from MAS EBA; cost from A004 OSB (21)
IC	$165.15	Smoking cessation counselling is billed to the province; minimal counselling = 30 minutes at $55.05 and IC = at least 90 minutes at $55.05 x 3 = $165.15; pamphlets/manuals included in the visit cost	Program from expert panel‡; cost from KO13 OSB (21)
NRT	$203.34	NRT was costed based on a typical regimen of Nicorette gum (i.e., 10–12 pieces a day in the first month; every 2–4 hours [6 pieces a day] in the second month; and every 4–8 hours [3 pieces a day] in the third month, up to 6 months). Costed up to 6 months at $22.15/pack (100 4 mg pieces = $0.2215/piece)	Regimen from 2009 CPS (19); cost from manufacturer (20)
IC + NRT	$368.49	Individual costs for IC and NRT, above	—
Bupropion	$37.92	Bupropion was costed based on a typical regimen (i.e., 150 mg/day in the first 3 days, then 300 mg/day for a minimum of 7 weeks, up to a maximum of 12 weeks). Costed up to 12 weeks at $0.2298/150 mg tablet	Regimen from 2009 CPS (19); cost from ODB formulary (18)

*Abbreviations: CPS, *Compendium of Pharmaceuticals and Specialties*; EBA, evidence-based analysis; GP, general practitioner; IC, intensive counselling; MAS, Medical Advisory Secretariat; NRT, nicotine replacement therapy; ODB, Ontario Drug Benefit; OSB, Ontario Schedule of Physician Benefits; UC, usual care.

†All costs are reported in Canadian dollars.

‡Personal communication, Expert Panel, March 2011.

All resources reported for smoking cessation programs (i.e., counselling and pharmacotherapy) are currently reimbursed by the province/Ministry of Health and Long-Term Care through OSB and ODB. NRT is now being offered through participating Family Health Teams (FHTs), combined with counselling. Coverage was announced in early 2011, while this analysis was being conducted (http://news.ontario.ca/mhp/en/2011/01/helping-more-ontarians-quit-smoking.html; accessed December 2011).

Multidisciplinary Care Teams

Resources reported in the trials investigated in the MDC EBA were costed and totalled for each trial. Total costs were then averaged to calculate a cost per patient over 6 to 12 months. Resources varied and included visits with GPs, dietitians, social workers, physiotherapists, respiratory nurses, and pharmacists. Resource utilization and frequency of visits and/or follow-up phone calls also varied between trials, and reporting was inconsistent; assumptions were made to quantify utilization whenever data inconsistencies were encountered.

Health care professional costs were obtained from the OSB and the *Guide to Interdisciplinary Provider Compensation* (22) for FHTs in Ontario. Table 7 describes the proportion of trials that reported the use of health care professionals and the unit cost associated with each visit. The frequency of visits was also obtained from the trials investigated. A total cost for the duration of the program was calculated and divided by the number of programs to obtain a program cost per patient of $1,041 ($427–$3,049). Costs were not weighted based on the trials reporting the resource, because only 6 trials were extracted for

MDC, but the weights are shown in Table 7 to show resource utilization. The cost of a MDC program was also varied in a 1-way sensitivity analysis using the maximum value of $3,049 per patient to reflect the differences in resource utilization reported in the trials.

Table 7: Cost per Visit with Multidisciplinary Care Teams*†

Health Care Professional	Trials Reporting Resource, %	Visit Cost	Assumptions	Sources
Dietitian	17	$29.91	Average maximum salary of a dietitian from a FHT reimbursed by the Ministry of Health and Long-Term Care for a 40 hour week ($62,219)	FHT guide (22)
General practitioner	67	$35.40	General re-assessment visit	A004 OSB (21)
Nurse	50	$35.80	COPD case manager (RN)	Mitmann et al (5)
Pharmacist	33	$42.73	Average maximum salary of a pharmacist from a FHT reimbursed by the Ministry of Health and Long-Term Care for a 40 hour week ($88,869)	FHT guide (22)
Physiotherapist	17	$32.00	Same salary as an occupational therapist from a FHT reimbursed by the Ministry of Health and Long-Term Care for a 40 hour week ($66,568)	FHT guide (22)
Respiratory therapist	33	$32.00	Same salary as an occupational therapist from a FHT reimbursed by the Ministry of Health and Long-Term Care for a 40 hour week ($66,568)	FHT guide (22)
Respirologist	17	$148.95	Consult with a respiratory disease specialist	A475 OSB (21)
Social worker	17	$32.00	Average maximum salary of a social worker from a FHT reimbursed by the Ministry of Health and Long-Term Care for a 40 hour week ($66,568)	FHT guide (22)

*Abbreviations: COPD, chronic obstructive pulmonary disease; FHT, Family Health Team; OSB, Ontario Schedule of Physician Benefits; RN, registered nurse.

†All costs are reported in Canadian dollars.

All resources reported in MDC (i.e., health care professional visits) are currently reimbursed by the Ministry of Health and Long-Term Care through FHTs and/or services listed in the OSB. Because utilization of these resources is not being captured by specific data sets for COPD, they are difficult to quantify.

Pulmonary Rehabilitation

Resources were costed based on a Toronto paper (23) that characterized PR programs in Canada, and an average cost per patient was calculated for short-term (average 4 weeks) outpatient treatment following an acute exacerbation. Resource utilization varied by province and setting. Costs were obtained from the OSB (21) and the *Guide to Interdisciplinary Provider Compensation* (22) and are reported in Table 8.

Table 8: Cost per Visit for a Short-Term Pulmonary Rehabilitation Program*†

Resource	Visit Cost	Assumptions	Sources
Dietitian	$29.91	Average maximum salary of a dietitian from a FHT reimbursed by the Ministry of Health and Long-Term Care for a 40 hour week ($62,219)	FHT guide (22)
General practitioner	$35.40	GP general re-assessment visit	A004 OSB (21)
Manager/director	$35.40	GP is manager/director of program	A004 OSB (21)
Nurse	$35.80	COPD case manager (RN)	Mitmann et al (5)
Occupational therapist	$32.00	Average maximum salary of an occupational therapist from a FHT reimbursed by the Ministry of Health and Long-Term Care for a 40 hour week ($66,568)	FHT guide (22)
Pharmacist	$42.73	Average maximum salary of a pharmacist from a FHT reimbursed by the Ministry of Health and Long-Term Care for a 40 hour week ($88,869)	FHT guide (22)
Physiotherapist	$32.00	Same salary as an occupational therapist from a FHT reimbursed by the Ministry of Health and Long-Term Care for a 40 hour week ($66,568)	FHT guide (22)
Respiratory therapist	$32.00	Same salary as an occupational therapist from a FHT reimbursed by the Ministry of Health and Long-Term Care for a 40 hour week ($66,568)	FHT guide (22)
Respirologist	$148.95	Consult with a respiratory disease specialist	A475 OSB (21)
Social worker	$32.00	Average maximum salary of a social worker from a FHT reimbursed by the Ministry of Health and Long-Term Care for a 40 hour week ($66,568)	FHT guide (22)

*Abbreviations: COPD, chronic obstructive pulmonary disease; GP, general practitioner; FHT, Family Health Team; OSB, Ontario Schedule of Physician Benefits; RN, registered nurse.

†All costs are reported in Canadian dollars.

Close to 100 programs were evaluated in the paper, providing a fair estimate of resource utilization by setting. (23) Costs were therefore weighted by setting and resource utilization to calculate a cost per patient for each resource in each setting. The authors also reported the mean (minimum, maximum) duration of a PR program. Table 9 provides an estimate of the total cost per patient over the duration of a PR program, assuming an outpatient setting.

Table 9: Total Cost per Patient over the Duration of an Outpatient Pulmonary Rehabilitation Program*

Parameter	Cost per Patient
Total cost per hour	$39.55
Mean hours per session	1.8
Mean number of sessions per week	5.5
Mean duration, weeks (minimum, maximum)	3.9 (1.7, 6.1)
Mean cost of program (minimum, maximum)	$1,526.92 ($665.58, $2,388.26)

*All costs are reported in Canadian dollars.
Source: Brooks et al, 2007 (23)

PR programs can be resource-intensive, (23) so resource costs can run high. The cost of a PR program was varied in the COPD model in a 1-way sensitivity analysis using the value of $2,863 per patient reported by Brooks et al (23) to reflect potential differences in resource utilization.

All resources reported in PR (i.e., health care professional visits) are currently reimbursed by the Ministry of Health and Long-Term Care or by the hospital global budget, depending on whether the program is outpatient or inpatient. PR resource utilization is not being captured properly in Ontario, and is therefore difficult to estimate.

Long-Term Oxygen Therapy

Ontario has a provincial program that provides LTOT to patients with severe hypoxemia. Based on the latest data provided by the Assistive Devices Program of the Ministry of Health and Long-Term Care, the average annual cost per patient for LTOT was $2,261 in fiscal year (FY) 2006 (Personal communication, Ministry of Health and Long-Term Care, January 2011). Resources offered through the program include the following: home assessment, 24 hour emergency service, maintenance and repair, training and education, oxygen supply system, and disposables (i.e., nasal cannula, tubing). It was assumed that LTOT costs would be incurred annually, since patients were assumed to stay on LTOT indefinitely. Table 10 describes the annual expenditures associated with LTOT for FYs 1997 to 2006.

Table 10: Ministry of Health and Long-Term Care Expenditures on Long-Term Oxygen Therapy by Fiscal Year*

Fiscal Year	Patients, n	Total Expenditure	Average Cost per Patient
1997/1998	20,740	$57,664,896	$2,780.37
1998/1999	20,589	$59,493,393	$2,889.57
1999/2000	22,785	$63,294,833	$2,777.92
2000/2001	21,507	$59,589,042	$2,770.68
2001/2002	20,632	$51,338,684	$2,488.30
2002/2003	22,627	$54,398,158	$2,404.13
2003/2004	22,522	$53,987,252	$2,397.09
2004/2005	25,085	$58,653,537	$2,338.19
2005/2006	25,478	$59,908,932	$2,351.40
2006/2007	28,654	$64,792,268	$2,261.19

*All costs are reported in Canadian dollars.
Source: Assistive Devices Program (Personal communication, Ministry of Health and Long-Term Care, January 2011).

Ventilation Strategies

Two in-hospital ventilation strategies were investigated: NPPV versus UMC and weaning with NPPV versus weaning with IMV. Because these strategies were delivered within a hospital setting and patients remained over an average LOS, the hospital event was costed, rather than the intervention alone.

OCCI (10) is a standard data set for hospitalization costs in the province based on most responsible diagnosis codes (International Classification of Diseases, 10th edition) and principal procedure codes (Canadian Classification of Health Interventions [CCI]). Codes were identified via the Canadian Institute for Health Information (24) and are reported in Table 11.

Table 11: Most Responsible Diagnosis for COPD Restricted to Ventilation*

Codes	Description
Most responsible diagnosis codes (ICD-10)	
J440	COPD with acute lower respiratory infection
J441	COPD with acute exacerbation unspecified
J448	Other specified COPD
J449	COPD unspecified
Principal procedure codes (CCI)	
1GZ31CAND	Invasive ventilation
1GZ31CBND	Noninvasive ventilation

*Abbreviations: CCI, Canadian Classification of Health Interventions; COPD, chronic obstructive pulmonary disease; ICD-10, International Classification of Diseases, 10th edition.
Source: Canadian Institute for Health Information, 2006 (24).

Based on these codes, the weighted average direct cost per diem for invasive and noninvasive ventilation in COPD were obtained from the most recent acute inpatient OCCI data (10) (i.e., FY 2008). The cost for UC for a COPD hospitalization was obtained from the Canadian literature: (5)

- invasive ventilation: $1,679 per diem
- noninvasive ventilation: $864 per diem
- usual medical care: $1,009 per diem

Direct costs included resources related to the provision of care, such as nursing care, operating room, intensive care unit, diagnostic imaging, pharmacy, and laboratory tests. Ventilator acquisition costs were not estimated. Indirect costs were also excluded from the analysis and included overhead expenses relating to the running of hospitals, such as administration, finance, human resources, and plant operations.

Based on the average LOS reported in the trials investigated in the ventilation EBAs, total costs for the hospitalization episode of each arm were calculated and reported. There were cost savings for both ventilation strategies versus their comparators, since ventilated patients stayed in hospital for fewer days. Assumptions and total costs per patient are reported in Tables 12 and 13.

Table 12: Costs and Assumptions Associated with NPPV versus UMC*†

Intervention	Cost per Diem	LOS, days	Total Cost	Assumptions	Sources
NPPV	$863.98	7.32	$6,324.33	Based on MAS EBA, there is a significant reduction of 2.86 days in LOS with NPPV vs. UC	OCCI (10)
UMC	$1,008.60	10	$10,086.00	Average LOS of 10 days and cost from Canadian literature	Mittman et al (5)
Difference NPPV–UC	−$144.62	−2.68	−$3,761.67	—	—

*Abbreviations: EBA, evidence-based analysis; LOS, length of stay; MAS, Medical Advisory Secretariat; OCCI, Ontario Case Costing Initiative; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

†All costs are reported in Canadian dollars.

Table 13: Costs and Assumptions Associated with Weaning with NPPV versus Weaning with IMV*†

Intervention	Cost per Diem	ICU, days	IMV, days	NPPV, days	UC, days	Total Cost	Assumptions
Weaning with NPPV	$863.98	11.4	7.98	3.40	—	$16,332.95	Weighted ICU LOS from MAS EBA; days not spent on IMV were spent on NPPV in ICU
Weaning with IMV	$1,678.56	16.6	11.5	—	5.06	$24,464.09	Weighted ICU LOS from MAS EBA; days not spent on IMV were spent on UC in ICU
Difference NPPV–IMV	−$814.58	−5.2	−3.52	—	—	−$8,131.14	—

*Abbreviations: EBA, evidence-based analysis; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; MAS, Medical Advisory Secretariat; NPPV, noninvasive positive pressure ventilation; UC, usual care.

†All costs are reported in Canadian dollars.

Source: Ontario Case Costing Initiative, 2011 (10).

All resources reported in the ventilation strategies are currently absorbed by the hospital global budget; averages are reported above.

Summary

Costs per patient associated with each intervention run in the COPD economic model are summarized in Table 14.

Table 14: Cost per Patient of Interventions Run in the COPD Model*†

Intervention	Duration of Intervention	Cost of Intervention per Patient	Perspective	Frequency of Cost per Patient
Smoking cessation programs				
UC	6–12 months	$35.40	Ministry of Health and Long-Term Care	1-time cost
IC vs. UC	6–12 months	$165.15	Ministry of Health and Long-Term Care	1-time cost
NRT vs. UC	6–12 months	$203.34	Ministry of Health and Long-Term Care	1-time cost
IC + NRT vs. placebo	6–12 months	$368.49	Ministry of Health and Long-Term Care	1-time cost
Bupropion vs. placebo	6–12 months	$37.92	Ministry of Health and Long-Term Care	1-time cost
Multidisciplinary care teams				
MDC vs. UC	6–12 months	$1,041.03	Ministry of Health and Long-Term Care	1-time cost
MDC vs. UC, sensitivity analysis	6–12 months	$3,048.88	Ministry of Health and Long-Term Care	1-time cost
Pulmonary rehabilitation				
PR vs. UC	6–12 months	$1,526.92	Ministry of Health and Long-Term Care or hospital	1-time cost
PR vs. UC, sensitivity analysis	6–12 months	$2,863.19	Ministry of Health and Long-Term Care or hospital	1-time cost
Long-term oxygen therapy				
LTOT vs. UC	Continuous	$2,261.19	Ministry of Health and Long-Term Care	Annual cost
Ventilation strategies				
NPPV + UMC vs. UMC				
Cost of NPPV	Hospital stay	$6,324.33	Hospital	1-time cost
Cost of UMC	Hospital stay	$10,086.00	Hospital	1-time cost
Weaning with NPPV vs. weaning with IMV				
Cost of weaning with NPPV	Hospital stay	$16,332.95	Hospital	1-time cost
Cost of weaning with IMV	Hospital stay	$24,464.09	Hospital	1-time cost

*Abbreviations: COPD, chronic obstructive pulmonary disease; IC, intensive counselling; IMV, invasive mechanical ventilation; LTOT, long-term oxygen therapy; MDC, multidisciplinary care; NPPV, noninvasive positive pressure ventilation; NRT, nicotine replacement therapy; PR, pulmonary rehabilitation; UC, usual care; UMC, usual medical care.

†All costs are reported in Canadian dollars.

Cost-Effectiveness Analysis Results

Table 15 describes the total lifetime incremental costs, life years, and QALYs for an intervention and its comparator. Also shown are the incremental cost per life year and cost per QALY.

Table 15: COPD Model Results—Study Intervention Minus Usual Care/Placebo*†

Intervention	Incremental Intervention Cost	Incremental Hospital Cost	Incremental Maintenance Cost	Total	Incremental Life Years	Incremental QALYs	Cost per Life Year	Cost per QALY
Smoking cessation programs								
IC vs. UC	$130	−$597	−$1,778	−$2,245	0.62	0.58	Dominates	Dominates
NRT vs. UC	$203	−$285	−$941	−$1,023	0.32	0.31	Dominates	Dominates
IC + NRT vs. placebo	$333	−$303	−$874	−$844	0.31	0.29	Dominates	Dominates
Bupropion vs. placebo	$38	−$131	−$402	−$495	0.14	0.13	Dominates	Dominates
Multidisciplinary care teams								
MDC vs. UC	$1,041	−$464	$111	$688	0.12	0.06	$10,686	$14,123
MDC, sensitivity analysis	$3,049	−$464	$111	$2,696	0.12	0.06	$41,860	$55,322
Pulmonary rehabilitation								
PR vs. UC	$1,527	−$978	$77	$626	0.04	0.03	$14,616	$17,938
PR, sensitivity analysis	$2,863	−$978	$77	$1,962	0.04	0.03	$45,849	$56,270
Long-term oxygen therapy								
LTOT vs. UC	$24,668	$4,218	$503	$29,389	1.21	0.75	$24,347	$38,993
Ventilation strategies								
NPPV + UMC vs. UMC	−$3,762	$583	$433	−$2746	0.19	0.13	Dominates	Dominates
Weaning with NPPV vs. weaning with IMV	−$8,131	$201	$146	−$7784	0.07	0.05	Dominates	Dominates

*Abbreviations: COPD, chronic obstructive pulmonary disease; IC, intensive counselling; IMV, invasive mechanical ventilation; LTOT, long-term oxygen therapy; MDC, multidisciplinary care; NPPV, noninvasive positive pressure ventilation; NRT, nicotine replacement therapy; PR, pulmonary rehabilitation; QALY, quality-adjusted life-year; UC, usual care; UMC, usual medical care.

†All costs are reported in Canadian dollars.

The costs and benefits are reported as the difference between the intervention and its comparator. The costs are broken down into lifetime intervention costs, lifetime exacerbation (hospitalization) costs, and lifetime maintenance costs (for non–hospital-related resources, such as clinical visits and drugs). The benefits are broken down into LYs and QALYs.

