Polysomnography in Patients With Obstructive Sleep Apnea

An Evidence-Based Analysis

June 2006
About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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About the Ontario Health Technology Assessment Series

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The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practicing medical experts and industry add important information 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 policy makers to make timely and relevant decisions to optimize patient outcomes.

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Abbreviations

AHI  Apnea hypopnea index
BMI  Body mass index
CCOHTA  Canadian Coordinating Office of Health Technology Assessment
CI  Confidence interval
CMS  Centers for Medicare and Medicaid Services
CPAP  Continuous positive airway pressure
OCCI  Ontario Case Costing Initiative
OR  Odds ratio
OSA  Obstructive sleep apnea
PSG  Polysomnography
QALY  Quality-adjusted life year
RDI  Respiratory disturbance index
ROC  Receiver operating characteristics
SD  Standard deviation
SE  Standard error
Executive Summary

Objective

The objective of this health technology policy assessment was to evaluate the clinical utility and cost-effectiveness of sleep studies in Ontario.

Clinical Need: Target Population and Condition

Sleep disorders are common and obstructive sleep apnea (OSA) is the predominant type. Obstructive sleep apnea is the repetitive complete obstruction (apnea) or partial obstruction (hypopnea) of the collapsible part of the upper airway during sleep. The syndrome is associated with excessive daytime sleepiness or chronic fatigue. Several studies have shown that OSA is associated with hypertension, stroke, and other cardiovascular disorders; many researchers believe that these cardiovascular disorders are consequences of OSA. This has generated increasing interest in recent years in sleep studies.

The Technology Being Reviewed

There is no ‘gold standard’ for the diagnosis of OSA, which makes it difficult to calibrate any test for diagnosis. Traditionally, polysomnography (PSG) in an attended setting (sleep laboratory) has been used as a reference standard for the diagnosis of OSA. Polysomnography measures several sleep variables, one of which is the apnea-hypopnea index (AHI) or respiratory disturbance index (RDI). The AHI is defined as the sum of apneas and hypopneas per hour of sleep; apnea is defined as the absence of airflow for \( \geq 10 \) seconds; and hypopnea is defined as reduction in respiratory effort with \( \geq 4\% \) oxygen desaturation. The RDI is defined as the sum of apneas, hypopneas, and abnormal respiratory events per hour of sleep. Often the two terms are used interchangeably. The AHI has been widely used to diagnose OSA, although with different cut-off levels, the basis for which are often unclear or arbitrarily determined. Generally, an AHI of more than five events per hour of sleep is considered abnormal and the patient is considered to have a sleep disorder. An abnormal AHI accompanied by excessive daytime sleepiness is the hallmark for OSA diagnosis. For patients diagnosed with OSA, continuous positive airway pressure (CPAP) therapy is the treatment of choice. Polysomnography may also be used for titrating CPAP to individual needs.

In January 2005, the College of Physicians and Surgeons of Ontario published the second edition of Independent Health Facilities: Clinical Practice Parameters and Facility Standards: Sleep Medicine, commonly known as “The Sleep Book.” The Sleep Book states that OSA is the most common primary respiratory sleep disorder and a full overnight sleep study is considered the current standard test for individuals in whom OSA is suspected (based on clinical signs and symptoms), particularly if CPAP or surgical therapy is being considered.

Polysomnography in a sleep laboratory is time-consuming and expensive. With the evolution of technology, portable devices have emerged that measure more or less the same sleep variables in sleep laboratories as in the home. Newer CPAP devices also have auto-titration features and can record sleep variables including AHI. These devices, if equally accurate, may reduce the dependency on sleep laboratories for the diagnosis of OSA and the titration of CPAP, and thus may be more cost-effective.
Difficulties arise, however, when trying to assess and compare the diagnostic efficacy of in-home PSG versus in-lab. The AHI measured from portable devices in-home is the sum of apneas and hypopneas per hour of time in bed, rather than of sleep, and the absolute diagnostic efficacy of in-lab PSG is unknown. To compare in-home PSG with in-lab PSG, several researchers have used correlation coefficients or sensitivity and specificity, while others have used Bland-Altman plots or receiver operating characteristics (ROC) curves. All these approaches, however, have potential pitfalls. Correlation coefficients do not measure agreement; sensitivity and specificity are not helpful when the true disease status is unknown; and Bland-Altman plots measure agreement (but are helpful when the range of clinical equivalence is known). Lastly, receiver operating characteristics curves are generated using logistic regression with the true disease status as the dependent variable and test values as the independent variable. Thus, each value of the test is used as a cut-point to measure sensitivity and specificity, which are then plotted on an x-y plane. The cut-point that maximizes both sensitivity and specificity is chosen as the cut-off level to discriminate between disease and no-disease states. In the absence of a gold standard to determine the true disease status, ROC curves are of minimal value.

At the request of the Ontario Health Technology Advisory Committee (OHTAC), MAS has thus reviewed the literature on PSG published over the last two years to examine new developments.

**Methods**

**Review Strategy**

There is a large body of literature on sleep studies and several reviews have been conducted. Two large cohort studies, the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study, are the main sources of evidence on sleep literature.

To examine new developments on PSG published in the past two years, MEDLINE, EMBASE, MEDLINE In-Process & Other Non-Indexed Citations, the Cochrane Database of Systematic Reviews and Cochrane CENTRAL, INAHTA, and websites of other health technology assessment agencies were searched. Any study that reported results of in-home or in-lab PSG was included. All articles that reported findings from the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study were also reviewed.

**Diffusion of Sleep Laboratories**

To estimate the diffusion of sleep laboratories, a list of sleep laboratories licensed under the Independent Health Facility Act was obtained. The annual number of sleep studies per 100,000 individuals in Ontario from 2000 to 2004 was also estimated using administrative databases.

**Summary of Findings**

**Literature Review**

A total of 315 articles were identified that were published in the past two years; 227 were excluded after reviewing titles and abstracts. A total of 59 articles were identified that reported findings of the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study.
Prevalence

Based on cross-sectional data from the Wisconsin Sleep Cohort Study of 602 men and women aged 30 to 60 years, it is estimated that the prevalence of sleep-disordered breathing is 9% in women and 24% in men, on the basis of more than five AHI events per hour of sleep. Among the women with sleep disorder breathing, 22.6% had daytime sleepiness and among the men, 15.5% had daytime sleepiness. Based on this, the prevalence of OSA in the middle-aged adult population is estimated to be 2% in women and 4% in men.