The total costs and benefits are impacted by the benefits extracted from the individual EBAs. Interventions that had an impact on mortality and no impact on hospitalization result in increased hospitalization and maintenance costs, since more people are staying alive and incurring events (i.e., costs). Smoking cessation programs had a benefit in terms of lung function and mortality. A benefit in lung function led to an improvement in disease; therefore, patients experienced fewer exacerbations, incurring fewer costs overall. MDC and PR had a benefit in terms of decreased hospital events. Fewer hospital events led to lower hospitalization costs but indirectly impacted inpatient mortality, leading to more people living with COPD and therefore incurring higher non–hospital-related costs. LTOT had a benefit in mortality; therefore, patients were living longer with disease and incurring more events and more costs. Finally, ventilation had a benefit in inpatient mortality; therefore, patients were living longer with COPD and incurring more events and more costs.

The model's parameter uncertainty was assessed using simulations. Using confidence intervals from the systematic review, distributions were assigned to the summary point estimates, and probabilistic sensitivity analyses were run. The CEACs for each comparison are presented below. The following figures show the probability that each intervention will be cost-effective according to different WTP thresholds per QALY.

Single CEACs are presented because the interventions investigated in the COPD mega-analysis were assessed in different patient populations with different COPD severities. Whenever possible, given that patient populations could be grouped and compared, an evaluation between curves is reported.

Smoking Cessation Programs

Figures 3 to 6 show that IC, IC + NRT, and bupropion have the highest probability of being cost-effective at all WTP values. NRT never has the highest probability of being cost-effective compared to other smoking cessation interventions, regardless of WTP threshold, although it is highly cost-effective.

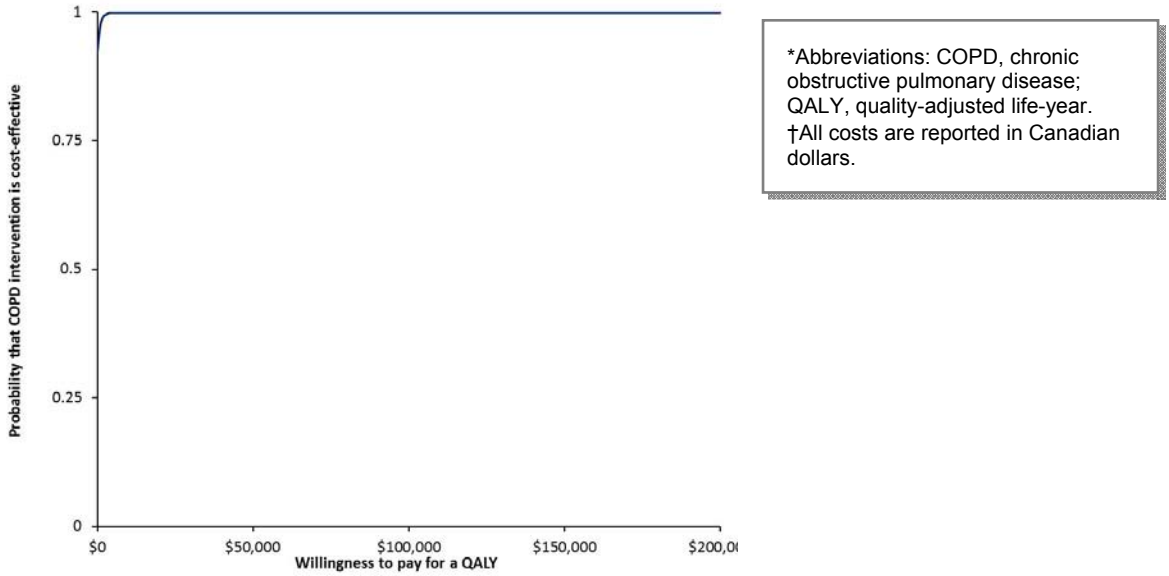


Figure 3: Cost-Effectiveness Acceptability of Intensive Counselling for Smoking Cessation*†

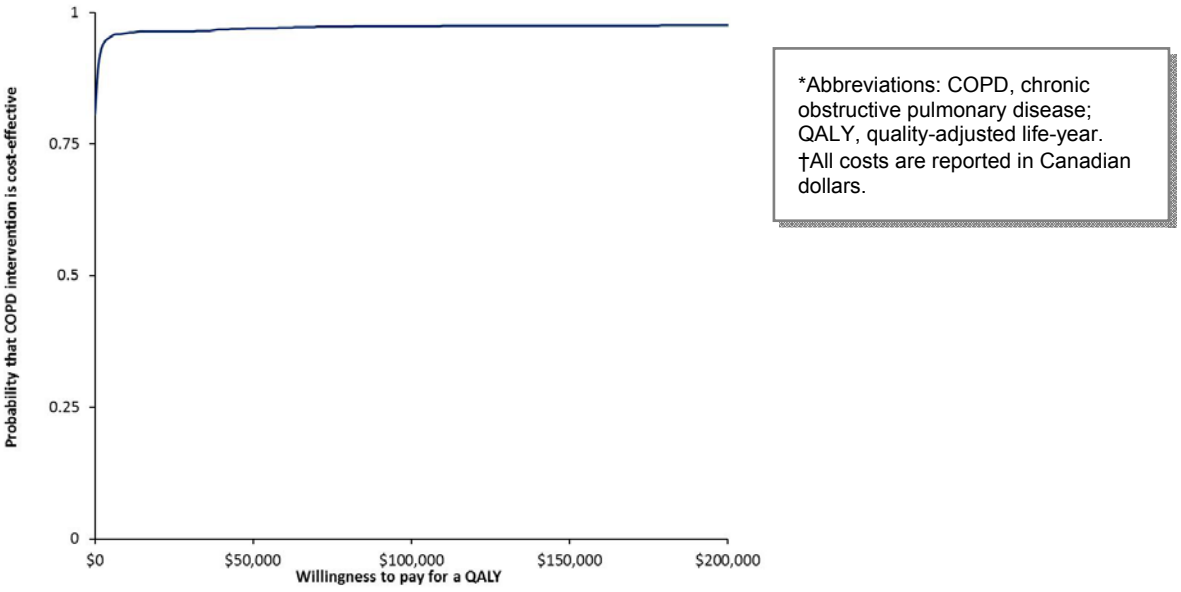


Figure 4: Cost-Effectiveness Acceptability of Nicotine Replacement Therapy for Smoking Cessation*†

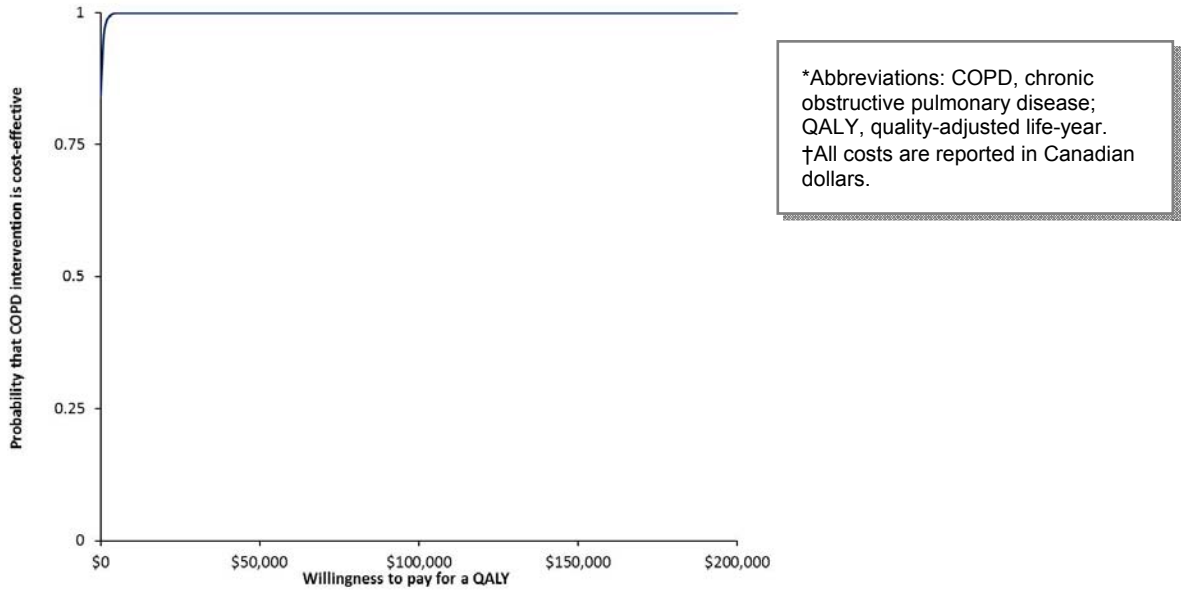


Figure 5: Cost-Effectiveness Acceptability of Intensive Counselling plus Nicotine Replacement Therapy for Smoking Cessation*†

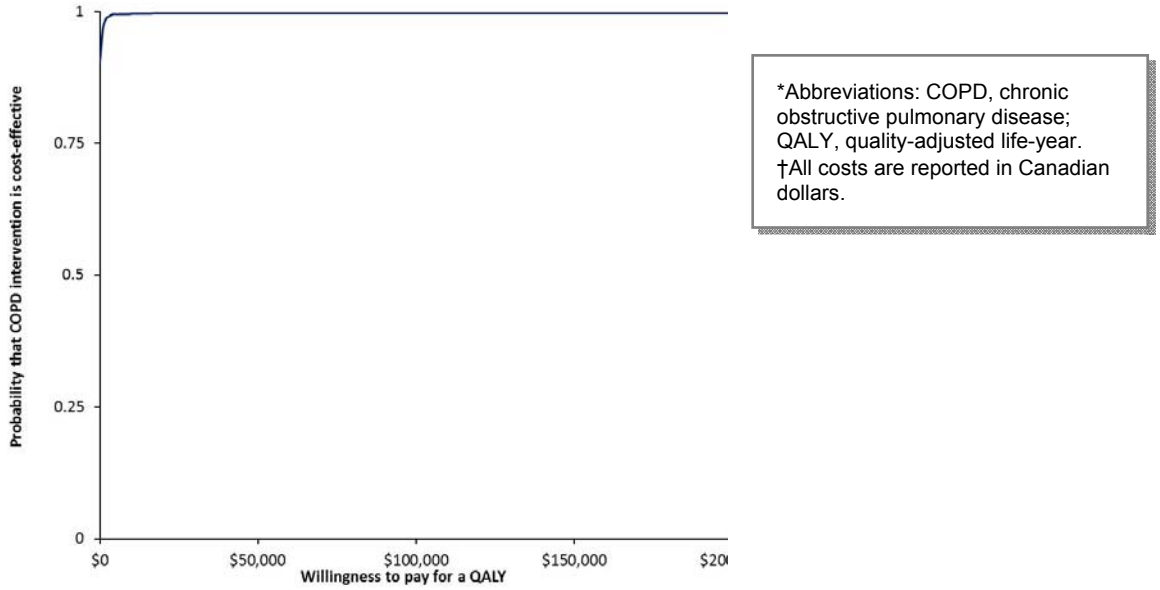


Figure 6: Cost-Effectiveness Acceptability of Bupropion for Smoking Cessation*†

Multidisciplinary Care Teams

MDC has the highest probability of being cost-effective above the threshold of $75,000 per QALY in the base case scenario (Figure 7). When the cost of the program is varied in a 1-way sensitivity analysis, the highest probability of MDC being cost-effective is above the threshold of $200,000 per QALY (Figure 8).

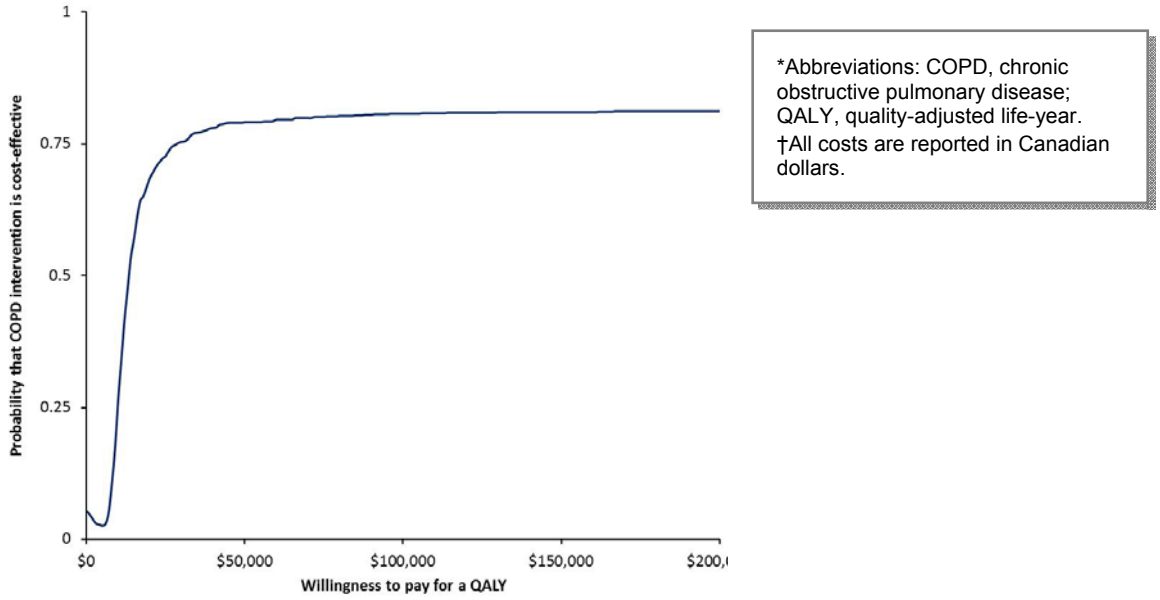


Figure 7: Cost-Effectiveness Acceptability of Multidisciplinary Care Teams (Base Case Cost)*†

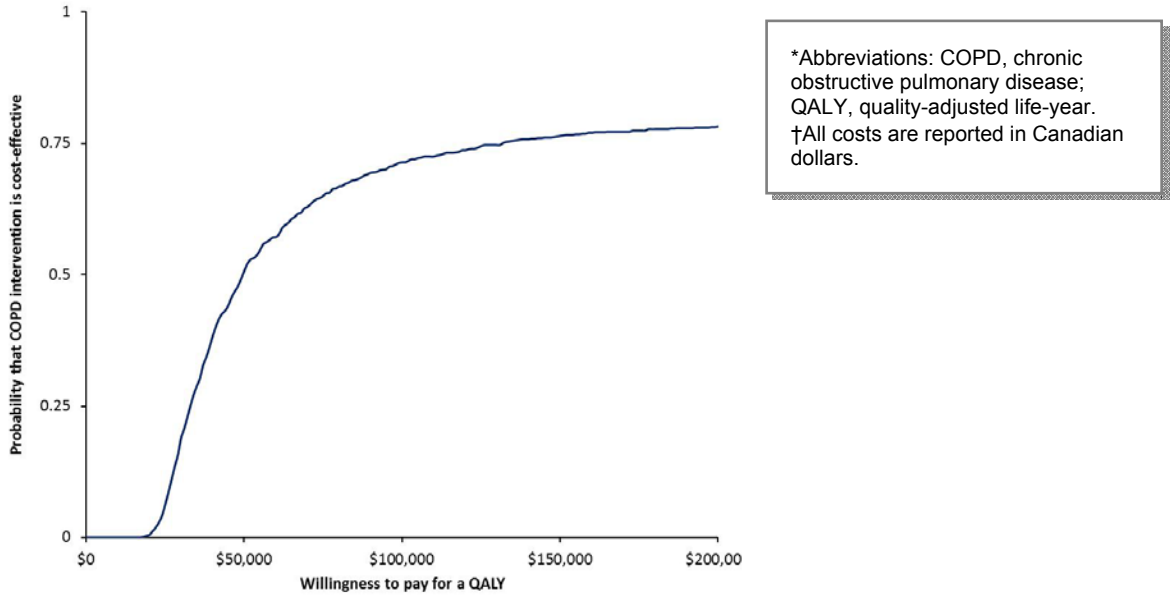
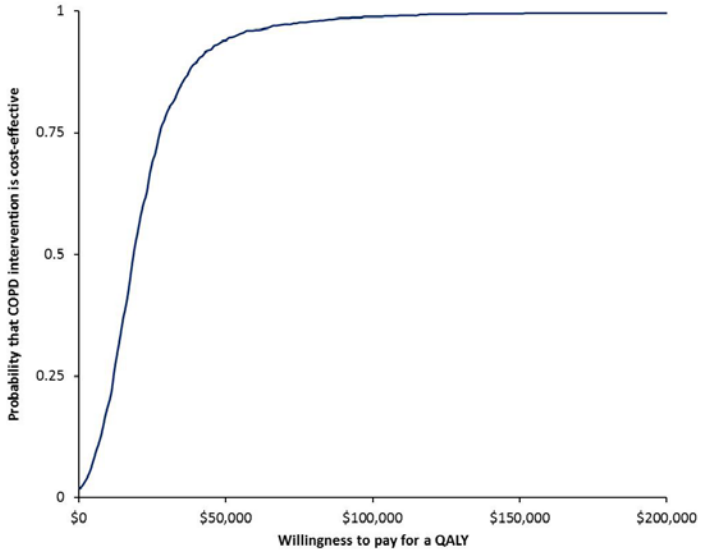


Figure 8: Cost-Effectiveness Acceptability of Multidisciplinary Care Teams (Varying Cost of Program per Patient)*†

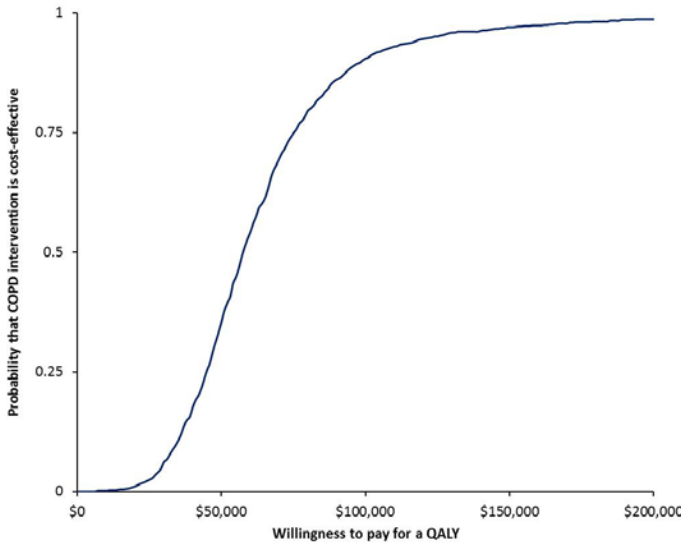
Pulmonary Rehabilitation

In the base case scenario, PR becomes more cost-effective at a WTP value of greater $50,000 per QALY (Figure 9). The 1-way sensitivity analysis showed that PR has a higher probability of being cost-effective above the WTP threshold of $200,000 per QALY (Figure 10).



*Abbreviations: COPD, chronic obstructive pulmonary disease; QALY, quality-adjusted life-year.
†All costs are reported in Canadian dollars.

Figure 9: Cost-Effectiveness Acceptability of Pulmonary Rehabilitation (Base Case Cost)*†

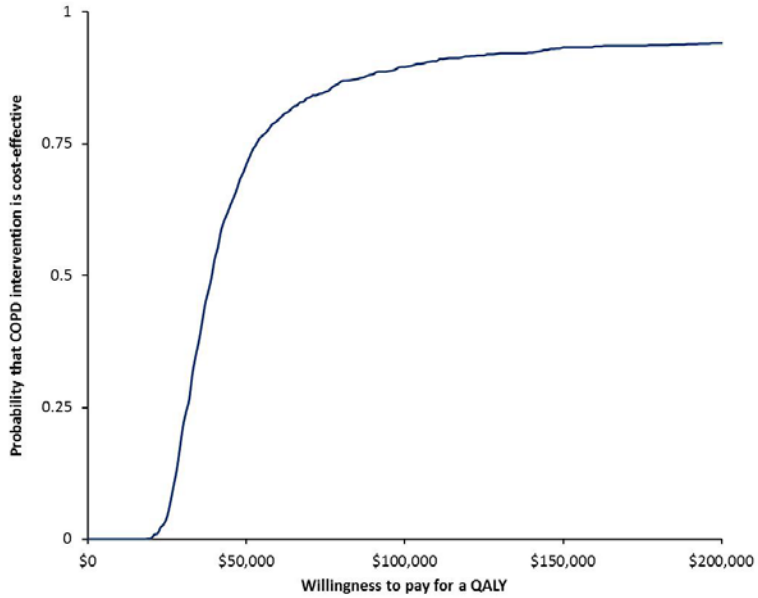


*Abbreviations: COPD, chronic obstructive pulmonary disease; QALY, quality-adjusted life-year.
†All costs are reported in Canadian dollars.

Figure 10: Cost-Effectiveness Acceptability of Pulmonary Rehabilitation (Varying Cost of Program per Patient)*†

Long-Term Oxygen Therapy

LTOT has the highest probability of being cost-effective at thresholds higher than $50,000 per QALY (Figure 11).



*Abbreviations: COPD, chronic obstructive pulmonary disease; QALY, quality-adjusted life-year.
†All costs are reported in Canadian dollars.

Figure 11: Cost-Effectiveness Acceptability of Long-Term Oxygen Therapy*†

Ventilation Strategies

NPPV has the highest probability of being cost-effective at all WTP thresholds (Figure 12). Weaning with NPPV remains highly cost-effective, but the probability of being cost-effective decreases slightly at the $50,000 per QALY threshold (Figure 13).

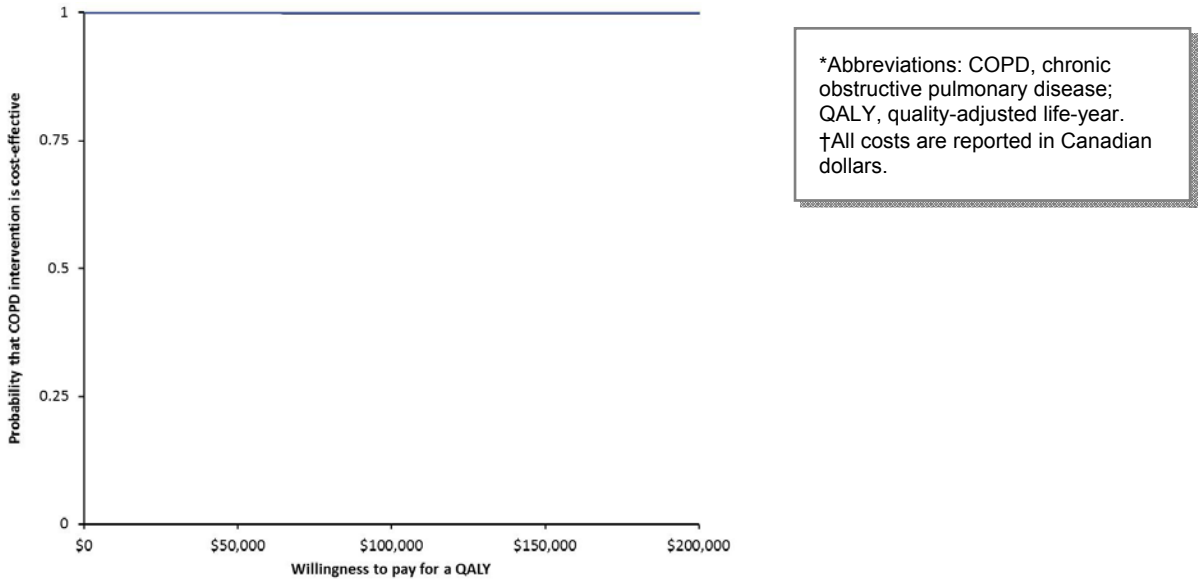


Figure 12: Cost-Effectiveness Acceptability of Noninvasive Ventilation*†

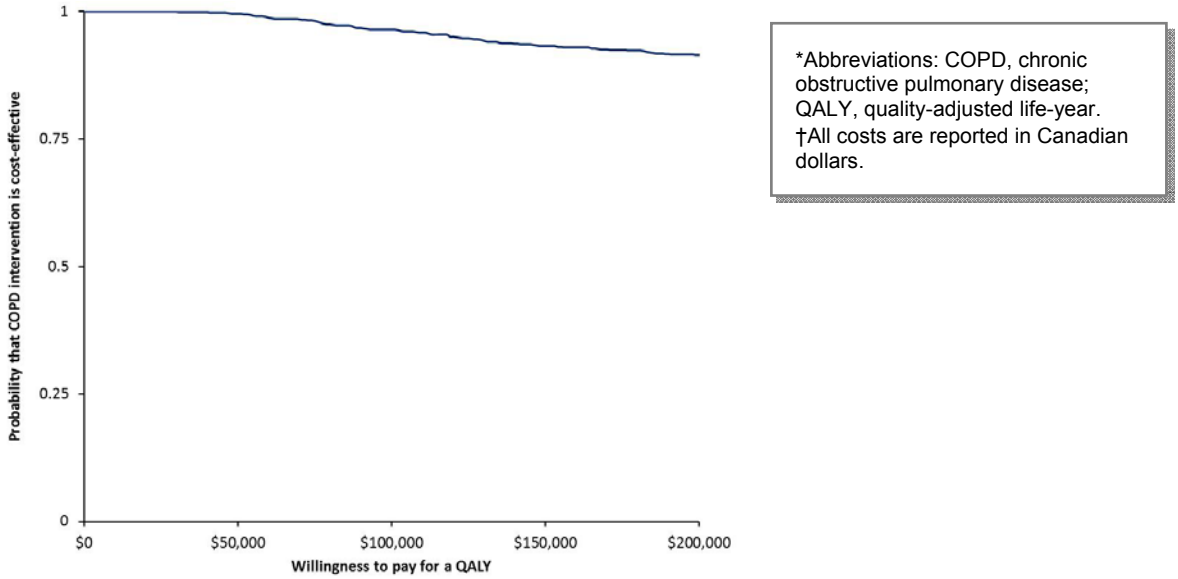


Figure 13: Cost-Effectiveness Acceptability of Weaning with Noninvasive Ventilation*†

Summary

All smoking cessation programs were dominant (i.e., less expensive and more effective overall). Assuming a base case program cost of $1,041 and $1,527 per patient for MDC and PR, the ICER was calculated to be $14,123 per QALY and $17,938 per QALY, respectively. When the costs of MDC and PR were varied in a 1-way sensitivity analysis to reflect variation in resource utilization reported in the literature, the ICER increased to $55,322 per QALY and $56,270 per QALY, respectively. Assuming a base case cost of $2,261 per year per patient for LTOT as reported by data from the Ontario provincial program, the ICER was calculated to be $38,993 per QALY. Ventilation strategies were dominant (i.e., cheaper and more effective), as reflected by the clinical evidence of significant in-hospital days avoided in the study group. The probability of cost-effectiveness for each intervention is shown in Table 16.

Table 16: COPD Model Results—Probability of Cost-Effectiveness by Ceiling Ratio*†

Intervention	Cost per QALY	Probability of Cost-Effectiveness by Ceiling Ratios				
		$25,000	$50,000	$75,000	$100,000	$200,000
Smoking cessation programs						
IC vs. UC	Dominates	1.00	1.00	1.00	1.00	1.00
NRT vs. UC	Dominates	0.96	0.97	0.97	0.97	0.98
IC + NRT vs. placebo	Dominates	1.00	1.00	1.00	1.00	1.00
Bupropion vs. placebo	Dominates	1.00	1.00	1.00	1.00	1.00
Multidisciplinary care teams						
MDC vs. UC	$14,123	0.73	0.79	0.80	0.81	0.81
MDC, sensitivity analysis	$55,322	0.06	0.51	0.65	0.71	0.75
Pulmonary rehabilitation						
PR vs. UC	$17,938	0.69	0.94	0.98	0.99	1.00
PR, sensitivity analysis	$56,270	0.03	0.36	0.75	0.91	0.99
Long-term oxygen therapy						
LTOT vs. UC	$38,993	0.04	0.71	0.85	0.90	0.94
Ventilation strategies						
NPPV + UMC vs. UMC	Dominates	1.00	1.00	1.00	1.00	1.00
Weaning with NPPV vs. weaning with IMV	Dominates	1.00	1.00	0.98	0.97	0.92

*Abbreviations: COPD, chronic obstructive pulmonary disease; IC, intensive counselling; IMV, invasive mechanical ventilation; LTOT, long-term oxygen therapy; MDC, multidisciplinary care; NPPV, noninvasive positive pressure ventilation; NRT, nicotine replacement therapy; PR, pulmonary rehabilitation; QALY, quality-adjusted life-year; UC, usual care; usual medical care.

†All costs are reported in Canadian dollars.

Budget Impact Analysis—Ontario Perspective

Incidence and Prevalence of COPD

COPD prevalence and incidence data were obtained from Canadian literature (25) and used to estimate the populations impacted by the interventions investigated in this report (Table 17).

Table 17: COPD Prevalence and Incidence in Ontario, 1996 to 2007*

Variable	Estimate	Source
Population in Ontario, Canada, in 2007 (aged ≥ 35 years)	7,082,086	Gershon et al (25)
Prevalence of COPD in Ontario, Canada, in 2007 (males and females aged ≥ 35 years)	708,743	Gershon et al (25)
Relative increase in prevalence from 1996 to 2007	23%	Gershon et al (25)
Incidence of COPD in Ontario, Canada, in 2007 (males and females aged ≥ 35 years)	60,198	Gershon et al (25)
Relative decrease in incidence from 1996 to 2007	28%	Gershon et al (25)
Very severe COPD	18%	ICES†
Severe COPD	21%	ICES†
Moderate COPD	60%	ICES†

*Abbreviations: COPD, chronic obstructive pulmonary disease; ICES, Institute of Clinical Evaluative Sciences.

†Personal communication, ICES, January 2011.

Impacted Populations

A number of assumptions were made to estimate impacted populations; these are described in the following sections.

Smoking Cessation Programs

The trials investigated in the smoking cessation EBA assessed patients with moderate COPD. Based on expert opinion (Personal communication, ICES, May 2011), it was assumed that 60% of COPD patients were smokers, and of these, 20% would seek treatment (Table 18).

Table 18: Assumptions Regarding Prevalent Patients Accessing Smoking Cessation Programs*

Variable	Proportion	Source
Prevalence of COPD in Ontario, Canada, in 2007 (males and females aged ≥ 35 years)	708,743	Gershon et al (25)
Moderate COPD	60%	ICES†
Smokers	60%	ICES†
Smokers motivated to seek treatment	20%	ICES†
Impacted population	51,029	

*Abbreviations: COPD, chronic obstructive pulmonary disease; ICES, Institute for Clinical and Evaluative Sciences.

†Personal communication, ICES, May 2011.

The same assumptions were used to calculate the incident population, assuming a relative decrease in incidence in subsequent years. (25)

Multidisciplinary Care Teams

Using the FHT model of care in Ontario, data from half of the FHTs that reported back in FY 2010 (Personal communication, Ministry of Health and Long-Term Care, May 2011) suggested that 81,289 patients with COPD are accessing a chronic disease management program (Table 19).

Table 19: Assumptions Regarding Prevalent Patients Accessing Multidisciplinary Care Teams*†

Variable	Proportion	Source
Number of patients accessing a chronic disease management program through FHTs, FY 2010	81,289	Personal communication, Ministry of Health and Long-Term Care, May 2011

*Abbreviations: FHT, Family Health Team; FY, fiscal year.

†Likely to be an underestimate; overall, multidisciplinary care resources being utilized in the province are unknown and difficult to measure.

The incident population was calculated by assuming a starting incident population of moderate (60%) to severe (21%) COPD (Personal communication, Expert, January 2011), and assuming a relative decrease in incidence in subsequent years. (25)

Nevertheless, due to lack of report by FHTs and the fact that programs outside the FHT model are not captured, this number is likely to be an underestimate and not necessarily representative of the Ontario population accessing multidisciplinary care for COPD.

Pulmonary Rehabilitation

Data on COPD-related hospitalization were pulled from Ontario administrative data sets (26) to calculate the potential impact of patients accessing PR programs. There were 22,485 hospitalizations due to COPD in FY 2009. Based on consultation with experts (Personal communication, Expert Panel, May 2011), it was assumed that half of hospitalized patients would access PR resources at least once, and half of these would repeat the therapy (Table 20).

Table 20: Assumptions Regarding Prevalent Patients Accessing Pulmonary Rehabilitation*

Variable	Proportion	Source
Patients hospitalized for COPD in FY 2009	22,485	Ministry of Health and Long-Term Care (26)
Patients accessing PR at least once post-acute exacerbation	50%	Expert panel†
Impacted population	11,243	—
Patients repeating PR once	50%	Expert panel†
Impacted population	5,621	—

*Abbreviations: COPD, chronic obstructive pulmonary disease; FY, fiscal year; PR, pulmonary rehabilitation.

†Personal communication, Expert panel, May 2011.

The incident population was calculated by assuming a starting incident population of moderate (60%) to severe (21%) COPD (Personal communication, Expert, January 2011) who would experience

exacerbations (3%) (27) and would access PR at least once (50%). Half of these would repeat treatment (Personal communication, Expert, May 2011). A relative decrease in incidence in subsequent years was also assumed. (25)

Long-Term Oxygen Therapy

The most recent data from the LTOT provincial program indicated that 28,654 patients with severe hypoxemia accessed services in FY 2006 (Table 21) (Personal communication, Ministry of Health and Long-Term Care, January 2011).

Table 21: Assumptions Regarding Prevalent Patients Accessing Long-Term Oxygen Therapy*

Variable	Proportion	Source
Number of patients accessing LTOT, FY 2006	28,654	Personal communication, Ministry of Health and Long-Term Care, January 2011

*Abbreviations: LTOT, long-term oxygen therapy; FY, fiscal year.

The incident population was calculated by assuming a starting incident population of very severe COPD (18%) (Personal communication, Expert, January 2011) with severe hypoxemia (25%) and severe respiratory failure (3%) (Personal communication, Expert, January 2011). A relative decrease in incidence in subsequent years was also assumed. (25)

Ventilation Strategies

Based on consultation with experts (Personal communication, Expert, May 2011), it was assumed that 15% of the patient population at risk (severe COPD for NPPV and very severe COPD for weaning with NPPV) were eligible for ventilation. Of these, 50% would choose to be ventilated. Of the very severe patients on IMV, 15% would fail breathing assessment and therefore continue to be ventilated. Table 22 describes the assumptions and impacted populations.

Table 22: Assumptions Regarding Prevalent Patients Accessing Ventilation*

Variable	Proportion	Source
Patients with severe COPD eligible for NPPV	22,325	Expert panel†
Patients with very severe COPD for weaning with NPPV	19,136	Expert panel†
Very severe patients who fail breathing assessment and continue to be ventilated	15%	Expert panel†
Patients opting for either ventilation type	50%	Expert panel†
Impacted population for NPPV	11,163	—
Impacted population for weaning with NPPV	1,435	—

*Abbreviations: COPD, chronic obstructive pulmonary disease; NPPV, noninvasive positive pressure ventilation.

†Personal communication, Expert Panel, May 2011.

The same assumptions were used to calculate incident population, assuming a relative decrease in incidence in subsequent years. (25)

Summary

The provincial burden reflects what the province is currently paying based on the costing assumptions reported here and the prevalent population accessing the interventions/services. Future projections were

based on COPD incidence, assuming a relative decrease in subsequent years. (25) Future projections did not capture patients who would fail and repeat treatment, reflecting the short-term nature of treatment and follow-up reported in the trials included in the MAS EBAs. Future projections also did not capture changes in disease prevalence. Current and future impacted populations are summarized in Table 23.

Table 23: Impacted Populations for COPD Interventions in Ontario*

Intervention	Assumptions	Prevalent Population, Current Burden	Incident Populations		
			Year 1	Year 2	Year 3
Smoking cessation programs					
IC vs. UC	Incidence and prevalence: assumed moderate COPD, smokers, motivated to seek treatment	51,029	4,334	3,108	2,228
NRT vs. UC	Incidence and prevalence: assumed moderate COPD, smokers, motivated to seek treatment	51,029	4,334	3,108	2,228
IC + NRT vs. placebo	Incidence and prevalence: assumed moderate COPD, smokers, motivated to seek treatment	51,029	4,334	3,108	2,228
Bupropion vs. placebo	Incidence and prevalence: assumed moderate COPD, smokers, motivated to seek treatment	51,029	4,334	3,108	2,228
Multidisciplinary care teams					
MDC vs. UC	Prevalence: assumed patients accessing COPD management program through FHTs. Incidence: assumed moderate and severe COPD	81,289†	48,760†	34,961†	25,067†
Pulmonary rehabilitation					
PR vs. UC, 1 treatment	Prevalence: assumed COPD patients post-exacerbation, at least 1 treatment. Incidence: assumed moderate and severe COPD, experiencing exacerbation, seeking treatment once	11,243	805	577	414
PR vs. UC, repeat treatment	Prevalence: assumed COPD patients post-exacerbation, repeat treatment. Incidence: assumed moderate and severe COPD, experiencing exacerbation, seeking repeat treatment	5,621	402	288	207
Long-term oxygen therapy					
LTOT vs. UC	Prevalence: assumed patient accessing LTOT through ADP, Ministry of Health and Long-Term Care. Incidence: assumed very severe COPD, with severe hypoxemia and severe respiratory failure	28,654	81	58	42
Ventilation strategies					
NPPV + UMC vs. UMC	Prevalence and incidence: assumed severe COPD, eligible for ventilation, choosing to be ventilated	11,163	948	680	487
Weaning with NPPV vs. weaning with IMV	Prevalence and incidence: assumed very severe COPD, eligible for ventilation, failing breathing assessment, choosing to be ventilated	1,435	122	87	63

*Abbreviations: ADP, Assistive Devices Program; COPD, chronic obstructive pulmonary disease; FHT, Family Health Team; IC, intensive counselling; IMV, invasive mechanical ventilation; LTOT, long-term oxygen therapy; MDC, multidisciplinary care; NPPV, noninvasive positive pressure ventilation; NRT, nicotine replacement therapy; PR, pulmonary rehabilitation; SA, sensitivity analysis; UC, usual care; UMC, usual medical care.