Snoring is present in 94% of OSA patients, but not all snorers have OSA. Women report daytime sleepiness less often compared with their male counterparts (of similar age, body mass index [BMI], and AHI). Prevalence of OSA tends to be higher in older age groups compared with younger age groups.

Diagnostic Value of Polysomnography

It is believed that PSG in the sleep laboratory is more accurate than in-home PSG. In the absence of a gold standard, however, claims of accuracy cannot be substantiated. In general, there is poor correlation between PSG variables and clinical variables. A variety of cut-off points of AHI (> 5, > 10, and > 15) are arbitrarily used to diagnose and categorize severity of OSA, though the clinical importance of these cut-off points has not been determined.

Recently, a study of the use of a therapeutic trial of CPAP to diagnose OSA was reported. The authors studied habitual snorers with daytime sleepiness in the absence of other medical or psychiatric disorders. Using PSG as the reference standard, the authors calculated the sensitivity of this test to be 80% and its specificity to be 97%. Further, they concluded that PSG could be avoided in 46% of this population.

Obstructive Sleep Apnea and Obesity

Obstructive sleep apnea is strongly associated with obesity. Obese individuals (BMI >30 kg/m²) are at higher risk for OSA compared with non-obese individuals and up to 75% of OSA patients are obese. It is hypothesized that obese individuals have large deposits of fat in the neck that cause the upper airway to collapse in the supine position during sleep. The observations reported from several studies support the hypothesis that AHIs (or RDIs) are significantly reduced with weight loss in obese individuals.

Obstructive Sleep Apnea and Cardiovascular Diseases

Associations have been shown between OSA and comorbidities such as diabetes mellitus and hypertension, which are known risk factors for myocardial infarction and stroke. Patients with more severe forms of OSA (based on AHI) report poorer quality of life and increased health care utilization compared with patients with milder forms of OSA. From animal models, it is hypothesized that sleep fragmentation results in glucose intolerance and hypertension. There is, however, no evidence from prospective studies in humans to establish a causal link between OSA and hypertension or diabetes mellitus. It is also not clear that the associations between OSA and other diseases are independent of obesity; in most of these studies, patients with higher values of AHI had higher values of BMI compared with patients with lower AHI values.

A recent meta-analysis of bariatric surgery has shown that weight loss in obese individuals (mean BMI = 46.8 kg/m²; range = 32.30–68.80) significantly improved their health profile. Diabetes was resolved in 76.8% of patients, hypertension was resolved in 61.7% of patients, hyperlipidemia improved in 70% of patients, and OSA resolved in 85.7% of patients. This suggests that obesity leads to OSA, diabetes, and hypertension, rather than OSA independently causing diabetes and hypertension.
Health Technology Assessments, Guidelines, and Recommendations

In April 2005, the Centers for Medicare and Medicaid Services (CMS) in the United States published its decision and review regarding in-home and in-lab sleep studies for the diagnosis and treatment of OSA with CPAP. In order to cover CPAP, CMS requires that a diagnosis of OSA be established using PSG in a sleep laboratory. After reviewing the literature, CMS concluded that the evidence was not adequate to determine that unattended portable sleep study was reasonable and necessary in the diagnosis of OSA.

In May 2005, the Canadian Coordinating Office of Health Technology Assessment (CCOHTA) published a review of guidelines for referral of patients to sleep laboratories. The review included 37 guidelines and associated reviews that covered 18 applications of sleep laboratory studies. The CCOHTA reported that the level of evidence for many applications was of limited quality, that some cited studies were not relevant to the recommendations made, that many recommendations reflect consensus positions only, and that there was a need for more good quality studies of many sleep laboratory applications.

Diffusion

As of the time of writing, there are 97 licensed sleep laboratories in Ontario. In 2000, the number of sleep studies performed in Ontario was 376/100,000 people. There was a steady rise in sleep studies in the following years such that in 2004, 769 sleep studies per 100,000 people were performed, for a total of 96,134 sleep studies. Based on prevalence estimates of the Wisconsin Sleep Cohort Study, it was estimated that 927,105 people aged 30 to 60 years have sleep-disordered breathing. Thus, there may be a 10-fold rise in the rate of sleep tests in the next few years.

Economic Analysis

In 2004, approximately 96,000 sleep studies were conducted in Ontario at a total cost of ~$47 million (Cdn). Since obesity is associated with sleep disordered breathing, MAS compared the costs of sleep studies to the cost of bariatric surgery. The cost of bariatric surgery is $17,350 per patient. In 2004, Ontario spent $4.7 million per year for 270 patients to undergo bariatric surgery in the province, and $8.2 million for 225 patients to seek out-of-country treatment. Using a Markov model, it was concluded that shifting costs from sleep studies to bariatric surgery would benefit more patients with OSA and may also prevent health consequences related to diabetes, hypertension, and hyperlipidemia. It is estimated that the annual cost of treating comorbid conditions in morbidly obese patients often exceeds $10,000 per patient. Thus, the downstream cost savings could be substantial.

Considerations for Policy Development

Weight loss is associated with a decrease in OSA severity. Treating and preventing obesity would also substantially reduce the economic burden associated with diabetes, hypertension, hyperlipidemia, and OSA. Promotion of healthy weights may be achieved by a multisectorial approach as recommended by the Chief Medical Officer of Health for Ontario. Bariatric surgery has the potential to help morbidly obese individuals (BMI > 35 kg/m² with an accompanying comorbid condition, or BMI > 40 kg/m²) lose weight. In January 2005, MAS completed an assessment of bariatric surgery, based on which OHTAC recommended an improvement in access to these surgeries for morbidly obese patients in Ontario.