†Likely to be an underestimate; overall, multidisciplinary care resources being utilized in the province are unknown and difficult to measure.

Budget Impact Analysis Results

Ontario currently pays for IC through physician billing (translating to a current burden of $8 million) and bupropion through ODB (translating to a current burden of almost $2 million). The burden of NRT was projected to be $10 million, with future expenditures of up to $1 million in Years 1 to 3 for incident cases.

Ontario currently pays for some chronic disease management programs. Based on the most recent FHT data, the costs of MDC programs to manage COPD were estimated at $85 million in FY 2010, with projected future expenditures of up to $51 million for incident cases, assuming the base case cost of program. However, this estimate does not accurately reflect the current costs to the province because of lack of report by FHTs, lack of capture of programs outside this model of care by any data set in the province, and because the resource utilization and frequency of visits/follow-up phone calls were based on the findings in the literature rather than the actual FHT COPD management programs in place in Ontario. Therefore, MDC resources being utilized in the province are unknown and difficult to measure.

Data on COPD-related hospitalization were pulled from Ontario administrative data sets (26) and based on consultation with experts (Personal communication, Ministry of Health and Long-Term Care, May 2011). Half of hospitalized patients will access PR resources at least once, and half of these will repeat therapy, translating to a potential burden of $17 million to $32 million, depending on the cost of the program. The costs of these resources are currently being absorbed by current systems, but since utilization is not being captured by any data set in the province, it is difficult to quantify and estimate. Provincial programs may be under-resourced, and patients may not be accessing these services effectively. (23)

Data from the LTOT provincial program (based on FY 2006 information) suggested that the burden was $65 million (Personal communication, Ministry of Health and Long-Term Care, January 2011), with potential expenditures of up to $0.2 million in Years 1 to 3 for incident cases.

From the clinical evidence on ventilation (i.e., a reduction of LOS in hospital), there were potential cost savings of $42 million and $12 million for NPPV and weaning with NPPV, respectively, if the study intervention were adopted. Future cost savings were projected to be up to $4 million and $1 million, respectively, for incident cases.

Current and projected expenditures are summarized in Table 24.

Table 24: Budget Impact Analyses of COPD Interventions*†

Intervention	Current Impact ($ millions)	Year 1 Impact ($ millions)	Year 2 Impact ($ millions)	Year 3 Impact ($ millions)	Funding
Smoking cessation programs					
UC in smoking cessation	1.8	0.2	0.1	0.1	Ministry of Health and Long-Term Care (physician billing)
IC vs. UC	8.4	0.7	0.5	0.4	Ministry of Health and Long-Term Care (physician billing)
NRT vs. UC	10.4	0.9	0.6	0.5	NRT is an out-of-pocket expense
IC + NRT vs. placebo	18.8	1.6	1.1	0.8	—
Bupropion vs. placebo	1.9	0.2	0.1	0.1	Ministry of Health and Long-Term Care (drug branch)
Multidisciplinary care teams					
MDC vs. UC‡	84.6	50.8	36.4	26.1	Ministry of Health and Long-Term Care (FHT programs)
MDC, sensitivity analysis‡	247.8	148.7	106.6	76.4	Ministry of Health and Long-Term Care (FHT programs)
Pulmonary rehabilitation					
PR (at least once) vs. UC	17.2	1.2	0.9	0.6	Ministry of Health and Long-Term Care or hospital programs
PR (at least once) sensitivity analysis	32.2	2.3	1.7	1.2	Ministry of Health and Long-Term Care or hospital programs
PR (repeat) vs. UC	17.2	0.6	0.4	0.3	Ministry of Health and Long-Term Care or hospital programs
PR (repeat) sensitivity analysis	32.2	1.2	0.8	0.6	Ministry of Health and Long-Term Care or hospital programs
Long-term oxygen therapy					
LTOT vs. UC	64.8	0.2	0.1	0.1	Ministry of Health and Long-Term Care (ADP)
Ventilation strategies					
NPPV + UMC vs. UMC	−42.0	−3.6	−2.6	−1.8	Hospital global budget
NPPV	70.6	6.0	4.3	3.1	Hospital global budget
UC	112.6	9.6	6.9	4.9	Hospital global budget
Weaning with NPPV vs. weaning with IMV	−11.7	−1.0	−0.7	−0.5	Hospital global budget
Weaning with NPPV	23.4	2.0	1.4	1.0	Hospital global budget
Weaning with IMV	35.1	3.0	2.1	1.5	Hospital global budget

*Abbreviations: COPD, chronic obstructive pulmonary disease; FHT, family health team; IC, intensive counselling; IMV, invasive mechanical ventilation; LTOT, long-term oxygen therapy; MDC, multidisciplinary care; NPPV, noninvasive positive pressure ventilation; NRT, nicotine replacement therapy; PR, pulmonary rehabilitation; UC, usual care; UMC, usual medical care.

†All costs are reported in Canadian dollars.

‡Likely to be an underestimate; overall, multidisciplinary care resources being utilized in the province are unknown and difficult to measure.

Limitations

There were several limitations to this analysis. Costing was limited to the resources used for each intervention investigated in the COPD mega-analysis EBAs. The costs of program implementation were not included in the analysis and require further investigation and expertise to identify.

Summary estimates of the impact of each intervention were captured from the MAS EBAs on individual interventions and are limited to the studies included in the investigations. The patient populations varied in the trials assessed and may not be generalizable to the context of Ontario health systems and services. Furthermore, caution should be exercised when comparing results across analyses, since the patient populations reflect different disease severities.

The model inputs populating the natural history of COPD are limited to the probabilities, costs, and utilities derived from the medical literature and are not based on a prospective collection of patient-level data from an Ontario COPD cohort. Therefore, assumptions were made to interpret outputs from the model in an Ontario context. Further to this, a utility value can be interpreted as a patient preference estimate, as opposed to a health benefit, since the weight assigned to a particular condition can vary greatly depending on the population being surveyed.

It was challenging to quantify the patient populations currently accessing services, as these are not necessarily captured by provincial data sets. Populations used in the analysis were based on assumptions from expert opinion and subject to variability between experts based on their individual experiences of treating patients with COPD.

COPD prevalence is increasing, and incidence is decreasing. It is feasible to assume that patients would repeat treatment, leading to higher costs in subsequent years based on prevalence data; however, only incident estimates were reported to reflect trial data, showing that patients will access services once on a short-term basis.

Conclusion

Currently, resources for most of these interventions are being absorbed through provider services, the ODB program, the Assistive Devices Program, and the hospital global budget. The most cost-effective intervention for COPD will depend on decision-makers' willingness to pay. Lack of provincial data sets capturing resource utilization for the various interventions poses a challenge for estimating the current burden and future expenditures.

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity	The amount of air that can be forcibly exhaled from the lungs after taking

(FVC)	the deepest breath possible.
Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.
Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[2]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.

[2] The mild-to-moderate classification was created for the purposes of the report.

Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.
Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.
Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Editorial Staff

Jeanne McKane

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

Appendices

Appendix 1: Literature Search Strategy

Databases: Ovid Medline/Medline IP, Embase & NHSEED, PubMed (for non-Medline records); HEED (Wiley)
Limits: 2009-present

COPD Concept
exp *Pulmonary Disease, Chronic Obstructive/
((chronic ADJ2 obstructi*) ADJ5 (airflow OR airway OR bronchitis OR bronchopulmonary OR lung)).ti.
(obstructi* ADJ2 (lung disease* OR pulmonary disease* OR pulmonary disorder* OR respiratory disease* OR respiratory tract disease*)).ti.
(COAD OR COPD).ti.
*Chronic Obstructive Lung Disease/
AND
Cost utility analyses
*Health Status Indicators/ OR *"Quality of Life"/
*Economics/
exp *"Costs and Cost Analysis"/
(econom* OR cost* OR pharmacoeconomic* OR pharmaco-economic*).ti.
((cost* ADJ utilit*) OR costutilit*).ti,ab.
(EuroQol* OR Euro Qol* OR EQ5D* OR EQ 5D*).mp.
(hui* OR health utilities index* OR health utilities indic* OR health utility index* OR health utility indic*).mp.
(SF6D OR SF 6D OR Short Form 6D OR ShortForm 6D OR Short-Form 6-Dimension* OR ShortForm 6-Dimension* OR Short-Form 6Dimension* OR ShortForm 6Dimension*).mp.
(standard ADJ2 gamble*).mp.
(Time Trade Off* OR Time TradeOff* OR TTO*).mp.
("preference based quality of life" OR (("preference based" OR "patient based") ADJ (utilit* OR measure?)) OR health preference? OR preference elicit* OR (patient* ADJ (utilit* OR preference*))).tw.
*Economic Evaluation/ OR "Cost Utility Analysis"/

Search run 2011Jul19
Embase 1980 to 2011 Week 28, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present

#	Searches	Results
1	exp *Pulmonary Disease, Chronic Obstructive/	44623
2	(chronic adj2 obstructi* adj5 (airflow or airway or bronchitis or bronchopulmonary or lung)).ti.	5592
3	(obstructi* adj2 (lung disease* or pulmonary disease* or pulmonary disorder* or respiratory disease* or respiratory tract disease*)).ti.	24427
4	(COAD or COPD).ti.	16581
5	*Chronic Obstructive Lung Disease/	44226
6	or/1-4	55292

7	or/2-5	54942
8	*Health Status Indicators/ or *"Quality of Life"/	100444
9	*Economics/	20958
10	exp *"Costs and Cost Analysis"/	87425
11	(econom* or cost* or pharmacoeconomic* or pharmaco-economic*).ti.	210443
12	((cost* adj utilit*) or costutilit*).ti,ab.	4145
13	(EuroQol* or Euro Qol* or EQ5D* or EQ 5D*).mp.	5681
14	(hui* or health utilities index* or health utilities indic* or health utility index* or health utility indic*).mp.	12126
15	(standard adj2 gamble*).mp.	1222
16	(Time Trade Off* or Time TradeOff* or TTO*).mp.	2786
17	("preference based quality of life" or (("preference based" or "patient based") adj (utilit* or measure?)) or health preference? or preference elicit* or (patient* adj (utilit* or preference*))).tw.	11667
18	*Economic Evaluation/ or "Cost Utility Analysis"/	4854
19	or/8-17	397517
20	or/11-18	242114
21	6 and 19 use prmz	1035
22	7 and 20 use emez	575
23	21 or 22	1610
24	limit 23 to yr="2009 -Current"	383
25	remove duplicates from 24	295

Database: EBM Reviews - NHS Economic Evaluation Database <3rd Quarter 2011>
Search Strategy:
1 exp Pulmonary Disease, Chronic Obstructive/ (77)
2 (chronic adj2 obstructi* adj5 (airflow or airway or bronchitis or bronchopulmonary or lung)).mp. (17)
3 (obstructi* adj2 (lung disease* or pulmonary disease* or pulmonary disorder* or respiratory disease* or respiratory tract disease*)).mp. (154)
4 (COAD or COPD).ti. (25)
5 *Health Status Indicators/ or *"Quality of Life"/ (0)
6 *Economics/ (0)
7 exp *"Costs and Cost Analysis"/ (0)
8 (econom* or cost* or pharmacoeconomic* or pharmaco-economic*).ti. (8217)
9 ((cost* adj utilit*) or costutilit*).ti,ab. (344)
10 (EuroQol* or Euro Qol* or EQ5D* or EQ 5D*).mp. (488)
11 (hui* or health utilities index* or health utilities indic* or health utility index* or health utility indic*).mp. (103)
12 (standard adj2 gamble*).mp. (177)
13 (Time Trade Off* or Time TradeOff* or TTO*).mp. (303)
14 ("preference based quality of life" or (("preference based" or "patient based") adj (utilit* or measure?)) or health preference? or preference elicit* or (patient* adj (utilit* or preference*))).tw. (367)
15 ((cost* adj utilit*) or costutilit*).if. (2232)
16 (or/1-4) and (or/5-15) (117)

17 limit 16 to yr="2009 -Current" (25)

PubMed
Search run 2011Jul19

Search	Most Recent Queries	Time	Result
#19	Search #6 AND #17 AND #18	15:07:44	21
#18	Search publisher[sb] OR in process[sb] OR pubmednotmedline[sb]	15:07:17	1616736
#17	Search #7 OR #8 OOR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	15:07:09	71323
#16	Search (preference based quality of life[tiab] OR ((preference based[tiab] OR patient based[tiab]) AND (utilit*[tiab] OR measure*[tiab])) OR health preference*[tiab] OR preference elicit*[tiab] OR (patient*[tiab] AND (utilit*[tiab] OR preference*[tiab]))	15:06:35	52176
#15	Search Time Trade Off*[all] OR Time TradeOff*[all] OR TTO*[all]	15:06:27	1597
#14	Search standard[all] AND gamble*[all]	15:06:19	859
#13	Search SF6D[all] OR SF 6D[all] OR Short Form 6D[all] OR ShortForm 6D[all] OR Short-Form 6-Dimension*[all] OR ShortForm 6-Dimension*[all] OR Short-Form 6Dimension*[all] OR ShortForm 6Dimension*[all]	15:06:08	262
#12	Search hui*[all] OR health utilities index*[all] OR health utilities indic*[all] OR health utility index*[all] OR health utility indic*[all]	15:05:55	12483
#11	Search EuroQol*[all] OR Euro Qol*[all] OR EQ5D*[all] OR EQ 5D*[all]	15:05:47	2513
#10	Search economic*[tiab] OR cost[tiab] OR costs[tiab] OR costing[tiab] OR cost* utilit*[tiab] OR costutilit*[tiab]	15:05:28	8190
#9	Search Costs and Cost Analysis[mh]	15:03:33	156444
#8	Search Economics[mh]	15:03:22	437731
#7	Search Health Status Indicators[mh] OR Quality of Life[mh]	15:02:28	230567
#6	Search #3 OR #4 OR #5	15:01:44	20551
#5	Search copd[ti]	15:01:32	7249
#4	Search (chronic[ti] AND obstructi*[ti]) AND (airflow[ti] OR airway[ti] OR bronchitis[ti] OR bronchopulmonary[ti] OR lung[ti])	15:01:06	3108
#3	Search Pulmonary Disease, Chronic Obstructive[mh]	14:59:49	15829

HEED
COPD + cost utility = 18 results

References

(1) Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001 Apr;163(5):1256-76.

(2) Saetta M, Di SA, Turato G, Facchini FM, Corbino L, Mapp CE, et al. CD8+ T-lymphocytes in peripheral airways of smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998 Mar;157(3 Pt 1):822-6.

(3) O'Donnell DE, Laveneziana P. The clinical importance of dynamic lung hyperinflation in COPD. COPD. 2006 Dec;3(4):219-32.

(4) Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [Internet]. [place unknown]: Global Initiative for Chronic Obstructive Lung Disease; [updated 2010; cited 2011 Jul 6]. Available from: http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf

(5) Mittmann N, Kuramoto L, Seung SJ, Haddon JM, Bradley-Kennedy C, Fitzgerald JM. The cost of moderate and severe COPD exacerbations to the Canadian healthcare system. Respir Med. 2008 Mar;102(3):413-21.

(6) GRADE Working Group. Grading quality of evidence and strength of recommendations. Br Med J. 2006;328(7454):1490-4.

(7) Hoogendoorn M, Feenstra TL, Hoogenveen RT, Rutten-van Molken MP. Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD. Thorax. 2010;65(8):711-8.

(8) Hoogendoorn M, van Wetering CR, Schols AM, Rutten-van Molken MP. Is INTERdisciplinary COMmunity-based COPD management (INTERCOM) cost-effective? Eur Respir J. 2010;35(1):79-87.

(9) Drummond M, McGuire A. Economic evaluation in health care - merging theory with practice. New York: Oxford University Press Inc.; 2001.

(10) Ontario Case Costing Initiative [Internet]. Toronto: Ontario Case Costing Initiative; [updated 2011 Jun; cited 2011 May]. Available from: http://www.occp.com/

(11) Canadian Agency for Drugs and Technologies in Health (CADTH). Guidelines for the economic evaluation of health technologies: Canada. Ottawa (ON); CADTH: 2006.

(12) Rutten-van Molken MP, Hoogendoorn M, Lamers LM. Holistic preferences for 1-year health profiles describing fluctuations in health: the case of chronic obstructive pulmonary disease. Pharmacoeconomics. 2009;27(6):465-77.

(13) Ringbaek T, Seersholm N, Viskum K. Standardised mortality rates in females and males with COPD and asthma. Eur Respir J. 2005 May;25(5):891-5.

(14) Hoogendoorn M, Feenstra TL, Hoogenveen RT, Al M, Molken MR. Association between lung function and exacerbation frequency in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2010;5:435-44.

(15) Rutten-van Molken MP, Oostenbrink JB, Miravitlles M, Monz BU. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. Eur J Health Econ. 2007 Jun;8(2):123-35.

(16) Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.

(17) Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005 Feb 15;142(4):233-9.

(18) Ontario drug benefit formulary [Internet]. Toronto: Ministry of Health and Long-Term Care (Ontario); [updated 2011 Apr 15; cited 2011 May]. Available from: http://www.health.gov.on.ca/english/providers/program/drugs/odbf_eformulary.html

(19) Compendium of pharmaceuticals and specialties (Canada). 44th ed. Ottawa (ON): Canadian Pharmacists Association; 2009.

(20) Glaxosmithkline Nicorette Nicotine Gum 4mg Starter Kit 110 [Internet]. [updated 2011; cited 2011 Mar]. Available from: http://www.shopping.com/GlaxoSmithKline-Nicorette-Nicotine-Gum-4mg-Starter-Kit-110-GlaxoSmithKline/info

(21) Schedule of benefits for physician services under the Health Insurance Act: effective March 24, 2010. Toronto: Ministry of Health and Long-Term Care (Ontario); 2010.

(22) Guide to interdisciplinary provider compensation. Toronto: Ministry of Health and Long-Term Care (Ontario); 2011 May. Available from: http://www.health.gov.on.ca/transformation/fht/guides/fht_inter_provider.pdf

(23) Brooks D, Sottana R, Bell B, Hanna M, Laframboise L, Selvanayagarajah S, et al. Characterization of pulmonary rehabilitation programs in Canada in 2005. Can Respir J. 2007;14(2):87-92.

(24) Canadian classification of health interventions - ICD-10-CA/CCI. Ottawa (ON): Canadian Institute for Health Information; 2006.

(25) Gershon AS, Wang C, Wilton AS, Raut R, To T. Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in ontario, Canada, 1996 to 2007: a population-based study. Arch Intern Med. 2010 Mar 22;170(6):560-5.