Habitual snorers with excessive daytime sleepiness have a high pretest probability of having OSA. These patients could be offered a therapeutic trial of CPAP to diagnose OSA, rather than a PSG. A majority of these patients are also obese and may benefit from weight loss. Individualized weight loss programs should, therefore, be offered and patients who are morbidly obese should be offered bariatric surgery.
That said, and in view of the still evolving understanding of the causes, consequences and optimal treatment of OSA, further research is warranted to identify which patients should be screened for OSA.
Objective

The objective of this health technology policy assessment was to evaluate the clinical utility and cost-effectiveness of sleep studies in Ontario.

Background

Clinical Need: Target Population and Condition

Sleep disorders are common and obstructive sleep apnea (OSA) is the predominant type. (1) Other types include insomnia, narcolepsy, restless leg syndrome, and sleepwalking. Obstructive sleep apnea is a repetitive complete obstruction (apnea) or partial obstruction (hypopnea) of the collapsible part of the upper airway during sleep; the syndrome is associated with excessive daytime sleepiness or chronic fatigue. (2) Several studies have shown that OSA is associated with accident risk, cognitive impairment, and cardiovascular disorders. (3) Intuitively, it could be argued that excessive daytime sleepiness in OSA patients would lower attention span and might increase the risk of accidents compared with people who do not have OSA. However, many researchers believe that the associated cardiovascular disorders are more serious consequences of OSA. This has raised awareness on the importance of OSA diagnosis.

In Canada, 370 sleep studies per 100,000 population are performed annually on average and 776/100,000 in Ontario. Corresponding rates internationally are 427/100,000 in the United States, 42.5/100,000 in the United Kingdom, 177/100,000 in Belgium, and 282/100,000 in Australia. (4) The rate of sleep studies performed in Ontario is thus very high in relation to other provinces in Canada, as well as other countries. This prompted a request to assess sleep laboratories.

Technology Being Reviewed

Obstructive sleep apnea, unlike other diseases such as cancer, cannot be diagnosed by a tissue biopsy. Thus, the absence of a gold standard by which to determine the true disease status makes it difficult to calibrate any test for OSA diagnosis. Traditionally, polysomnography (PSG) in an attended setting (sleep laboratory) has been used as a reference standard for the diagnosis of OSA. This requires observing patients while they are asleep. (5) A patient stays overnight in the sleep laboratory and is constantly monitored by a technician.

Polysomnography includes electroencephalography, electroocculography, submental electromyography, electrocardiography, respiratory movement or respiratory effort, nasal or oral airflow, pulse oximetry, and limb movement electromyography. (6) Thus, PSG monitors sleep stages, respiratory effort, oxygen saturation, heart rate, body position, and limb movements. These data are used to calculate the apnea-hypopnea index (AHI) or respiratory disturbance index (RDI). The AHI is the sum of apneas and hypopneas per hour of sleep with apnea defined as the absence of airflow for $\geq 10$ seconds and hypopnea as reduction in respiratory effort with $\geq 4\%$ oxygen desaturation. The RDI is the sum of apneas, hypopneas, and abnormal respiratory events per hour of sleep. Often, the terms are used interchangeably.

The AHI has been widely used to diagnose OSA, although with different cut-off levels, the basis for which are often unclear or arbitrarily determined. Generally, an AHI of greater than five events per hour of sleep is considered abnormal and the patient is considered to have a sleep disorder. An abnormal AHI
accompanied by excessive daytime sleepiness is the hallmark for the diagnosis of OSA. For patients
diagnosed with OSA, continuous positive airway pressure therapy (CPAP) is the treatment of choice.
Polysomnography may also used for titrating CPAP to individual needs.

In January 2005, the College of Physicians and Surgeons of Ontario published the second edition of
Independent Health Facilities: Clinical Practice Parameters and Facility Standards: Sleep Medicine,
commonly known as “The Sleep Book.” The document was designed to assist physicians in their clinical
decision-making by providing a framework for assessing and treating clinical conditions commonly cared
for by a variety of specialties. The primary purpose was to assist physicians in developing their own
quality management program and to act as a guide for assessing the quality of patient care provided in
these facilities. The Sleep Book reports that OSA is the most common primary respiratory sleep disorder
and full overnight sleep study is the current standard for those individuals in whom OSA is suspected
(based on clinical signs and symptoms), particularly if CPAP or surgical therapy are being considered.

Polysomnography in a sleep laboratory is time-consuming and expensive. With the evolution of
technology, portable devices have emerged that measure more or less the same sleep variables whether in
sleep laboratories or in-home. The American Sleep Disorders Association classifies these devices into
four types: Type I devices are considered the standard laboratory-based PSG. Type II devices are
comprehensive portable PSG devices with a minimum of seven channels that measure the same
parameters as those by Type I devices, including sleep staging. Type III devices have a minimum of
four channels and measure only the cardiorespiratory parameters of sleep. The AHI calculated from these
devices is calculated per hour of time in bed, rather than per hour of sleep. Type IV devices measure only
oxygen saturation or airflow. Newer CPAP devices also have auto-titration features. These devices, if
equally accurate, may reduce the dependency on sleep laboratories for the diagnosis of OSA and the
titration of CPAP and thus may be more cost-effective.

Difficulties arise, however, when trying to assess and compare the diagnostic efficacy of in-home PSG
versus in-lab. The AHI measured from portable devices in-home is the sum of apneas and hypopneas per
hour of time in bed, rather than of sleep, and the absolute diagnostic efficacy of in-lab PSG is unknown.
To compare in-home PSG with in-lab PSG, several researchers have used correlation coefficients or
sensitivity and specificity, while others have used Bland-Altman plots or receiver operating
characteristics (ROC) curves. All these approaches, however, have potential pitfalls. Correlation
coefficients do not measure agreement; sensitivity and specificity are not helpful when the true disease
status is unknown; and Bland-Altman plots measure agreement (but are helpful when the range of clinical
equivalence is known). Lastly, receiver operating characteristics curves are generated using logistic
regression with the true disease status as the dependent variable and test values as the independent
variable. Thus, each value of the test is used as a cut-point to measure sensitivity and specificity, which
are then plotted on an x-y plane. The cut-point that maximizes both sensitivity and specificity is chosen as
the cut-off level to discriminate between disease and no-disease states. In the absence of a gold standard
to determine the true disease status, ROC curves are of minimal value.
Literature Review on Effectiveness

Research Questions

1. What is the clinical utility of sleep laboratory studies?
2. What is the diffusion of sleep laboratory technology in Ontario?
3. Are sleep laboratory studies cost-effective?