(26) Ontario Ministry of Health and Long-Term Care. IntelliHEALTH Ontario [database online]. Toronto (ON): Ontario Ministry of Health and Long-Term Care; [updated 2008; cited 2011 May]. Available from: https://www.intellihealth.moh.gov.on.ca/

(27) Lawati NA, FitzGerald JM. Acute exacerbation of chronic obstructive pulmonary disease. BC Med J. 2008;50(3):138-42.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-8871-3 (PDF)

Ontario
Health Quality Ontario
Qualité des services
de santé Ontario

Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

M Giacomini, D DeJean, D Simeonov, A Smith

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 13, pp. 1–47, March 2012

Suggested Citation

This report should be cited as follows:
Giacomini M, DeJean D, Simeonov D, Smith A. Experiences of living and dying with COPD: a systematic review and synthesis of the qualitative empirical literature. Ont Health Technol Assess Ser [Internet]. 2012 March;12(13):1-47. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Qualitative_March.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to: MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit:
http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

COPD	Chronic obstructive pulmonary disease
FEV	Forced expiratory volume

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-Term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this analysis was to review empirical qualitative research on the experiences of patients with chronic obstructive pulmonary disease (COPD), informal caregivers ("carers"), and health care providers—from the point of diagnosis, through daily living and exacerbation episodes, to the end of life.

Clinical Need and Target Population

Qualitative empirical studies (from social sciences, clinical, and related fields) can offer important information about how patients experience their condition. This exploration of the qualitative literature offers insights into patients' perspectives on COPD, their needs, and how interventions might affect their experiences. The experiences of caregivers are also explored.

Research Question

What do patients with COPD, their informal caregivers ("carers"), and health care providers experience over the course of COPD?

Research Methods

Literature Search

Search Strategy

Literature searches for studies published from January 1, 2000, to November 2010 were performed on November 29, 2010, using OVID MEDLINE; on November 26, 2010, using ISI Web of Science; and on November 28, 2010, using EBSCO Cumulative Index to Nursing and Allied Health Literature (CINAHL). Titles and abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. One additional report, highly relevant to the synthesis, appeared in early 2011 during the drafting of this analysis and was included post hoc.

Inclusion Criteria

English-language full reports

- studies published between January 1, 2000, and November 2010
- primary qualitative empirical research (using any descriptive or interpretive qualitative methodology, including the qualitative component of mixed-methods studies) and secondary syntheses of primary qualitative empirical research
- studies addressing any aspect of the experiences of living or dying with COPD from the perspective of persons at risk, patients, health care providers, or informal carers; studies addressing multiple conditions were included if COPD was addressed explicitly

Exclusion Criteria

- studies addressing topics other than the experiences of living or dying with COPD from the perspective of persons at risk, patients, health care providers, or informal carers
- studies labelled "qualitative" but not using a qualitative descriptive or interpretive methodology (e.g., case studies, experiments, or observational analysis using qualitative categorical variables)
- quantitative research (i.e., using statistical hypothesis testing, using primarily quantitative data or analyses, or expressing results in quantitative or statistical terms)

- studies that did not pose an empirical research objective or question, or involve the primary or secondary analysis of empirical data

Outcomes of Interest

- qualitative descriptions and interpretations (narrative or theoretical) of personal and social experiences of COPD

Summary of Findings

Experiences at Diagnosis

- Patients typically seek initial treatment for an acute episode rather than for chronic early symptoms of COPD.
- Many patients initially misunderstand terms such as *COPD, chronic obstructive pulmonary disease,* or *exacerbation*.
- Patients may not realize that COPD is incurable and fatal; some physicians themselves do not consider early COPD to be a fatal disease.
- Smokers may not readily understand or agree with the idea that smoking caused or worsens their COPD. Those who believe there is a causal link may feel regret or shame.

Experiences of Living Day to Day

- COPD patients experience alternating good days and bad days. A roller-coaster pattern of ups and downs becomes apparent, and COPD becomes a way of life.
- Patients use many means (social, psychological, medical, organizational) to control what they can, and to cope with what they cannot. Economic hardship, comorbidities, language barriers, and low health literacy can make coping more difficult.
- Increasing vulnerability and unpredictable setbacks make patients dependent on others for practical assistance, but functional limitations, institutional living or self-consciousness can isolate patients from the people they need.
- For smokers, medical advice to quit can conflict with increased desire to smoke as a coping strategy.
- Many of the factors that isolate COPD patients from social contact also isolate them from health care.

Experiences of Exacerbations

- Patients may not always attribute repeated exacerbations to advancing disease, instead seeing them as temporary setbacks caused by activities, environmental factors, faltering self-management, or infection.
- Lack of confidence in community-based services leads some patients to seek hospital admission, but patients also feel vulnerable when hospitalized. They may feel dependent on others for care or traumatized by hospital care routines.
- Upon hospital discharge following an exacerbation, patients may face new levels of uncertainty about their illness, prognosis, care providers, and supports.

Experiences of the End of Life

- Patients tend to be poorly informed about the long-term prognosis of COPD and what to expect toward the end of life; this lack of understanding impairs quality of life as the disease progresses.
- As the end of life approaches, COPD patients face the usual challenges of daily living, but in a context of increasing exacerbations and deepening dependency. Activities and mobility decrease, and life may become confined.
- Some clinicians have difficulty identifying the beginning of "the end of life," given the unpredictable course of COPD. Long-term physician-patient relationships, familiarity and understanding, trust, good communication skills, sensitivity, and secure discussion settings can help facilitate end-of-life discussions.
- Divergent meanings and goals of palliative care in COPD lead to confusion about whether such services are the responsibility of home care, primary care, specialty care, or even critical care. Palliative end-of-life care may not be anticipated prior to referral for such care. A palliative care referral can convey the demoralizing message that providers have "given up."

Experiences of Carers

- Carers' challenges often echo patients' challenges, and include anxiety, uncertainty about the future, helplessness, powerlessness, depression, difficulties maintaining employment, loss of mobility and freedoms, strained relationships, and growing social isolation.
- Carers feel pressured by their many roles, struggling to maintain patience when they feel overwhelmed, and often feeling guilty about not doing enough.
- Carers often face their own health problems and may have difficulty sustaining employment.

Synthesis: A Disease Trajectory Reflecting Patient Experiences

- The flux of needs in COPD calls for service continuity and flexibility to allow both health care providers and patients to respond to the unpredictable yet increasing demands of the disease over time.

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-Term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this analysis was to review empirical qualitative research on the experiences of patients with chronic obstructive pulmonary disease (COPD), informal caregivers ("carers"), and health care providers—from the point of diagnosis, through daily living and exacerbation episodes, to the end of life.

Clinical Need and Target Population

Qualitative empirical studies (from social sciences, clinical, and related fields) can offer important information about how patients experience their condition. This exploration of the qualitative literature offers insights into patients' perspectives on COPD, their needs, and how interventions might affect their experiences.

The findings of the qualitative research are summarized as they relate to 4 broad, episodic patient experiences over the course of COPD: diagnosis and prognosis; living day to day; exacerbations; and the end of life. A fifth category addresses carer experiences.

Systematic Review

Research Question

What do patients with COPD, their informal caregivers ("carers"), and health care providers experience over the course of COPD?

Research Methods

Literature Search

Search Strategy

Literature searches for studies published from January 1, 2000, through November 2010, were performed on November 29, 2010, using OVID MEDLINE; on November 26, 2010, using ISI Web of Science; and on November 28, 2010, using EBSCO Cumulative Index to Nursing and Allied Health Literature (CINAHL). Titles and abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. One additional report, highly relevant to the synthesis, appeared in early 2011 during the drafting of this analysis and was included post hoc.

Inclusion Criteria

English-language full reports

- studies published from January 1, 2000 through November 2010
- primary qualitative empirical research (using any descriptive or interpretive qualitative methodology, including the qualitative component of mixed-methods studies) and secondary syntheses of primary qualitative empirical research
- studies addressing any aspect of the experiences of living or dying with COPD from the perspective of persons at risk, patients, health care providers, or informal carers; studies addressing multiple conditions were included if COPD was addressed explicitly

Exclusion Criteria

- studies addressing topics other than the experiences of living or dying with COPD, from the perspective of persons at risk, patients, health care providers, or informal carers
- studies labelled "qualitative" but not using a qualitative descriptive or interpretive methodology (e.g., case studies, experiments, or observational analysis using qualitative categorical variables)
- quantitative research (i.e., using statistical hypothesis testing, using primarily quantitative data or analyses, or expressing results in quantitative or statistical terms)
- studies that did not pose an empirical research objective or question, or involve the primary or secondary analysis of empirical data

Outcomes of Interest

- qualitative descriptions and interpretations (narrative or theoretical) of personal and social experiences of COPD

Qualitative Analysis

Full papers were retrieved and read by 2 investigators. Papers were grouped by broad topical focus and read closely by 1 investigator to generate a narrative summarizing the main findings under each topic. A second investigator reviewed the same papers, revised the narrative (by consensus with the first reviewer), and incorporated any relevant findings from papers in other topic groups (for example, some papers on smoking experiences also addressed day-to-day living issues). In all, each primary research paper was reviewed 2 to 3 times by at least 2 investigators.

A synthesis was developed to relate the findings to the clinical trajectory of COPD, highlighting key patient, caregiver, and health care provider experiences reported at specific phases of the disease course. Drafts of the full report were presented sequentially to the Ontario Health Technology Advisory Committee, the Medical Advisory Secretariat, and the COPD Expert Panel for multidisciplinary feedback.

Results of Systematic Review

The database search yielded 24,906 citations published between January 1, 2000, and November 2010 (including some duplicates). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded from the analysis.

A total of 100 papers met the inclusion criteria. One additional report, highly relevant to the synthesis, appeared in early 2011 during the drafting of this analysis and was included post hoc.

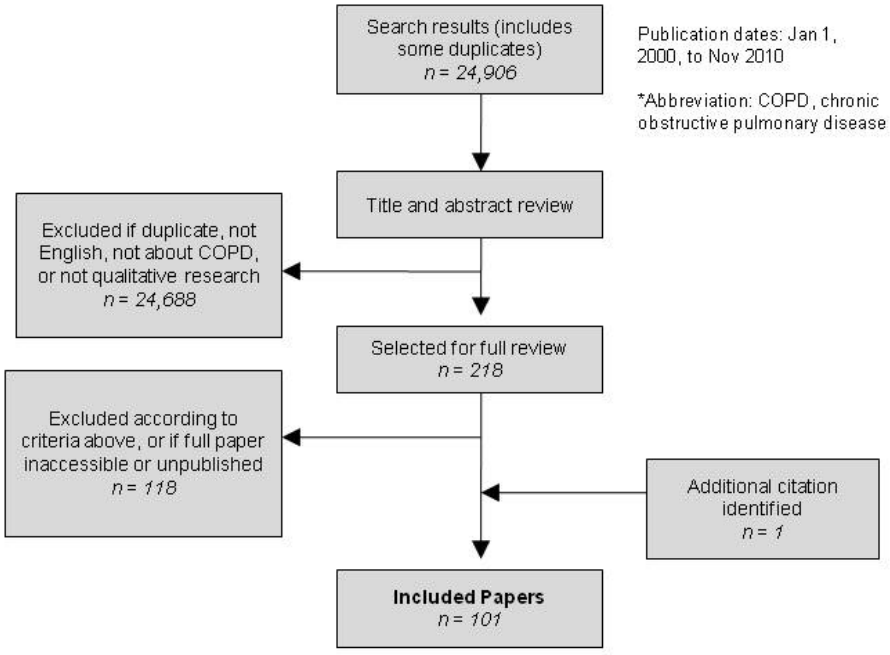


Figure 1: Citation Flow Chart*

Together, the papers included in the analysis represent an estimated 82 discrete studies and involve an estimated 1,404 people with COPD ("patients"), 397 health care providers in clinical or administrative professions, and 275 carers across many care and community settings. Studies from the United Kingdom and United States dominated the literature; Canadian research contributed 11 published papers from 7 studies (Table 1).

Table 1: Summary of Qualitative Studies Reviewed

Country	Patients, n*	Carers, n*	Health Care Providers, n*	Studies, n*	Papers, n
United Kingdom	450	90	158	30	36
United States	303	127	101	15	20
Multinational	148	0	0	2	2
Canada	119	15	27	7	11
Australia	109	28	16	5	8
Netherlands	102	0	20	4	5
Sweden	60	0	47	6	6
Thailand	31	0	0	1	1
Taiwan	25	0	0	2	2
Norway	21	0	8	2	2
Iceland	12	11	0	3	3
Denmark	10	0	0	1	1
Hong Kong	9	0	0	2	2
Finland	5	4	0	1	1
New Zealand	0	0	20	1	1
Total	**1,404**	**275**	**397**	**82**	**101**

*Estimated.

Findings covered 4 broad categories of patient experiences over the course of COPD: diagnosis, living day-to-day, exacerbations, and the end of life. A fifth category addressed carer experiences.

Experiences at Diagnosis

Receiving a COPD Diagnosis

Before a diagnosis of COPD, many people see early symptoms and limitations as their own "normal" way of life, and too mild or ordinary to warrant medical attention. (1;2;3;4) Patients may initially attribute their symptoms and limitations to smoking or aging; (1;5) they typically seek initial treatment for an acute episode rather than for the chronic, early symptoms of COPD. (6;7;8;9)

Physicians may not communicate a diagnosis of COPD clearly; (10;11;12) diagnostic and prognostic information is often given in stages, as medical events arise. (13) Patients may learn that they have COPD only after several visits, or from sources other than their physician. (8;12;14) In addition, terminology can confuse the message at diagnosis; for example, primary care clinicians may use other diagnostic terms (e.g., *emphysema*) or even euphemisms (e.g., *chest problems*). (8;15;16) Usually, the terms *chronic obstructive pulmonary disease* and *COPD* are unfamiliar to patients. (8;14;15;17)

Understanding the Implications of COPD

Patients sometimes worry that the *C* in COPD stands for *cancer* and are relieved to learn that it does not; smokers in particular mistakenly interpret COPD as good news in this context. (16;18) Patients may be unaware that COPD is incurable and fatal; (11;16) some physicians themselves do not consider early COPD to be a fatal disease. (13) The seriousness of COPD becomes clearer as the disease progresses and as patients realize that it will be a permanent feature of their lives. (19)

Some patients express a need for information at the time of diagnosis, including prognosis and management strategies, (9;10;11;14;20;21;22) but others prefer less explicit prognostic information and may avoid education or discussions for fear of learning things that will worry them. (15;20;21;22;23) The poor long-term prognosis of COPD is best communicated within a strong physician-patient relationship, and with compassion and empathy (10;13;20).

Role of Smoking

Smokers have divergent beliefs about whether smoking caused their COPD. Many know that smoking causes lung cancer, but few realize that it also causes COPD. (18;24;25) Smokers with COPD may favour other causal explanations, such as family history, hazard or pollution exposures, age, or chance. (3;4;17;26;27) Some may choose to believe that they have not smoked often enough, or recently enough, to bring on COPD. (19;28) Some are unaware that smoking will worsen their COPD, (14;28) and some find that quitting does not improve their health. (27;28) Clinicians' advice to quit may be seen as routine, and not directly related to a diagnosis of COPD. (9)

Smokers who do attribute their COPD to smoking often feel profound regret, guilt, or shame. (1;3;19;27). Some clinicians reinforce this self-blame and stigma, (10;26;27) while others consciously avoid blaming. (13) Some smokers with COPD may feel that they are not entitled to health care or sympathy from others, (1;19;27) and some avoid health care visits to avoid "preaching" about smoking. (3)

Experiences of Living Day to Day

Daily Life

Patients with COPD experience an ongoing cycle of good and bad days. (29) Living with daily breathlessness is a perpetual, exhausting struggle, and living becomes hard work. (6;30) The experience of dyspnea involves not only breathlessness, but also fatigue and modified or limited activities (1;5;8;10;31;32) and negative mental states, including depression. (10;22;31;33) Basic activities of daily living may be affected, including sleeping, getting out of bed, bending over, bathing, dressing, eating, performing domestic chores or occupational duties, walking, driving, using public transportation, travelling, drinking, singing, dancing, having sex, shopping, playing instruments or sports, talking, carrying heavy objects, and even sitting in a doctor's waiting room. (4;10;19;23;25;30;33;34;35;36;37;38;39;40;41;42;43;44) Activities are delegated, limited, modified, or stopped due to breathlessness—sometimes temporarily, sometimes permanently (5;35;44;45;46;47)—and the loss of these activities affects enjoyment of life. (33;41) Pervasive (sometimes undertreated) pain often accompanies breathlessness. (32)

Emotions and Quality of Life

Patients may endure episodic fears, anxieties, panic, or dread (19;33)—of breathlessness, (5;22;34;37;45;47;48;49) of being left alone, (50) of hospitalization, (19;37;38) or even of going home from the hospital. (19;37;38;51) Mortal fears often arise of suffocating, dying suddenly during an attack of dyspnea, or dying when asleep. (37;39;47;49;50;52)

Breathlessness and anxiety interact in complex ways. (6;32;53) Independence is threatened, as patients begin to need help for basic bodily care and functions due to severe breathlessness. (34;54) Self-confidence and self-esteem falter under feelings of powerlessness, helplessness, and hopelessness. (10;19;23;35;36;37;39;55;56) Sadness and vulnerability are common, (45;57) while anger, frustration, and irritability grow. (10;34;58)

The experience of overall quality of life with COPD is multidimensional, (59) and patients' social and physical environments affect what they can achieve. (33) Objective quality-of-life instruments may be difficult to complete, and may fail to capture relevant domains. (60) Domains that patients use to evaluate their own quality of life include physical effects, medication dependency, disruption of relationships, emotional reactions, life disruptions, and self-esteem. (39)

Constant planning and balancing is required to incorporate the particular demands of COPD into daily life. (19;43;61;62) Coping becomes relentless, round-the-clock work. (63) Over time, patients become experts in their own condition and develop their own methods for coping. (49) Self-management strategies include energy conservation through pacing, planning, or modifying activities; (44;58;62;63;64;65) breathing techniques; (62;63;64;65;66) exercise; (62;63;64;65) exercise avoidance; (62;63) possessing medications and following medication regimens; (19;33;63;64;65) assistance equipment; (7;10) and controlling or avoiding threatening environments. (33;43;58;62;66) Many coping strategies require resources of time, money, or expertise. Economic hardship, comorbidities, language barriers, and low health literacy can all impair self-care, health care, and coping. (67)

With diminishing abilities and growing vulnerability come challenges to patients' identity, and even to meaning of life. COPD affects patients' ability to fulfill meaningful social roles, (6;19) and they reflect on and grieve the loss of identity, activity, or productivity. (4;6;19;33;39;48) Age and sex can affect role expectations and the challenges that come with them. (6;8) Patients may see themselves as being old or sick, (6;33) and they may greatly value the ability to even partially fulfill normal roles. (36;41) Some come to establish a relationship with their disease, build a different life around it, and seek new sources of meaning in their lives. (4;6;8;19;33) Some find comfort in spiritual beliefs, or in cultivating a broader perspective (such as appreciating what they have left, doing what they still can, and "making every day count"). (43;44;48) At later stages of disease, life may seem reduced to little more than existence, (45) or a continuous struggle for acceptance of profoundly diminished prospects. (30)

Despite the ongoing struggles that come with COPD, not all patients readily perceive a downward trajectory in their health over time. Some attribute worsening symptoms not to the progression of their disease, but rather, to temporary, immediate causes such as self-management failures or environmental changes. (2;31) The steady decline of COPD becomes most recognizable in hindsight, at later stages of disease. (9;16;42)

Relationships with Others

Increasing vulnerability and unpredictable setbacks make patients dependent on others for practical assistance, comfort, and moral support. (34;37;39;41) The involvement of others in caregiving can contribute richly to patients' quality of life, ability to cope, and social relationships. (49;56;68) Conversely, COPD patients who live alone and are unable to hire extra help may become especially

vulnerable. (10) Rehabilitation programs may replace some of the social contact and support that COPD patients lose as a result of their disease, and are valuable for this reason. (4;14;69) Incapacity due to advancing disease may require patients to relocate to other types of housing, assisted settings, or locations closer to health services, although not all can obtain optimal housing. (2;3) Both home-based and institution-based care presents patients with strong emotional and pragmatic tradeoffs. (30)

Sadly, patients' isolation often grows together with their increasing need to "have someone there." Functional limitations, institutional living, or self-consciousness can isolate COPD patients from the people they need. (8;9;10;30) Sometimes family and friends withdraw because of the disease. (23;70) Many aspects of COPD isolate patients from others, including the inability to walk, talk, leave home, or leave their chair or bed; fear of weather, second-hand smoke, or environmental pollution; inflexible planning and routines; strained or lost contact with family, friends, or coworkers; reluctance to ask for help or expectations that assistance will not help enough; embarrassment about the causes, symptoms, behaviour, or equipment associated with COPD; the strain of trying to appear normal; the invisibility of some distressing symptoms; and perceived lack of sympathy or compassion from others. (5;19;23;24;30;33;34;36;37;39;41;45;58;66;68;70)

Challenges of Smoking Cessation

COPD patients who smoke respond to advice to quit in complex ways. Some do not understand that smoking accelerates COPD, the onset of disability, and death. (8;17;28) Some become more motivated to quit upon realizing that they are experiencing the complications of smoking, (1;26;27;62) but others may feel incapable of doing do, or may see quitting as a never-ending struggle. (3;39) Paradoxically, the challenges of living with COPD can also increase the desire to smoke as a means of coping. (3;27;39) While COPD brings pain, difficulty, grievous loss, and a shrinking social world, smoking can provide pleasure, comfort, support, and sense of community with other smokers. (3;19;27;39) While COPD makes patients feel ill, tired, or old, smoking can bolster a stronger self-image. (3;19;39)

Interactions with the Health Care System

COPD patients often suffer poor relationships with health care providers, and experience hastiness, poor listening, or lack of compassion. (10) Patients sometimes feel that their subjective distress seems invisible to clinicians, who focus on objective health indicators. (10;24;42;53) Physicians infrequently investigate, address, or refer for the substantial nonmedical assistance needs of COPD patients. (5;9)

Access to care is a pervasive issue, for many reasons. Many of the factors that isolate COPD patients socially also isolate them from health care. (24;25;54) Some patients feel unwelcome when they visit health care providers because their condition seems hopeless, or because they continue to smoke. (3;10;24) Poor continuity of care is a common complaint, and can hamper both access to care and rapport between patient and health care provider. (25;71) Patients may feel compelled to be undemanding and agreeable to avoid losing their physician. (10;22;24;25) Medical visits become logistically difficult due to impaired mobility, time-limited oxygen supplies, etc., and for these reasons patients sometimes avoid visits during exacerbations, when they are most needed. (22;24;25;42;51) Some patients undermedicate to stockpile medications for future exacerbations, when they will self-medicate to avoid physician visits. (10)

Experiences of Exacerbations

Recognition

Acute breathlessness is the most terrifying aspect of living with COPD. Patients do not always expect to recover from an exacerbation, and it raises fears of sudden death. (6;10;72;73) It can be frightening to be alone; breathlessness creates feelings of urgent need for help from others, and the presence of others may help alleviate terror. (14;23;34;70;73)

Patients vary in their recognition of clinically defined exacerbations, and often describe the experience with nonclinical language (e.g., *attack, bad day, chest infection, crisis*). (29;74) Indeed, the term *exacerbation* lacks meaning for patients across many countries and languages. (74) As well, patients' own descriptions of events may not correspond with clinical measures; for example, patients may report that they have no problem breathing because they have ceased all activity due to severe breathlessness. (75) Restricting activity is a typical way to maintain a feeling of normalcy and avoiding asking for help. (5) Self-management strategies include decreased activity, medication, relaxation, and altered breathing patterns. (76) Because patients seem "normal" at rest, observers may underestimate how ill they really are. (24)

Many patients are first diagnosed with COPD during a severe exacerbation. (8) Although an exacerbation is considered a discrete event from a clinical point of view, patients experience exacerbations within a continuous flux of good days and bad days. Exacerbations are the low points in a familiar but unpredictable cycle, and are not always recognized as emerging medical crises. (29;72;75) Patients may feel reluctant or unable to seek medical help during an exacerbation. (22;25;29;42;51;75) A sudden inability to cope with life's demands, in addition to frightening changes in symptoms, typically drives patients to seek care. (29) Some who defer care end up hospitalized and demoralized. (22)

Treatment

Patients may distrust clinicians' competence when they don't receive expected treatments, or when interventions are disappointing: for example, when they are not given antibiotics for what seems to be a chest infection; (10;39) when pulmonary rehabilitation doesn't improve symptoms; or when hospital staff respond casually to symptoms that the patient believes are an emergency. (6;69;72;73) Lack of confidence in community-based services leads some patients to seek hospital admission. (77) Some exacerbations require hospital care, but patients may feel especially vulnerable while hospitalized; they may feel dependent on others for care, or traumatized by frightening, exhausting hospital care routines. (51;54;73) While in hospital, many patients wish for better communication about their treatments, progress, and post-discharge care. (51;78)

Recovery

Upon hospital discharge following an exacerbation, patients may face new levels of uncertainty about their illness, prognosis, care providers, and supports. (38;51;71) Patients may find security in self-treatments such as oxygen therapy and "standby" medications. (51) They typically hope that after recovering from an exacerbation, they will return to their normal daily life. (23;70) Exacerbations may not be recalled as considerable medical events; instead, they may be remembered for their impact on activities, plans, and daily life. (29) Patients may interpret recovery from an exacerbation as a sign of improvement in their COPD; temporary improvement obscures the overall downward trend in their health. (2)

Experiences of the End of Life

Understanding the Prognosis of COPD

Although it is fairly certain that COPD will eventually be fatal, the timing of decline and death is highly uncertain. (79) Such uncertainty may make physicians unsure about whether and when to discuss the prognosis of COPD with patients. (10) Patients often learn about their prognosis from a source other than their physician, and typically well after their initial diagnosis. (80) Patients tend to be poorly informed about the long-term prognosis of their disease and what to expect toward the end of life (especially compared to those with diseases such as cancer or acquired immune deficiency syndrome); this lack of understanding impairs their quality of life as the disease progresses. (11;15;80) Some may envision their death from COPD occurring at the end of their natural life (rather than prematurely), (2;10;11) and some

may deliberately avoid contemplating death. (47) Nevertheless, although the long-term picture may be fuzzy, patients may fear and think about death, particularly during acute exacerbations, not knowing which one may be their last. (2;19;22;47)

Experiences of Dying

Patients may realize that death is imminent when COPD is very advanced and seems to take over every aspect of life, or entirely exhausts them. (19;81) They worry about *how* they might die—in particular, about suffocating during a final attack of breathlessness. (5;11;47) They may want health care providers to address their fears of dying breathless or in pain, (20;47) or to provide a clear new care plan. (20) The perception that clinicians are too busy inhibits some patients from sharing their psychosocial needs at the end of life. (7) Nurses may offer more time for conversation, and often play a translating role between physicians and patients. (13;82) Some patients prefer a hospital death, as hospitalization ensures that they will not be alone and alleviates family care burdens. (47)

As the end of life approaches, COPD patients face the usual challenges of daily living, but with increasing of exacerbations and deepening dependency. Activities and mobility decrease, and life may become confined to the home, or even to a single chair. (5;50) Declining health often deepens social isolation and loneliness, (45;46;57) but being involved with and appreciated by others provides end-stage COPD patients with a significant source of comfort, meaning in life, and reason to "go on." (30;45) Patients become more dependent on their families, (25;34;36;37;39;41) and they may worry about the impact of their sudden death on surviving family members. (57) Peace of mind before dying may become an important goal. (47) Anxieties and fears about the future, and about dying, persist or grow. (50;57) Maintaining hope—for improvement, remission, or cure—becomes a central feature of psychological coping. (49;56;83)

Communication with Health Care Providers

Patients may look to their physicians for information, behaviour, or cues (e.g., language, or new medications) that can be interpreted as optimistic signs. (10;83;84) Patients may feel compelled to "take a chance" on dramatic interventions (e.g., lung volume reduction surgery) when they perceive that they have few options and "nothing to lose." (85) A lack of hopeful messages from clinicians can be devastating, and referral to palliative care may be interpreted as hopelessness. (7;10;50) In contrast, however, the absence of prognostic information can also cause some patients make overly pessimistic assumptions. (5) When no more treatment options are available, patients may realize that they are approaching the end of life. (83) Upon hearing that their disease is terminal, patients typically compartmentalize, balance, integrate, or redirect their hopes elsewhere. (20)

There are many reasons why clinicians may find it difficult to communicate the terminal prognosis of COPD or initiate advance care planning. Some have difficulty identifying the beginning of "the end of life," given the unpredictable course of COPD. (16;47;86) During appointments, there may be multiple health issues to address and inadequate time for conversations about long-term prospects. (16) During exacerbations, when patients' thoughts of death are most acute and physicians are most engaged with their care, clinicians tend to focus on crisis management and often have insufficient time, opportunity, or privacy for difficult conversations, reflection on the bigger picture, and end-of-life planning. (7;16;79;87;88). Specialists care for patients only sporadically, and may not know them well. (79) Clinicians are aware that poorly timed end-of-life discussions may traumatize patients or families, and may hesitate for fear of harming them, or dashing their hopes; (8;20;79) some fear that patients might forgo life-enhancing interventions such as smoking cessation or exercise. (16) Not all clinicians are adequately informed or prepared to pursue palliative care for COPD. (13;87) As well, clinicians grapple with difficult emotions of their own, such as sadness or anxiety; some prefer to let patients initiate end-of-life discussions. (79) Many COPD patients are unwilling to discuss the prospect of dying,

(11;20;22;46;79;81;82) but some want to know when death is imminent, so that they can prepare. (47) Long-term physician-patient relationships, familiarity and understanding, trust, good communication skills, sensitivity to patients' receptiveness about end-of-life topics, and secure discussion settings can help facilitate end-of-life discussions. (20;34;82;86;89;90)

Patients may selectively forgo interventions such as intubation when they realize they are dying, but individual patients vary in their tolerance for burden-benefit ratios. (81;84) Patients' preferences may change over the course of the disease. In particular, they may become willing to tolerate greater burdens for smaller incremental benefits, (84;86) and this calls into question the value of advance care plans. (84) Some patients prefer to make decisions only when they are needed. (84)

Palliative Care

The term *palliative care* lacks a stable definition among COPD health care providers. (7) Some consider the defining feature to be palliation itself (i.e., symptom management at any stage of life or disease, possibly in concert with therapeutic intervention), while others restrict the term to end-of-life care (i.e., comfort care in lieu of therapeutic care). (7) End-of-life palliative services have traditionally targeted patients with cancer, acquired immune deficiency syndrome, or neurodegenerative disease, but COPD patients face more uncertain prognoses, as well as chronic symptoms, limitations, and psychosocial challenges. (15;80;90) The transition point to "end of life" is difficult to pinpoint in the long, cyclic trajectory of COPD, so a chronic model of palliative care (i.e., one not focused on an "end stage") may best suit patients' needs. (15)

Divergent meanings and goals of palliative care in COPD lead to confusion about whether such services are the responsibility of home care, primary care, specialty care, or even critical care. (7;34;87) For COPD patients, a meaningful evaluation of palliative services would focus on care processes in addition to palliation-relevant outcomes. (91) For example, preserving continuity of care and established, compassionate provider relationships are important to COPD patients, and the loss of such relationships can cause suffering. (20;89;90;91) Other valued features may include supportiveness, communication, accessibility, clinical skill, teamwork, family involvement, patient education, personalized care, attention to patient values, and respect for patients' lifestyle, culture, decisions, and wishes (80;90;91).

Critical care clinicians caring for end-stage COPD in an intensive care setting identify special challenges, such as meeting high emotional needs, effectively managing dyspnea and anxiety, and negotiating life support and rescue-oriented critical care as these become more futile. (87) Important quality domains for hospital-based palliative care include (92) teams with appropriate and well-trained members; formalized care pathways; communication with patients regarding care options and preferences; available specialist and generalist services; and communication and collaboration with other acute and community care providers. (92)

Experiences of Carers

Psychosocial Effects

Carers' challenges often echo those of COPD patients, including anxiety, uncertainty about the future, helplessness, powerlessness, depression, difficulties maintaining employment, loss of mobility and freedoms, strained relationships, and growing social isolation. (48;83;93;94;95) Like patients, carers may also be poorly informed about the nature of COPD, its management, and long-term prospects; this uncertainty contributes to carer stress. (93) They ride an "emotional roller coaster" over the course of the disease, with its evolving demands. (94) Carers monitor patients to anticipate their needs, and many actively manage patients' activities to control breathing. (94)

Carers may face overwhelming anxiety during (and in anticipation of) patients' episodes of breathlessness; they feel compelled to help, but there is little they can do. (53;94;96;97) The unpredictability of exacerbations can make it frightening for carers to leave patients; fears tend to increase at night and often impair carers' sleep. (93;94;97;98) Acute episodes of breathlessness may heighten carers' uncertainty and pessimism. (83;93;95) However, carers may also come to accept the unpredictability of COPD and develop new resilience and strategies for confronting problems as they arise. (93;99;100)

The patient's declining health increases carer fatigue and depression. (98) COPD often puts stresses on relationships between carers and their loved ones; carers may grieve the loss of certain patient character traits, medications may create frightening personality changes, breathing problems may impair communication and intimacy, and compulsory togetherness may bring challenges. (69;94;98)

Multiple Roles

Carers can feel pressured by their many roles ("nurse, doctor, psychologist, and carer" in addition to family member), struggle to maintain patience when they feel overwhelmed, and feel guilty about not doing enough. (12;93) Toward the end of life, carers often serve as the "backbone" of the care team, with additional responsibilities and burdens. (7) Care duties can bring resentment, satisfaction, or both. (93) Burnout results when caregivers have no breaks or escape from caregiving roles, or no one to share the burden or boredom. (48;98)

Strong social support, including reassuring and frequent contact with health care providers, helps carers cope with and sustain their role, but caregiving also limits carers' capacity for needed interactions with others. (12;28;48;94;95;98) The reasons for social isolation are many, including reluctance to leave the patient, and the need for privacy. (94;95) Many carers find it difficult to ask for help; they may feel duty-bound to provide the care themselves, or they may feel that they alone fully understand the patient's needs. (12;53;94;95;96;98) During acute episodes, patients may call on family members first, leaving them responsible to call for professional help. (96) During crises, carers' desire to control caregiving may be cast aside. (95) Hospitalization may appeal when carers feel burnt out, or when patients feel inadequately cared for at home. (77) Carers may interpret palliative end-of-life care as an unwelcome sign that patients and physicians have "given up." (50) Professional support that is responsive to urgent, unpredictable needs may be the most important kind of support for carers. (94)

Increased Burden

Carers often face their own health problems, or struggle to care adequately for themselves as they place the patient's needs before their own. (95;98) Carers with serious health problems may worry about becoming unable to care for the patient. (95) Patients also fear burdening their families, as their disabilities and dependence grow, and may feel shame or try to be stronger because of this. (22;33;45;46;57;101). Family caregivers may also face difficulties sustaining employment and supporting their family. (69) With added disease-related expenses and the patient's loss of income, carers' paid employment becomes both more important and more challenging. (69) Some carers continue to work out of financial necessity, while others choose to work for the outlet it offers. (69;98) At work, however, carers may be preoccupied, and contact with the patient is important; they appreciate understanding and flexible employers. (69)

Synthesis: A Disease Trajectory Reflecting Patient Experiences

After the qualitative research findings were gathered they were synthesized, and evidence-grounded insights were related to prevailing clinical theories of the COPD disease trajectory. A more patient-centred model of the COPD trajectory was then proposed for clinical, health services, and policy applications.

Clinicians widely recognize the COPD trajectory as one of steady decline in health status and function, punctuated by increasing exacerbations, and ending in death from COPD. The shape of the theorized trajectory has evolved over decades, to relate key COPD stages to interventions, services, and patient needs. In 1977, Fletcher and Peto (102) modelled lung function against years of life to illustrate how smoking cessation at different stages could affect longevity (Figure 2). This model is still used clinically to explain the value of quitting smoking to patients, for example. (13)

Figure 2: COPD Disease Trajectory: Traditional View*

*Abbreviations: COPD, chronic obstructive pulmonary disease; FEV, forced expiratory volume.

Reprinted from BMJ, Vol. 6077; Fletcher C, Peto R: The Natural History of Chronic Airflow Obstruction, p. 1645–1648 with permission from BMJ Publishing Group Ltd.

In 2001, Lynn (103) presented a cyclic trajectory for end-stage organ failure (including lung failure), suggesting that the downward trajectory of COPD is punctuated with health crises and recoveries along its course, but lacks a distinctive end-of-life turning point at which to initiate hospice services. This differs crucially from the trajectory of cancer, with its characteristic sharp downward inflection in the terminal stage. Lynn's theorized trajectory has been supported empirically by a prospective cohort analysis, modelling activities of daily living over time for end-stage organ failure. (104)

More recently, in an editorial commentary on 1 of the qualitative studies included in this review, (13) Lehman (105) proposed a more patient-centred trajectory for understanding COPD in the context of physician-patient discussions about prognosis and end of life (Figure 3).