Review Strategy

The objective of the literature review was to address the question: What is the clinical utility of sleep laboratory studies?

There is a large body of literature on sleep studies, and several reviews have been conducted. Two large cohort studies, the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study, are the main source of evidence on sleep literature. The MAS reviewed all literature published on PSG over the past two years to examine new developments in the diagnosis of OSA. MEDLINE, EMBASE, MEDLINE In-Process & Other Non-Indexed Citations, the Cochrane Database of Systematic Reviews and Cochrane CENTRAL, INAHTA, and websites of other health technology assessment agencies were searched. All studies reporting results of a PSG in a sleep laboratory or in-home were included. Studies that did not use PSG were excluded. In addition, to understand the clinical importance of diagnosing and treating OSA, articles that reported findings from the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study were also reviewed.

Results of Literature Review

A total of 315 articles were identified that were published in the past 2 years; 227 were excluded after reviewing titles and abstracts. A total of 59 articles were identified that reported findings of the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study. Table 1 shows the quality of evidence of included studies. Please note that the table does not apply to diagnostic studies.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Level of Evidence</th>
<th>Number of Eligible Studies</th>
</tr>
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<tbody>
<tr>
<td>Large RCT, systematic reviews of RCT</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Large RCT unpublished but reported to an international scientific meeting</td>
<td>1(g)†</td>
<td>0</td>
</tr>
<tr>
<td>Small RCT</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Small RCT unpublished but reported to an international scientific meeting</td>
<td>2(g)</td>
<td>0</td>
</tr>
<tr>
<td>Non-RCT with contemporaneous controls</td>
<td>3a</td>
<td>4</td>
</tr>
<tr>
<td>Non-RCT with historical controls</td>
<td>3b</td>
<td>0</td>
</tr>
<tr>
<td>Non-RCT presented at international conference</td>
<td>3(g)</td>
<td>0</td>
</tr>
<tr>
<td>Surveillance (database or register)</td>
<td>4a</td>
<td>0</td>
</tr>
<tr>
<td>Case series (multisite)</td>
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</tr>
<tr>
<td>Case series (single site)</td>
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<tr>
<td>Retrospective review, modeling</td>
<td>4d</td>
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<tr>
<td>Case series presented at international conference</td>
<td>4(g)</td>
<td>0</td>
</tr>
</tbody>
</table>

*RCT indicates randomized controlled trial.
Summary of Existing Health Technology Assessments

In April 2005, the CMS in the United States published its decision and review regarding sleep studies in-home compared with in-lab for the diagnosis and treatment of OSA with CPAP. (7) In order to cover CPAP, CMS requires that a diagnosis of OSA be established using PSG in a sleep laboratory. After reviewing the literature, CMS concluded that the evidence was not adequate to determine that unattended portable sleep study was reasonable and necessary in the diagnosis of OSA.

In May 2005, the CCOHTA published a review of guidelines for referral of patients to sleep laboratories. (6) The review included 37 guidelines and associated reviews that covered 18 applications of sleep laboratory studies. The CCOHTA reported that the level of evidence for many applications was of limited quality, that some cited studies were not relevant to the recommendations made, that many recommendations reflect consensus positions only, and that there was a need for more good quality studies of many sleep laboratory applications.

Medical Advisory Secretariat Review

The findings of the MAS review are presented under the following themes:

Prevalence

A well-cited article based on cross-sectional data from the Wisconsin Sleep Cohort Study reported findings on 602 men and women aged 30 to 60 years. (2) The authors estimated that the prevalence of sleep disordered breathing was 9% in women and 24% in men on the basis of more than five AHI events per hour of sleep. Among the women with sleep disorder breathing, 22.6% had daytime sleepiness and among the men, 15.5% had daytime sleepiness. Based on this, the prevalence of OSA in the middle-aged adult population is estimated to be 2% in women and 4% in men.

Snoring is present in 94% of OSA patients, but not all snorers have OSA. Women report daytime sleepiness less often compared with their male counterparts (of similar age, BMI, and AHI). The prevalence of OSA also tends to be higher in older age groups compared with younger age groups. Many patients with suspected OSA also have positional sleep apnea. (8) Positional sleep apnea is defined as a 50% reduction in AHI during non-supine sleep in relation to supine sleep. In one study, it was estimated that 26% of patients with a positive sleep test had positional sleep apnea. (8) Patients with positional sleep apnea may benefit from positional therapy designed to prevent the supine position during sleep.

Diagnostic Value of Polysomnography

It is believed that PSG in-lab is more accurate than PSG in-home. In the absence of a gold standard, however, claims of accuracy cannot be substantiated. In general, there is poor correlation between PSG variables and clinical variables. A variety of cut-off points of AHI (> 5, > 10, and > 15) are arbitrarily used to diagnose and categorize severity of OSA. Thus, these cut-off points have undetermined clinical importance. (2)

Recently, one study used a therapeutic trial of CPAP to diagnose OSA. (9) The authors studied habitual snorers with daytime sleepiness that did not have any other medical or psychiatric disorders. Using PSG
as the reference standard, the authors calculated the sensitivity of the test to be 80% and specificity to be 97%. They concluded that PSG could be avoided in 46% of this population.

**Obstructive Sleep Apnea and Obesity**

Obstructive sleep apnea is strongly associated with obesity. (10;11) Obese individuals (BMI > 30 kg/m²) are at a higher risk for OSA. For example, Up to 75% of OSA patients seen at the University Health Network in Toronto are obese (Personal communication, March 2005). It is hypothesized that obese individuals have large deposits of fat in the neck that causes the upper airway to collapse in the supine position during sleep. The observations reported from several studies supports the hypothesis that AHIs (or RDIs) are significantly reduced with weight loss in obese individuals. (12-14) For example, Dixon et al. (14) prospectively followed 25 severely obese patients for 17 ± 10 months following bariatric surgery. The mean BMI was 52.7 ± 9.5 kg/m² at baseline compared with 37.2 ± 7.2 kg/m² at the end of study (P < .001); mean AHI was 61.6 ± 31.9/hr compared with 13.4 ± 13/hr at the end of study (P < .001); 23 of the 25 patients(92%) needed CPAP at baseline compared with 24% at the end of study (P < .001).

Weight loss is one of the few interventions that may cure OSA. (15) This may be achieved by modification of lifestyle, diet, medication, and bariatric surgery. The current epidemic of obesity is likely to drive an increase in obesity-related sleep disorders, including OSA, as well as other comorbid conditions. Thus, the Chief Medical Officer of Health for Ontario has recognized the overweight and obesity epidemic as one of the biggest challenges, and has recommended a comprehensive and multisectorial strategy to help the people of Ontario achieve and maintain a healthy weight. (16) In January 2005, MAS completed an assessment of bariatric surgery, based on which the Ontario Health Technology Advisory Committee (OHTAC) recommended improving access to these surgeries for morbidly obese patients in Ontario.

**Obstructive Sleep Apnea and Cardiovascular Diseases**

Associations between OSA and hypertension have been demonstrated: patients with a more severe form of OSA (based on AHI) have a higher prevalence of hypertension compared with patients who have milder forms. (17-21) It is, as yet, unclear, whether these associations are independent of obesity. In most of these studies, patients with higher AHI values also had higher BMI values compared to those patients with lower AHI values. From animal models, it was initially hypothesized that OSA can lead to sustained hypertension. (22) In a review published in 2000, however, Young and Peppard (23) concluded that there was no evidence from prospective studies in humans to establish a causal link between OSA and hypertension.

Since then, few studies have reported findings from prospectively collected data. In 2000, Peppard et al. (24) published their findings from the Wisconsin Sleep Cohort Study on 893 participants on whom they had follow-up data for at least 4 years. The authors defined hypertension as a blood pressure of at least 140/90 mm Hg, or the use of antihypertensive medications. They divided the cohort by baseline values of AHI into four groups: 1) AHI = 0; 2) AHI = 0.1–4.9; 3) AHI = 5–14.9; and 4) AHI ≥15. Using the first group as the reference group, they compared the other groups for rates of hypertension at the end-point via logistic regression. After adjusting for baseline hypertension, BMI, alcohol, and cigarette use, they computed odds ratios (ORs) and 95% confidence intervals (CIs). They found that the odds of hypertension were higher in groups 2 to 4 compared with group 1 [OR = 1.42 (2 vs. 1), 2.03 (3 vs. 1), 2.89 (4 vs. 1); P = .002 for trend]. As seen in Table 2, however, it is evident that BMI also tended to be higher in the groups with higher values of AHI compared to groups with lower AHI values. The authors
also acknowledged that the measures of body habitus (BMI and waist and neck circumference) were strong confounding variables.
Table 2: Characteristics of the Participants who Completed One or Both Follow-Up Sleep Studies, According to the Apnea-Hypopnea Index at Baseline

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>BASE-LINE APNEA–HYPOPNEA INDEX</th>
<th>ENTIRE GROUP (N=893)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (N=187)</td>
<td>0.1–4.9 (N=507)</td>
</tr>
<tr>
<td></td>
<td>Sex — no. (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>107 (57)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>80 (43)</td>
</tr>
<tr>
<td></td>
<td>Age — yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At base line</td>
<td>45±7</td>
</tr>
<tr>
<td></td>
<td>At follow-up</td>
<td>49±7</td>
</tr>
<tr>
<td></td>
<td>Apnea–hypopnea index — events/hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At base line</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>At follow-up</td>
<td>2±4</td>
</tr>
<tr>
<td></td>
<td>Median value at base line</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Median value at follow-up</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure — mm Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At base line</td>
<td>120±14</td>
</tr>
<tr>
<td></td>
<td>At follow-up</td>
<td>118±15</td>
</tr>
<tr>
<td></td>
<td>Diastolic blood pressure — mm Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At base line</td>
<td>79±9</td>
</tr>
<tr>
<td></td>
<td>At follow-up</td>
<td>75±10</td>
</tr>
<tr>
<td></td>
<td>Use of antihypertensive medications — no. (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At base line</td>
<td>12 (6)</td>
</tr>
<tr>
<td></td>
<td>At follow-up</td>
<td>18 (10)</td>
</tr>
<tr>
<td></td>
<td>Stage 1 or worse hypertension (blood pressure ≥140/90 mm Hg or use of antihypertensive medications) — no. (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At base line</td>
<td>34 (18)</td>
</tr>
<tr>
<td></td>
<td>At follow-up</td>
<td>32 (17)</td>
</tr>
<tr>
<td></td>
<td>Stage 2 or worse hypertension (blood pressure ≥160/100 mm Hg or use of antihypertensive medications) — no. (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At base line</td>
<td>13 (7)</td>
</tr>
<tr>
<td></td>
<td>At follow-up</td>
<td>19 (10)</td>
</tr>
<tr>
<td></td>
<td>Body-mass index</td>
<td>27±5</td>
</tr>
<tr>
<td></td>
<td>At base line</td>
<td>29±6</td>
</tr>
<tr>
<td></td>
<td>At follow-up</td>
<td>3±5</td>
</tr>
<tr>
<td></td>
<td>Alcoholic drinks — no. of drinks/wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At base line</td>
<td>3±4</td>
</tr>
<tr>
<td></td>
<td>At follow-up</td>
<td>3±4</td>
</tr>
<tr>
<td></td>
<td>Current cigarette smoker — no. (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At base line</td>
<td>34 (18)</td>
</tr>
<tr>
<td></td>
<td>At follow-up</td>
<td>32 (17)</td>
</tr>
</tbody>
</table>

*Data are from 893 follow-up sleep studies; 799 participants completed the four-year follow-up study, and 184 also completed the eight-year follow-up study. For the 184 participants who completed both the four-year and the eight-year follow-up studies, four-year follow-up data were used to calculate the baseline values and eight-year follow-up data were used to calculate the follow-up values. Plus-minus values are means ±SD.