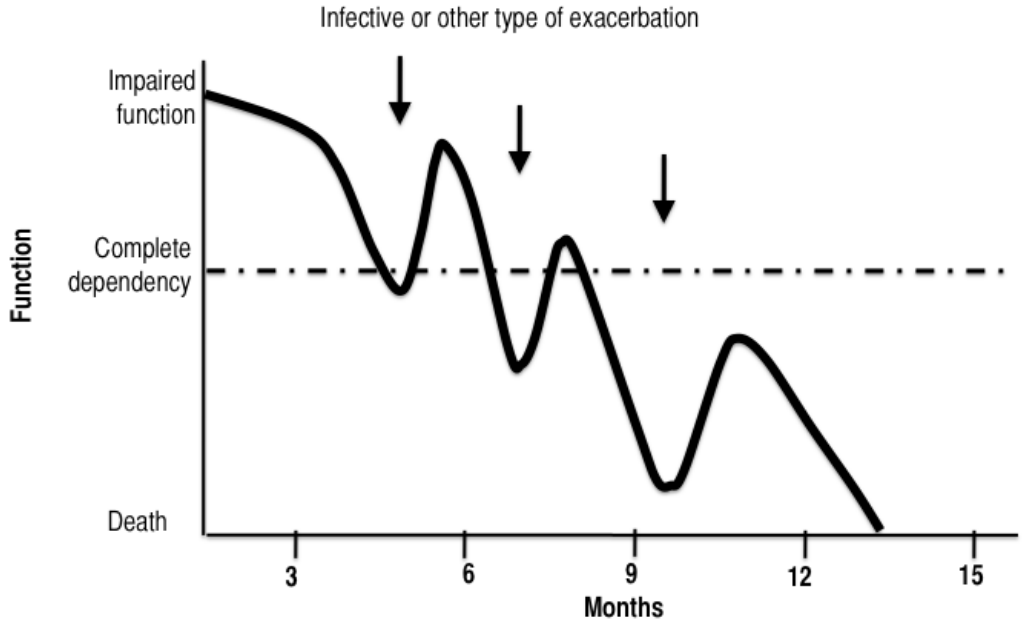


Figure 3: COPD Disease Trajectory: Updated Clinical View*

*Abbreviation: COPD, chronic obstructive pulmonary disease.
Reprinted from Br J Gen Pract, Vol. 54; Lehman R. How Long Can I Go on Like This? Dying from Cardiorespiratory Disease, p. 892–893, with permission from the Royal College of General Practitioners.

Lehman's model preserves the roller coaster–like cycles of Lynn's curve and the lack of a discrete transition to an end stage, but it replaces Fletcher and Peto's lung function (y-axis) with patients' overall functioning. The model highlights patients' inevitable yet rocky transition to a state of complete dependency, when they need social services, support, technologies, and interventions to do what they can no longer do for themselves. Support services also often aim to control the level of care, deferring hospitalization or long-term care as long as is reasonable. Both physicians and patients expect death from an exacerbation, but "the doctor may be little better than anyone else at predicting which dip is going to be the final one." (105)

Patients with other chronic, fatal diseases, such as cancer, normally reach each of 2 crucial turning points—total dependency and end of life—only once. These are usually regarded of as points of no return, and allow for predictable service transitions between major institutions of health care: home, home care, hospital, and hospice. On the COPD roller coaster, however, patients' needs vacillate above and below the line of total dependency, and no one specific event may demarcate the "end of life" stage, except perhaps the final acute exacerbation, which is difficult to predict and may be relatively brief.

Over a period of years, COPD patients may move repeatedly between levels, institutions, and providers of care. Demands on informal caregivers also wax and wane as needs change over time. Such a disease trajectory creates recurring challenges and the need for timely decisions, smooth transitions, appropriateness, and continuity of care. Many aspects of palliative care are needed throughout the disease course, with a gradual shift in emphasis from controlling symptoms to coping with dying: "The patient's physiology almost never dictates an abrupt change from 'cure' to 'care.' Instead, aggressive and palliative treatments will be mixed, with advance care planning occurring alongside emergency medical services, dyspnea relief alongside pacemaker placement, and family support alongside resuscitation." (103) COPD

requires a different model and philosophy of palliative care than the 2-stage hospice model that has evolved for diseases such as cancer. (2;83;103)

The review of qualitative research studies described above suggests 2 further refinements to our understanding of debilitation and dying with COPD, as well as related service needs over time. Figure 4 represents a slight modification to Lehman's trajectory, representing the prevailing clinical view of the COPD course, one of "…inexorable decline: a prolonged period of disabling dyspnea and increasingly frequent hospital admission reflecting deteriorating lung function and usually presaging a premature death." (15) Accordingly, Figure 4 depicts increasing frequency and severity of crises over time. In addition, a major source of clinical uncertainty (as well as failed communication between physicians and patients) comes from the difficulty of predicting time to disease progression or death for a given patient. Figure 3 depicts this uncertainty with a broken x-axis, representing uncertain units of time despite a relatively certain decline.

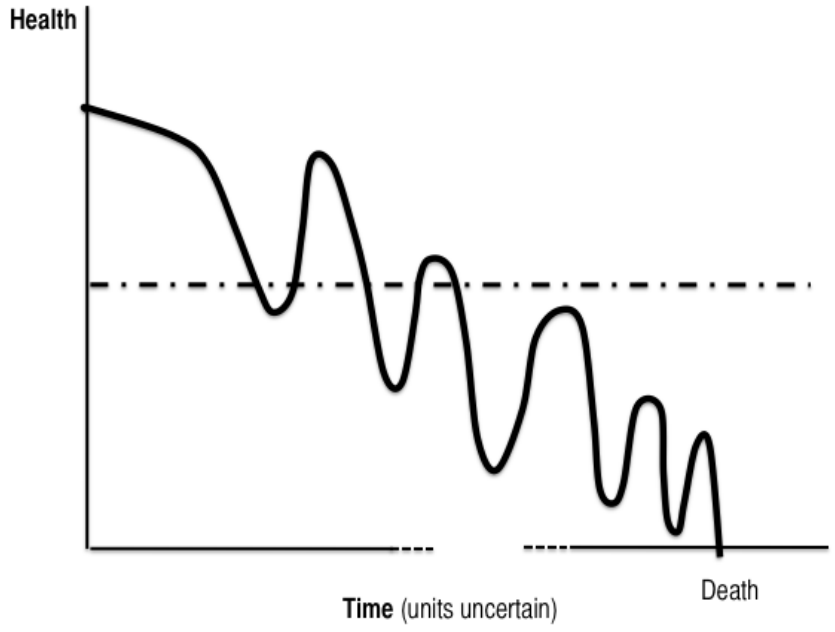


Figure 4: COPD Disease Trajectory: Current Clinical View*

*Abbreviation: COPD, chronic obstructive pulmonary disease.

Adapted from Br J Gen Pract, Vol. 54; Lehman R: How Long Can I Go on Like This? Dying from Cardiorespiratory Disease, p. 892–893 and verbal characterization in Thorax, Vol. 55; Gore JM, Brophy CJ, Greenstone MA. How Well Do We Care for Patients with End Stage Chronic Obstructive Pulmonary Disease (COPD)? A Comparison of Palliative Care and Quality of Life in COPD and Lung Cancer, p. 1000–1006.

Figure 5 proposes an even more patient-centred trajectory, based on relevant findings from this review. This proposed trajectory focuses on the problem of staging the disease course in ways that are meaningful to clinicians, patients, and health policy makers, with a view to supporting better planning, targeting, and continuity of services and interventions.

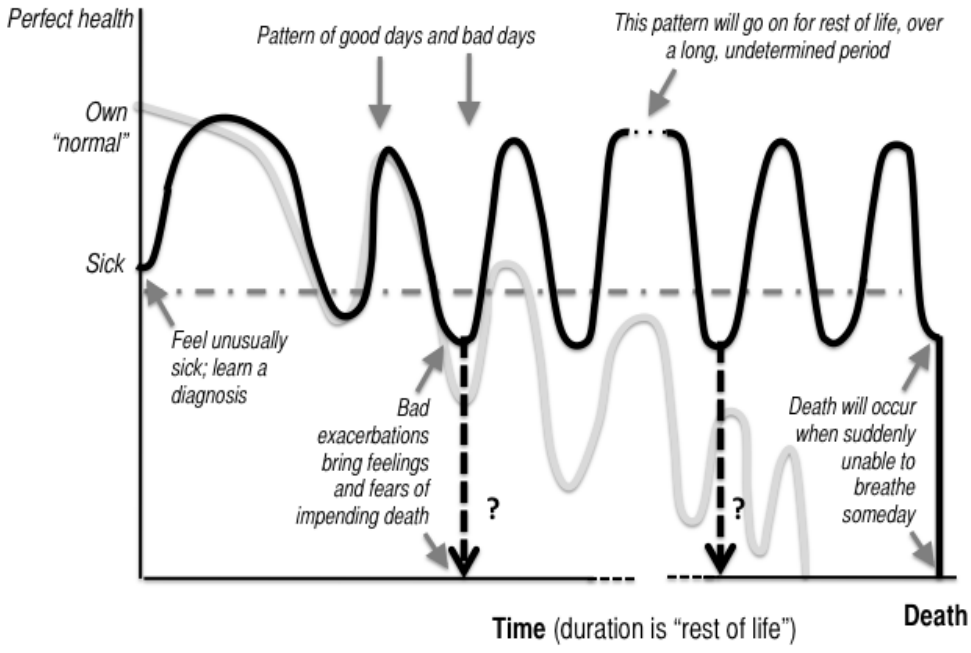


Figure 5: COPD Disease Trajectory: Common Patient Experiences and Expectations*

*Abbreviation: COPD, chronic obstructive pulmonary disease.
Note: The clinical trajectory of Figure 4 appears in grey here, for comparison.

This model is proposed with 3 caveats. First, this trajectory does not apply to all patients at all stages of the disease; rather, it characterizes what many patients seem to experience and expect, especially at early and middle stages. Second, most patients would not depict their experiences using a graph, as we do here; the illustration is simply meant to help translate patient experiences for clinical, health services, and policy audiences. Finally, this model does not capture the entirety of the patient experience covered in the extensive body of qualitative research on COPD.

Patient experiences may deviate from clinical expectations in a number of ways. Before diagnosis, patients experience the suboptimal health that clinicians might call "early COPD," but that patients know as their own "normal," and not necessarily as illness. On the occasion of their diagnosis, many patients are seeking care not for their "normal" symptoms, but because they are feeling unusually unwell (what they might interpret as an "infection," but what a clinician might recognize as an "exacerbation"). It may be difficult for patients to pinpoint a moment of diagnosis; the nature of their condition and the exact diagnosis come into focus over time, using personal experience and piecemeal information from various sources.

Patients experience alternating good days and bad days, and a "roller coaster" pattern of ups and downs becomes apparent. COPD becomes as much as a way of life as an illness; patients use many means (social, psychological, medical, organizational) to control what they can, and to cope with what they cannot. The sense of what is normal, and the tolerability of health problems and interventions, both evolve with the disease.

Bad days, or exacerbations, may not be experienced as a net decline in health, but rather as temporary setbacks. Sporadic exacerbations may not be attributed to advancing disease, but rather to specific activities, changes in the weather, environmental factors, faltering self-management, or infection.

Although patients pass back and forth over Lehman's line of total dependency during some exacerbations, they may not expect permanent total dependency. Sporadic dependency is challenging and disruptive, and patients may yearn for others who will "be there" for them during crises, but informal social support and formal social services are difficult to establish around intermittent and emergent needs. The patient's social life also follows its own steady downward trajectory.

Late in the disease, the severity, duration, or frequency of bad days reveals a permanent decline in health. Even so, patients may still envision death (from COPD) to be in the distant, unpredictable future. The term "chronic" conveys a lifelong disease, rather than a terminal illness. Patients hope to recover from exacerbations, but also fear dying from suffocation or breathlessness during these crises. Palliative end-of-life care may not be envisioned until patients are actually referred for such care, and the referral may convey the demoralizing message that providers have "given up."

COPD interventions and services tend to be organized around key points in the disease trajectory, such as diagnosis, daily living with disability, exacerbations requiring hospitalization, complete dependency, and dying, yet the contours of the COPD disease trajectory do not offer discrete turning points around which to plan. Rather, the flux of needs in COPD calls for service continuity and flexibility to allow health care providers and patients to respond to the unpredictable yet increasing demands of the disease over time.

Conclusions

Experiences at Diagnosis

- Patients typically seek initial treatment for an acute episode rather than for chronic early symptoms of COPD.
- Many patients initially misunderstand terms such as *COPD, chronic obstructive pulmonary disease,* or *exacerbation*.
- Patients may not realize that COPD is incurable and fatal; some physicians themselves to not consider early COPD to be a fatal disease.
- Smokers may not readily understand or agree with the idea that smoking causes or worsens COPD. Those who accept the causal link may feel regret or shame.

Experiences of Living Day to Day

- COPD patients experience alternating good days and bad days. A roller-coaster pattern of ups and downs becomes apparent, and COPD becomes a way of life.
- Patients use many means (social, psychological, medical, organizational) to control what they can, and to cope with what they cannot. Economic hardship, comorbidities, language barriers, and low health literacy can make coping more difficult.
- Increasing vulnerability and unpredictable setbacks make patients dependent on others for practical assistance, but functional limitations, institutional living or self-consciousness can isolate patients from the people they need.
- For smokers, medical advice to quit can conflict with increased desire to smoke as a coping strategy.
- Many of the factors that isolate COPD patients from social contact also isolate them from health care.

Experiences of Exacerbations

- Patients may not always attribute repeated exacerbations to advancing disease, instead seeing them as temporary setbacks caused by activities, environmental factors, faltering self-management, or infection.
- Lack of confidence in community-based services leads some patients to seek hospital admission, but patients also feel vulnerable when hospitalized. They may feel dependent on others for care or traumatized by hospital care routines.
- Upon hospital discharge following an exacerbation, patients may face new levels of uncertainty about their illness, prognosis, care providers, and supports.

Experiences of the End of Life

- Patients tend to be poorly informed about the long-term prognosis of COPD and what to expect toward the end of life; this lack of understanding impairs quality of life as the disease progresses.
- As the end of life approaches, COPD patients face the usual challenges of daily living, but in a context of increasing exacerbations and deepening dependency. Activities and mobility decrease, and life may become confined.

- Some clinicians have difficulty identifying the beginning of "the end of life," given the unpredictable course of COPD. Long-term physician-patient relationships, familiarity and understanding, trust, good communication skills, sensitivity, and secure discussion settings can help facilitate end-of-life discussions.
- Divergent definitions and goals of palliative care in COPD lead to confusion about whether such services are the responsibility of home care, primary care, specialty care, or even critical care. Palliative end-of-life care may not be anticipated prior to referral for such care. A palliative care referral can convey the demoralizing message that providers have "given up."

Experiences of Carers

- Carers' challenges often echo patients' challenges, and include anxiety, uncertainty about the future, helplessness, powerlessness, depression, difficulties maintaining employment, loss of mobility and freedoms, strained relationships, and growing social isolation.
- Carers feel pressured by their many roles, struggling to maintain patience when they feel overwhelmed, and often feeling guilty about not doing enough.
- Carers often face their own health problems and may have difficulty sustaining employment.

Synthesis: A Disease Trajectory Reflecting Patient Experience

- The flux of needs in COPD calls for service continuity and flexibility to allow both health care providers and patients to respond to the unpredictable yet increasing demands of the disease over time.

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.

Forced vital capacity (FVC)	The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.
Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.
Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[1]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is

[1] The mild-to-moderate classification was created for the purposes of the report.

"palliative" in that treatment is not curative of the underlying disease.

Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.
Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.
Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Editorial Staff

Jeanne McKane

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

This study was funded by the Canadian Institutes of Health Research, Grant # TOO-105430. Deirdre DeJean and Andrea Smith were supported by CIHR Frederick Banting and Charles Best Canada Graduate Scholarships (CGS) Doctoral Awards. We thank the Ontario Ministry of Health and Long-Term Care for its support for the Centre for Health Economics and Policy Analysis (CHEPA) at McMaster University, whose collegial environment made this project possible.

Appendices

Appendix 1: Literature Search Strategies

OVID MEDLINE

1	exp Pulmonary Disease, Chronic Obstructive
2	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab.
3	(copd or coad).ti,ab.
4	chronic airflow obstruction.ti,ab.
5	exp Emphysema/
6	((chronic adj2 bronchitis) or emphysema).ti,ab.
7	or/1-6
8	limit 7 to (english language and humans and yr="2000 -Current")

ISI Web of Science

1	Chronic obstructive lung* disease* (in title)
2	chronic obstructive pulmonary disease* (in title)
3	chronic obstructive pulmonary disorder* (in title)
4	chronic obstructive airway* disease* (in title)
5	chronic obstructive airway* disorder* (in title)
6	chronic obstructive airflow* disease* (in title)
7	chronic obstructive airflow* disorder* (in title)
8	chronic obstructive respiratory disease*
9	chronic obstructive respiratory disorder*
10	(copd or coad) (in title)
11	chronic airflow obstruction (in title)
12	chronic bronchitis (in topic)
13	emphysema (in title)
14	or/1-13
15	limit to English, human, January 1, 2000 to Current

EBSCO Cumulative Index to Nursing and Allied Health Literature (CINAHL)

1	(MH "Pulmonary Disease, Chronic Obstructive+")
2	(chronic obstructive and (lung* or pulmonary or airway* or airflow or respiratory) and (disease* or disorder*))
3	copd or coad
4	(MH "Emphysema+")
5	chronic bronchitis or emphysema
6	S1 or S2 or S3 or S4 or S5
7	Limiters - Published Date from: 20000101-20101231 and English and Human

References

(1) Arne M, Emtner M, Janson S, Wilde-Larsson B. COPD patients perspectives at the time of diagnosis: a qualitative study. Prim Care Respir J. 2007;16(14):215-21.

(2) Pinnock H, Kendall M, Murray SA, Worth A, Levack P, Porter M, et al. Living and dying with severe chronic obstructive pulmonary disease: multi-perspective longitudinal qualitative study. BMJ. 2011;342:d142.

(3) Jonsdottir R, Jonsdottir H. The experience of women with advanced chronic obstructive pulmonary disease of repeatedly relapsing to smoking. Scand J Caring Sci. 2007;21(3):297-304.

(4) Chan SCC. Chronic obstructive pulmonary disease and engagement in occupation. Am J Occup Ther. 2004;58(4):408-15.

(5) Habraken JM, Pols J, Bindels PJE, Willems DL. The silence of patients with end-stage COPD: a qualitative study. Br J Gen Pract 2008;58(557):844-9.

(6) Gysels M, Bausewein C, Higginson IJ. Experiences of breathlessness: a systematic review of the qualitative literature. Palliat Support Care. 2007;5(3):281-302.

(7) Spence A, Hasson F, Waldron M, Kernohan WG, McLaughlin D, Watson B, et al. Professionals delivering palliative care to people with COPD: qualitative study. Palliat Med. 2009;23(2):126-31.

(8) Walters JA, Hansen EC, Walters EH, Wood-Baker R. Under-diagnosis of chronic obstructive pulmonary disease: a qualitative study in primary care. Respir Med. 2008;102(5):738-43.

(9) Gysels M, Higginson IJ. The experience of breathlessness: the social course of chronic obstructive pulmonary disease. J Pain Symptom Manage. 2010;39(3):555-63.

(10) Oliver SM. Living with failing lungs: the doctor-patient relationship. Fam Pract. 2001;18(4):430-9.