In 2003, Kaneko et al. (25) published findings from a randomized controlled trial comparing CPAP to medical treatment in only 24 patients with heart failure and OSA. The mean systolic blood pressure was 128 [standard error (SE) = 7] at baseline, and 134 (SE = 8) at 1 month in the medical treatment group, compared with 126 (SE = 6) at baseline and 116 (SE = 5) at 1 month in the CPAP group (P = .008). There were no significant differences in diastolic blood pressure. However, the authors did not report impact on hypertension using the conventional definition of blood pressure greater than 140/90 mm Hg; thus, the clinical importance of these findings is unclear.
In 2004, Gotsopoulos et al. (26) published findings from a randomized crossover trial comparing mandibular advancement splint for 4 weeks to oral appliance (control) for 4 weeks, in 61 patients with OSA. At the end of study, mean AHI was 12 (SE = 2) in the splint group compared with 24 (SE = 2) in the control group ($P < .0001$). Mean systolic blood pressure while awake was 131.6 (SE = 1.5) at baseline, which reduced to 126.7 (SE = 1.7) in the splint group compared with 130.1 (SE = 1.5) in the control group at the end of study ($P = .003$). Similarly, mean diastolic blood pressure reduced from 80.9 (SE = 1.0) at baseline to 77.2 (SE = 1.2) in the splint group compared with 80.7 (SE = 1.0) in the control group ($P < .0001$). Again, the clinical importance of these findings is not clear.

In 2005, Dursunoglu et al. (27) investigated acute effects of automatic CPAP on blood pressure in 12 patients with OSA and hypertension. They compared systolic and diastolic blood pressure measurements after overnight CPAP with baseline values. There were no significant differences.

Also in 2005, Hermida et al. (28) published the results of CPAP therapy on ambulatory blood pressure at 2 and 4 months post-CPAP. In this study, 64 of 83 patients (77%) treated with CPAP had hypertension at baseline. After 4 months, 61 (74%) were still hypertensive ($P > .05$). The authors suggested that OSA patients must be evaluated for hypertension and treated with antihypertensive drugs rather than CPAP alone.

Several studies have documented an association between sleep disordered breathing and diabetes. (29-31) Though, as is the case with hypertension, these associations are based on cross-sectional data and hence provide no evidence for a cause-effect relationship. Only one of these three studies reported BMI values stratified by diabetes status. Resnick et al. (29) studied 4,872 participants in the Sleep Heart Health Study. They reported that the mean BMI was 31.3 [standard deviation (SD) = 6.0] in 470 participants with diabetes compared with a BMI of 28.1 (SD = 5.1) in 4,402 non-diabetic participants ($P < .001$). The authors also reported a positive association between BMI and RDI.

In 2005, Reichmuth et al. published findings from a longitudinal analysis of the Wisconsin Sleep Cohort study. (32) Of the 1,382 participants studied at baseline, BMI tended to increase across each category of AHI. That is, mean BMI was 27.9 in the group with an AHI <5, 32.0 in the AHI 5–15 group, and 34.2 in the AHI ≥15 group. Of these 1,382 participants (each followed for 4-year follow-up intervals), 978 with no diabetes at the beginning of a follow-up interval provided data to estimate the risk of developing diabetes. The OR for developing diabetes with an AHI ≥15, compared with an AHI <5, after adjusting for age, sex, and body habitus, was not significant. ($OR = 1.62, CI = 0.67–3.65; P = .24$).

Also in 2005, Arzt et al. (33) published findings from a cross-sectional and longitudinal analysis of the Wisconsin Sleep Cohort study to examine the association of sleep-disordered breathing and stroke. In the cross-sectional analysis, they had 1,475 participants whom they divided into 3 groups: 1) AHI <5; 2) AHI 5–20; and 3) AHI ≥20. Table 3 shows the characteristics of this cohort in which participants in groups 2 and 3 had higher BMI and higher rates of hypertension and diabetes compared with group 1. The authors reported that the odds of prevalent strokes were significantly higher in participants with an AHI ≥20 compared with participants with an AHI <5 (OR = 3.83, CI = 1.17–12.56; $P = .03$), after adjusting for age, sex, BMI, alcohol, smoking, diabetes, and hypertension.

In the longitudinal analysis of follow-up data conducted at 4-year intervals, there were 1,189 participants. The incidence rate of stroke was 1.33/1,000 person-year in the group with an AHI <5; 0.54/1,000 person-years in the group with an AHI of 5–20; and 5.75/1,000 person-years in the group with an AHI of ≥20. The OR for the group with an AHI ≥20 compared with the group with an AHI <5 was not significant after adjusting for BMI ($OR = 3.08, CI = 0.74–12.81; P = .12$). The authors reported a weak association between BMI and incident strokes ($\beta$ coefficient = 0.0494; $P = .063$).
Unfortunately, Arzt et al. did not specifically examine the effect of obesity by dichotomizing BMI values using a cut-point of 30 kg/m². In fact, the consistent observation that a more severe form of OSA is associated with higher BMI values suggests that obesity leads to cardiovascular consequences as well as OSA, and that this risk may be higher in obese patients in the presence of OSA.

In 2005, Doherty et al. (34) reported long-term effects of CPAP on cardiovascular outcomes in OSA patients compared with untreated OSA patients followed for an average of 7.5 years. The untreated group was comprised of patients who were noncompliant with CPAP. In the cohort of 107 patients treated with CPAP, there were eight deaths: three related to cancer, two related to ischemic heart disease, and one each due to suicide and lung disease. In the cohort of 61 untreated patients, there were nine deaths: three were sudden deaths presumably of cardiac cause, two were due to stroke, two were due to myocardial infarction, and one due to heart failure. Survival was significantly decreased in the untreated group \((P = .009)\). The authors concluded that CPAP has a protective effect against cardiovascular mortality. They defended their conclusion by stating that the groups were similar at baseline \((P \text{ values were nonsignificant for comparisons of baseline characteristics})\) and that patients are usually noncompliant with CPAP because they feel claustrophobic and have blocked nasal passages, not because of a negative attitude toward therapy in general.

A number of observations are relevant to these findings. First, nonsignificant \(P\) values for comparisons of baseline characteristics usually represent a lack of statistical power and thus may not support the claim of similarity between groups. Second, the facts that three deaths in the untreated group occurred among patients with pre-existing heart disease and three patients in the untreated group had cardiac arrhythmia at baseline compared with only one patient in the CPAP group, indicate that the patients in the untreated group had relatively poor health profile compared with the CPAP group. Last, the notion that most OSA patients are noncompliant with CPAP because of claustrophobia or blocked nasal passages defeats the case for the use of CPAP in OSA patients. Furthermore, there was no mention regarding possible lack of compliance in the untreated group with medications for comorbid conditions.

Two prospective cohort studies have examined the effect of OSA on cardiovascular outcomes defined as a composite end point of stroke or death. Marin et al. (35) recruited 377 simple snorers (AHI <5), 403 untreated patients with mild to moderate OSA (AHI 5–30), 235 untreated patients with severe OSA (AHI >30), 372 patients treated with CPAP who were also compliant (including 349 patients with an
AHI >30 and 23 with an AHI 5–30), and 264 healthy men. Untreated patients were those who refused CPAP therapy. Healthy men were matched for age and BMI with untreated patients who had severe OSA. Baseline characteristics are shown in Table 4.

Table 4: Participant Characteristics (Marin et al. 2005)

<table>
<thead>
<tr>
<th></th>
<th>Healthy men (n=264)</th>
<th>Snorers (n=377)</th>
<th>Untreated mild-moderate OSAH (n=403)</th>
<th>Untreated severe OSAH (n=235)</th>
<th>OSAH treated with CPAP (n=372)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.6 (8.1)</td>
<td>49.9 (9.1)</td>
<td>50.3 (8.1)</td>
<td>49.9 (7.2)</td>
<td>49.9 (8.5)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>29.8 (4.4)</td>
<td>26.1 (3.6)*</td>
<td>27.5 (4.4)*</td>
<td>30.3 (4.4)</td>
<td>30.7 (4.4)*</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>14.8</td>
<td>17.7</td>
<td>24.8*</td>
<td>34.9*</td>
<td>35.1*</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>6.1</td>
<td>7.5</td>
<td>8.5</td>
<td>9.9</td>
<td>11.3*</td>
</tr>
<tr>
<td>Lipid disorders (%)</td>
<td>6.8</td>
<td>7.2</td>
<td>7.4</td>
<td>7.7</td>
<td>7.9</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>22.9</td>
<td>23.1</td>
<td>24.3</td>
<td>25.1</td>
<td>25.2</td>
</tr>
<tr>
<td>Alcohol use (%)</td>
<td>27.7</td>
<td>28.2</td>
<td>28.3</td>
<td>28.1</td>
<td>29.2</td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>2.6</td>
<td>3.4</td>
<td>5.2</td>
<td>8.2*</td>
<td>8.5†</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.41 (0.28)</td>
<td>6.44 (0.05)</td>
<td>6.45 (0.13)*</td>
<td>6.47 (0.31)*</td>
<td>6.46 (0.17)*</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.31 (0.09)</td>
<td>1.31 (0.05)</td>
<td>1.32 (0.03)</td>
<td>1.32 (0.11)</td>
<td>1.32 (0.03)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>121.3 (1.8)</td>
<td>121.7 (0.8)*</td>
<td>122.7 (0.6)*</td>
<td>124.7 (1.7)*</td>
<td>124.8 (1.3)*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>75.3 (1.1)</td>
<td>75.4 (0.5)</td>
<td>76.1 (0.4)*</td>
<td>78.8 (1.4)*</td>
<td>78.9 (0.6)*</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>5.33 (0.12)</td>
<td>5.34 (0.05)</td>
<td>5.36 (0.08)*</td>
<td>5.38 (0.05)*</td>
<td>5.39 (0.03)*</td>
</tr>
<tr>
<td>Apnoea-hypopnoea index</td>
<td>1.2 (0.2)</td>
<td>3.5 (0.8)</td>
<td>18.2 (3.5)*</td>
<td>43.3 (5.7)*</td>
<td>47.4 (4.9)*</td>
</tr>
</tbody>
</table>

Reprinted from The Lancet, 365. 9464, Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. 1046-53 Copyright (2006) with permission from Elsevier.

By matching for age and BMI, the authors were able to balance the groups (as seen in Table 4). A significantly higher proportion of OSA patients were found to have hypertension, diabetes, and cardiovascular disease, compared with healthy men (control group). New cardiovascular events occurred more frequently in untreated patients with severe OSA compared with healthy men (Figure 1). The authors used a multiple logistic regression model to adjust for age, presence of cardiovascular disease, hypertension, diabetes, lipid disorders, smoking status, alcohol use, systolic and diastolic blood pressure, blood glucose, total cholesterol, triglycerides, and current use of antihypertensive, lipid lowering, and antidiabetic drugs. After adjusting for these variables, OR was 2.87 (CI = 1.17–7.51) for the untreated severe OSA group compared with the control group. Age (OR = 1.09; CI = 1.04–1.12) and pre-existing cardiovascular disease (OR = 2.54; CI = 1.3–4.99) were also significant predictors of new cardiovascular events in this model. The authors concluded that severe OSA patients are at higher risk of cardiovascular events compared with healthy men and that CPAP treatment reduces this risk.

The results of this study should be seen in the context of its limitations as it was not a randomized trial. Obstructive sleep apnea patients had poorer health profiles at baseline compared with healthy men. However, the reported baseline characteristics of patients with severe untreated OSA were similar to CPAP-treated patients. Thus, it could be argued that the lower event rate in CPAP treatment group was due to CPAP therapy. It could also be argued that the patients who were compliant with CPAP therapy were also compliant with the medical management of comorbid conditions, while patients who refused CPAP therapy were also noncompliant with other forms of therapy. This could have biased the results in favour of CPAP therapy. In addition, there may be correlations among many of the variables included in the multivariate analyses. The authors did not report whether they checked for multicollinearity or whether they performed any other model diagnostics. These are standard procedures for complex analyses to ensure that the robustness of results.
Yaggi et al. (36) enrolled 1,022 patients who underwent PSG and recorded subsequent events (stroke and death). Of their total sample, 697 (68%) had OSA (AHI > 5) and 325 did not have OSA (controls). Their baseline characteristics are shown in Table 5.