(11) Gardiner C, Gott M, Small N, Payne S, Seamark D, Barnes S, et al. Living with advanced chronic obstructive pulmonary disease: patients concerns regarding death and dying. Palliat Med. 2009;23(8):691-7.

(12) Hasson F, Spence A, Waldron M, Kernohan G, McLaughlin D, Watson B, et al. Experiences and needs of bereaved carers during palliative and end-of-life care for people with chronic obstructive pulmonary disease. J Palliat Care. 2009;25(3):157-63.

(13) Halliwell J, Mulcahy P, Buetow S, Bray Y, Coster G, Osman LM. GP discussion of prognosis with patients with severe chronic obstructive pulmonary disease: a qualitative study. Br J Gen Pract. 2004;54(509):904-8.

(14) Rodgers S, Dyas J, Molyneux AWP, Ward MJ, Revill SM. Evaluation of the information needs of patients with chronic obstructive pulmonary disease following pulmonary rehabilitation: a focus group study. Chron Respir Dis. 2007;4(4):195-203.

(15) Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. Thorax. 2000;55(12):1000-6.

(16) Gott M, Gardiner C, Payne S, Small N, Seamark D, Halpin D. Barriers to advance care planning for older people with chronic obstructive pulmonary disease: patient and professional perspectives. Australasian Ageing. 2009;28(32):A100.

(17) Hansen EC, Walters J, Baker RW. Explaining chronic obstructive pulmonary disease (COPD): perceptions of the role played by smoking. Sociol Health Illn. 2007;29(5):730-49.

(18) Parker DR, Goldman RE, Eaton CB. A qualitative study of individuals at risk for or who have chronic obstructive pulmonary disease: what do they understand about their disease? Lung. 2008;186(5):313-6.

(19) Lindqvist G, Hallberg LRM. "Feelings of guilt due to self-inflicted disease": a grounded theory of suffering from chronic obstructive pulmonary disease (COPD). J Health Psychol. 2010;15(3):456-66.

(20) Curtis JR, Engelberg R, Young JP, Vig LK, Reinke LF, Wenrich MD, et al. An approach to understanding the interaction of hope and desire for explicit prognostic information among individuals with severe chronic obstructive pulmonary disease or advanced cancer. J Palliat Med. 2008;11(4):610-20.

(21) Harris M, Wildgoose D, Veale AJ, Smith BJ. Providing reviews of evidence to COPD patients: qualitative study of barriers and facilitating factors to patient-mediated practice change. Chron Respir Dis. 2010;7(1):19-28.

(22) Hasson F, Spence A, Waldron M, Kernohan G, McLaughlin D, Watson B, et al. I can not get a breath: experiences of living with advanced chronic obstructive pulmonary disease. Int J Palliat Nurs. 2008;14(11):526-31.

(23) O'Neill ES. Illness representations and coping of women with chronic obstructive pulmonary disease: a pilot study. Heart Lung. 2002;31(4):295-302.

(24) Gysels M, Higginson IJ. Access to services for patients with chronic obstructive pulmonary disease: the invisibility of breathlessness. J Pain Symptom Manage. 2008;36(5):451-60.

(25) Shipman C, White S, Gysels M, White P. Access to care in advanced COPD: factors that influence contact with general practice services. Prim Care Respir J. 2009;18(4):273-8.

(26) Bailey PH, Montgomery P, Boyles CM. COPD stories of complex causal "truths" "Sure I've smoked all my life/but I also put in 37 years at the mine" J Clin Nurs. 2009;18(14):1994-2002.

(27) Schofield I, Kerr S, Tolson D. An exploration of the smoking-related health beliefs of older people with chronic obstructive pulmonary disease. J Clin Nurs. 2007;16(9):1726-35.

(28) Caress A, Luker K, Chalmers K. Promoting the health of people with chronic obstructive pulmonary disease: patients' and carers' views. J Clin Nurs. 2010;19(3-4):564-73.

(29) Adams R, Chavannes N, Jones K, Ostergaard MS, Price D. Exacerbations of chronic obstructive pulmonary disease—a patients' perspective. Prim Care Respir J. 2006;15(2):102-9.

(30) Elofsson LC, Öhlén J. Meanings of being old and living with chronic obstructive pulmonary disease. Palliat Med. 2004;18(7):611-8.

(31) Victorson DE, Anton S, Hamilton A, Yount S, Cella D. A conceptual model of the experience of dyspnea and functional limitations in chronic obstructive pulmonary disease. Value Health. 2009;12(6):1018-25.

(32) Lohne V, Heer HCD, Andersen M, Miaskowski C, Kongerud J, Rustoen T. Qualitative study of pain of patients with chronic obstructive pulmonary disease. Heart Lung. 2010;39(3):226-34.

(33) Nicolson P, Anderson P. Quality of life, distress and self-esteem: a focus group study of people with chronic bronchitis. Br J Health Psychol. 2003;8(Pt3):251-70.

(34) Barnett M. Caring for a patient with COPD: a reflective account. Nurs Stand. 2005 May 18-24;19(36):41-6.

(35) Clancy K, Hallet C, Caress A. The meaning of living with chronic obstructive pulmonary disease. J Nurs Healthc Chronic Illn. 2009;1(1):78-86.

(36) Fraser DD, Kee CC, Minick P. Living with chronic obstructive pulmonary disease: insiders' perspectives. J Adv Nurs. 2006;55(5):550-8.

(37) Guthrie SJ, Hill KM, Muers ME. Living with severe COPD. A qualitative exploration of the experience of patients in Leeds. Respir Med. 2001;95(3):196-204.

(38) Jeng C, Tsao L-I, Ho C-H, Chang P-C. Experiences of daily activities within two weeks after hospital discharge among Taiwanese elderly patients with chronic obstructive pulmonary disease. J Nurs Res. 2002;10(3):168-76.

(39) Nicolson P, Anderson P. The patient's burden: physical and psychological effects of acute exacerbations of chronic bronchitis. J Antimicrob Chemother. 2000;45(suppl2):25-32.

(40) Odencrants S, Ehnfors M, Grobe SJ. Living with chronic obstructive pulmonary disease: part I. Struggling with meal-related situations: experiences among persons with COPD. Scand J Caring Sci. 2005;19(3):230-9.

(41) Williams V, Bruton A, Ellis-Hill C, McPherson K. What really matters to patients living with chronic obstructive pulmonary disease? An exploratory study. Chron Respir Dis. 2007;4(2):77-85.

(42) Wilson DM, Ross C, Goodridge D, Davis P, Landreville A, Roebuck K. The care needs of community-dwelling seniors suffering from advanced chronic obstructive pulmonary disease. Can J Aging. 2008;27(4):347-57.

(43) Bentkover JD, Beresford J, Rogers B, Schachtner AE, Swensen A, Dastani HB. Patient, caregiver, and physician perceptions of management of chronic obstructive pulmonary disease: findings from qualitative research. Value Health. 2008;11(3):A278.

(44) Kerr A, Ballinger C. Living with chronic lung disease: an occupational perspective. J Occup Sci. 2010;17(1):34-9.

(45) Ek K, Ternestedt B-M. Living with chronic obstructive pulmonary disease at the end of life: a phenomenological study. J Adv Nurs. 2008;62(4):470-8.

(46) Jones I, Kirby A, Ormiston P, Loomba Y, Chan K-K, Rout J, et al. The needs of patients dying of chronic obstructive pulmonary disease in the community. Fam Pract. 2004;21(3):310-3.

(47) Hall S, Legault A, Côté J. Dying means suffocating: perceptions of people living with severe COPD facing the end of life. Int J Palliat Nurs. 2010;16(9):451-7.

(48) Seamark DA, Blake SD, Seamark CJ, Halpin DM. Living with severe chronic obstructive pulmonary disease (COPD): perceptions of patients and their carers. An interpretative phenomenological analysis. Palliat Med. 2004;18(7):619-25.

(49) Duangpaeng S, Eusawas P, Laungamornlert S, Gasemgitvatana S, Sritanyarat W. Chronic dyspnea self-management of Thai adults with COPD. Thai J Nurs Res. 2002;6(4):200-15.

(50) Elkington H, White P, Addington-Hall J, Higgs R, Pettinari C. The last year of life of COPD: a qualitative study of symptoms and services. Respir Med. 2004;98(5):439-45.

(51) Gruffydd-Jones K, Langley-Johnson C, Dyer C, Badlan K, Ward S. What are the needs of patients following discharge from hospital after an acute exacerbation of chronic obstructive pulmonary disease (COPD)? Prim Care Respir J. 2007;16(6):363-8.

(52) Shackell BS, Jones RCM, Harding G, Pearse S, Campbell J. "Am I going to see the next morning?"A qualitative study of patients' perspectives of sleep in COPD. Prim Care Respir J. 2007;16(6):378-83.

(53) Bailey PH. The dyspnea-anxiety-dyspnea cycle—COPD patients' stories of breathlessness: "It's scary/when you can't breathe". Qual Health Res. 2004;14(6):760-78.

(54) Lomborg K, Bjorn A, Dahl R, Kirkevold M. Body care experienced by people hospitalized with severe respiratory disease. J Adv Nurs. 2005;50(3):262-71.

(55) Torheim H, Gjengedal E. How to cope with the mask? Experiences of mask treatment in patients with acute chronic obstructive pulmonary disease-exacerbations. Scand J Caring Sci. 2010;24(3):499-506.

(56) Milne L, Moyle W, Cooke M. Hope: a construct central to living with chronic obstructive pulmonary disease. Int J Older People Nurs. 2009;4(4):299-306.

(57) Fitzsimons D, Mullan D, Wilson JS, Conway B, Corcoran B, Dempster M, et al. The challenge of patients' unmet palliative care needs in the final stages of chronic illness. Palliat Med. 2007;21(4):313-22.

(58) Gullick J, Stainton MC. Living with chronic obstructive pulmonary disease: developing conscious body management in a shrinking life-world. J Adv Nurs. 2008;64(6):605-14.

(59) Bendtsen P, Leijon M, Sofie Sommer A, Kristenson M. Measuring health-related quality of life in patients with chronic obstructive pulmonary disease in a routine hospital setting: feasibility and perceived value. Health Qual Life Outcomes. 2003;1:5.

(60) Farquhar M, Ewing G, Higginson IJ, Booth S. The experience of using the SEIQoL-DW with patients with advanced chronic obstructive pulmonary disease (COPD): issues of process and outcome. Qual Life Res. 2010;19(5):619-29.

(61) Jeon YH, Jowsey T, Yen L, Glasgow NJ, Essue B, Kljakovic M, et al. Achieving a balanced life in the face of chronic illness. Aust J Prim Health. 2010;16(1):66-74.

(62) Chen K-H, Chen M-L, Lee S, Cho H-Y, Weng L-C. Self-management behaviours for patients with chronic obstructive pulmonary disease: a qualitative study. J Adv Nurs. 2008;64(6):595-604.

(63) Cicutto L, Brooks D, Henderson K. Self-care issues from the perspective of individuals with chronic obstructive pulmonary disease. Patient Educ Couns. 2004;55(2):168-76.

(64) Bourbeau J, Nault D, Dang-Tan T. Self-management and behaviour modification in COPD. Patient Educ Couns. 2004;52(3):271-7.

(65) Monninkhof E, van der Aa M, van der Valk P, van der Palen J, Zielhuis G, Koning K, et al. A qualitative evaluation of a comprehensive self-management programme for COPD patients: effectiveness from the patients' perspective. Patient Educ Couns. 2004;55(2):177-84.

(66) Nield M. Dyspnea self-management in African Americans with chronic lung disease. Heart Lung. 2000;29(1):50-5.

(67) Jeon YH, Essue B, Jan S, Wells R, Whitworth JA. Economic hardship associated with managing chronic illness: a qualitative inquiry. BMC Health Serv Res. 2009;9(1):182.

(68) Mars GMJ, Kempen GIJM, Mesters I, Proot IM, Van Eijk JTM. Characteristics of social participation as defined by older adults with a chronic physical illness. Disabil Rehabil. 2008;30(17):1298-308.

(69) Gysels M, Higginson IJ. Reconciling employment with caring for a husband with an advanced illness. BMC Health Serv Res. 2009;9(1):216.

(70) Thomsen D, Jensen BØ. Patients' experiences of everyday life after lung transplantation. J Clin Nurs. 2009;18(24):3472-9.

(71) Cowie L, Morgan M, White P, Gulliford M. Experience of continuity of care of patients with multiple long-term conditions in England. J Health Serv Res Policy. 2009;14(2):82-7.

(72) Bailey PH, Tilley S. Storytelling and the interpretation of meaning in qualitative research. J Adv Nurs. 2002;38(6):574-83.

(73) Heinzer MMV, Bish C, Detwiler R. Acute dyspnea as perceived by patients with chronic obstructive pulmonary disease. Clin Nurs Res. 2003;12(1):85-101.

(74) Kessler R, Ståhl E, Vogelmeier C, Haughney J, Trudeau E, Löfdahl C-G, et al. Patient understanding, detection, and experience of COPD exacerbations: an observational, interview-based study. Chest. 2006;130(1):133-42.

(75) Michaels C, Meek PM. The language of breathing among individuals with chronic obstructive pulmonary disease. Heart Lung. 2004;33(6):390-400.

(76) Thomas LA. Effective dyspnea management strategies identified by elders with end-stage chronic obstructive pulmonary disease. Appl Nurs Res. 2009;22(2):79-85.

(77) Yu DSF, Lee DTF, Wu J. The revolving door syndrome: the Chinese COPD patients' perspectives. J Clin Nurs. 2007;16(9):1758-60.

(78) Forbes MOS. Prolonged ventilator dependence: perspective of the chronic obstructive pulmonary disease patient. Clin Nurs Res. 2007;16(3):231-50.

(79) Crawford A. Respiratory practitioners' experience of end-of-life discussions in COPD. Br J Nurs. 2010;19(18):1164-9.

(80) Curtis JR, Wenrich MD, Carline JD, Shannon SE, Ambrozy DM, Ramsey PG. Patients' perspectives on physician skill in end-of-life care: differences between patients with COPD, cancer, and AIDS. Chest. 2002;122(1):356-62.

(81) Fried TR, O'Leary JR. Using the experiences of bereaved caregivers to inform patient- and caregiver-centered advance care planning. J Gen Intern Med. 2008;23(1):1602-7.

(82) Reinke LF, Shannon SE, Engelberg RA, Young JP, Curtis JR. Supporting hope and prognostic information: nurses' perspectives on their role when patients have life-limiting prognoses. J Pain Symptom Manage. 2010;39(6):982-92.

(83) Reinke LF, Engelberg RA, Shannon SE, Wenrich MD, Vig EK, Back AL, et al. Transitions regarding palliative and end-of-life care in severe chronic obstructive pulmonary disease or advanced cancer: themes identified by patients, families, and clinicians. J Palliat Med. 2008;11(4):601-9.

(84) Fried TR, Bradley EH. What matters to seriously ill older persons making end-of-life treatment decisions? A qualitative study. J Palliat Med. 2003;6(2):237-44.

(85) Gullick JG, Colleen Stainton M. Taking a chance: the experience of lung volume reduction procedures for chronic obstructive pulmonary disease. Chronic Illn. 2009;5(4):293-304.

(86) Borgsteede SD, Deliens L, Graafland-Riedstra C, Francke AL, van der Wal G, Willems DL. Communication about euthanasia in general practice: opinions and experiences of patients and their general practitioners. Patient Educ Couns. 2007;66(2):156-61.

(87) Goodridge D, Duggleby W, Gjevre J, Rennie D. Caring for critically ill patients with advanced COPD at the end of life: a qualitative study. Intensive Crit Care Nurs. 2008;24(3):162-70.

(88) Goodridge D, Duggleby W, Gjevre J, Rennie D. Exploring the quality of dying of patients with chronic obstructive pulmonary disease in the intensive care unit: a mixed methods study. Nurs Crit Care. 2009;14(2):51-60.

(89) Back AL, Young JP, McCown E, Engelberg RA, Vig EK, Reinke LF, et al. Abandonment at the end of life from patient, caregiver, nurse, and physician perspectives: loss of continuity and lack of closure. Arch Intern Med. 2009 Mar 9;169(5):474-9.

(90) Curtis JR, Wenrich MD, Carline JD, Shannon SE, Ambrozy DM, Ramsey PG. Understanding physicians' skills at providing end-of-life care perspectives of patients, families, and health care workers. J Gen Intern Med. 2001;16(1):41-9.

(91) Borgsteede SD, Graafland-Riedstra C, Deliens L, Francke AL, van Eijk JT, Willems DL. Good end-of-life care according to patients and their GPs. Br J Gen Pract. 2006;56(552):20-6.

(92) Roberts CM, Seiger A, Buckingham R, Stone RA. Clinician perceived good practice in end-of-life care for patients with COPD. Palliat Med. 2008;22(7):855-8.

(93) Spence A, Hasson F, Waldron M, Kernohan G, McLaughlin D, Cochrane B, et al. Active carers: living with chronic obstructive pulmonary disease. Int J Palliat Nurs. 2008;14(8):368-72.

(94) Boyle AH. Living with a spouse with chronic obstructive pulmonary disease: the meaning of wives' experiences. J Nurs Healthc Chronic Illn. 2009;1(4):273-82.

(95) Gysels MH, Higginson IJ. Caring for a person in advanced illness and suffering from breathlessness at home: threats and resources. Palliat Support Care. 2009;7(2):153-62.

(96) Bailey PH. Death stories: acute exacerbations of chronic obstructive pulmonary disease. Qual Health Res. 2001;11(3):322-38.

(97) Booth S, Silvester S, Todd C. Breathlessness in cancer and chronic obstructive pulmonary disease: using a qualitative approach to describe the experience of patients and carers. Palliat Support Care. 2003;1(4):337-44.

(98) Bergs D. "The hidden client"-women caring for husbands with COPD: their experience of quality of life. J Clin Nurs. 2002;11(5):613-21.

(99) Jonsdottir H. Research-as-if-practice: a study of family nursing partnership with couples experiencing severe breathing difficulties. J Fam Nurs. 2007;13(4):443-60.

(100) Kanervisto M, Kaistila T, Paavilainen E. Severe chronic obstructive pulmonary disease in a family's everyday life in Finland: perceptions of people with chronic obstructive pulmonary disease and their spouses. Nurs Health Sci. 2007;9(1):40-7.

(101) Cotterell P. Striving for independence: experiences and needs of service users with life limiting conditions. J Adv Nurs. 2008;62(6):665-73.

(102) Fletcher C, Peto R. The natural history of chronic airflow obstruction. BMJ. 1977;6077(1):1645-8.

(103) Lynn J. Serving patients who may die soon and their families: the role of hospice and other services. JAMA. 2001;285(7):925-32.

(104) Lunney JR, Lynn J, Folley DJ, Lipson S, Guralnik JM. Patterns of functional decline at the end of life. JAMA. 2003;289(18):2387-92.

(105) Lehman R. How long can I go on like this? Dying from cardiorespiratory disease. Br J Gen Pract. 2004;54(509):892-3.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-9157-7
(PDF)