Figure 1: Cumulative Percentage of Individuals With New Fatal (A) and Nonfatal (B) Cardiovascular Events in Each of the Five Groups

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Table 5: Baseline Characteristics of Patients With Obstructive Sleep Apnea Syndrome and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with the Syndrome (N=697)</th>
<th>Controls (N=325)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>60.9</td>
<td>58.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>77</td>
<td>59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White race (%)</td>
<td>84</td>
<td>89</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean body-mass index†</td>
<td>33.8</td>
<td>30.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>10</td>
<td>11</td>
<td>0.61</td>
</tr>
<tr>
<td>Current consumption of alcohol (%)</td>
<td>24</td>
<td>20</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>60</td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>16</td>
<td>10</td>
<td>0.03</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>7</td>
<td>4</td>
<td>0.07</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>25</td>
<td>21</td>
<td>0.20</td>
</tr>
<tr>
<td>Lipid-lowering therapy (%)</td>
<td>25</td>
<td>21</td>
<td>0.20</td>
</tr>
<tr>
<td>Antiplatelet therapy (%)</td>
<td>34</td>
<td>32</td>
<td>0.62</td>
</tr>
<tr>
<td>Mean score on Epworth Sleepiness Scale</td>
<td>11</td>
<td>10</td>
<td>0.004</td>
</tr>
<tr>
<td>Habitual snoring (%)</td>
<td>83</td>
<td>64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean apnea–hypopnea index</td>
<td>35</td>
<td>2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lowest level of arterial oxygen saturation during sleep (%)</td>
<td>80.5</td>
<td>87.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arousal index</td>
<td>53</td>
<td>26</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Race was determined by the investigators.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

Out of 697 patients in the OSA group, 124 (18%) were lost to follow-up and out of 325 patients in the control group, 56 (17%) were lost to follow-up. The event rate of stroke or death was 3.48/100 person-years in the OSA group and 1.60/100 person-years in the control group. After adjusting for age, sex, race, smoking status, alcohol consumption, BMI, diabetes, hyperlipidemia, atrial fibrillation, and hypertension, the hazard ratio was 1.97 (CI = 1.12–3.48). The authors concluded that OSA significantly increases the risk of stroke and death and the increase is independent of other risk factors.
These results should also be used in the same context of limitations as of Marin et al. The OSA group had a poorer health profile compared with the control group. Many of the variables included in the multivariate analyses might be correlated but the authors make no mention of model checking; therefore, the difference in stroke or death cannot be solely attributed to OSA.

The effect of obesity has been further substantiated by a meta-analysis (13) of bariatric surgery, which demonstrated that weight loss in obese individuals (mean BMI = 46.85 kg/m²; range = 32.30–68.80) significantly improves health profiles; hypertension was resolved in 61.7% of patients, diabetes was resolved in 76.8% of patients, hyperlipidemia improved in 70% of patients, and OSA resolved in 85.7% of patients. This suggests that obesity leads to OSA, diabetes, and hypertension, rather than OSA independently causing hypertension, diabetes, or stroke.

Economic Analysis

Economic Literature Review: Summary

The Medical Advisory Secretariat literature search identified 3 articles that contained some form of economic analysis in OSA patients. In the first article, Pelletier-Fleury et al. (37) compared costs and sleep outcomes between 82 patients randomized to immediate PSG, with 89 patients randomized to PSG within 6 months. Costs (in Euros) were related to comorbid conditions (and medications) including hypertension, stroke, angina, diabetes, hyperlipidemia, and depression. Outcomes were sleepiness as measured by the Epworth Sleepiness Scale, percentage of positive responses to Nottingham Health Profile items, and scores of the five dimensions of the Nottingham Health Profile. The authors stratified OSA patients into two subgroups: 1) AHI < 30 events/hour; and 2) AHI ≥ 30 events/hour, and calculated costs per patient associated with a difference of 1-point decrease in the Epworth score, 1% decrease in positive responses to the Nottingham Health Profile, or 1 point decrease in the five dimensions of the Nottingham Health Profile. They found that the incremental cost-effectiveness ratios were lower in the subgroup with an AHI ≥ 30 events/hour. The authors argued for early management of patients with a more severe form of OSA.

Albarrak et al. (38) compared 10-year utilization rates of health resources in 342 patients with OSA (cases), to patients without OSA (age matched controls), using the Manitoba Health Database. They had data from 5 years prior to the diagnosis of OSA to 5 years post-CPAP in OSA patients. There was a significant difference in physician visits (mean = 1.85, SE = 0.52; P < .05) and physician fees between cases and controls (mean = $61.44 (Cdn), SE = 29.51; P < .05). Mean visits and fees were higher in cases compared with controls, however, there was a significant drop in physician visits and physician fees in the cases from 1 year prior to diagnosis to 2 and 5 years post-diagnosis. This was mostly due to a reduction in utilization of psychiatric and respiratory services.

Ayas et al. (39) assessed cost-effectiveness of CPAP therapy in relation to no therapy in OSA patients. They assumed that CPAP therapy would reduce accident rates in OSA patients and used a Markov model to relate costs with quality of life over 5 years. From a third-party payer’s perspective, the incremental cost of CPAP was $3,354 (US) per quality-adjusted life year (QALY) gained; from a societal perspective this value was $314 (US). The authors concluded that CPAP therapy was economically attractive in OSA patients.

The results published by Pelletier-Fleury et al. (37) are not useful for clinical or policy decision-making as the clinical relevance of the reported outcomes is ambiguous. The findings of Albarrak et al. (38)
suggest that untreated OSA patients may unnecessarily utilize psychiatric and respiratory services. Thus, CPAP may be cost-saving because when OSA patients are treated, other resources are freed up. The Ayas et al. (39) model did not capture this aspect of cost-saving. They modelled the effect of CPAP on accident rates only. To estimate this effect they used before-after data on accident rates in patients on CPAP and conducted a meta-analysis. Intuitively, this approach overestimates the effect as most individuals would apply greater caution while driving after becoming involved in an accident; thus, reduction in accident rates in a before-and-after design cannot be solely attributed to CPAP therapy.

**Ontario-Based Economic Analysis**

### Notes and Disclaimer

The MAS uses a standardized costing methodology for all of its economic analyses of technologies. The main cost categories and the associated methods from the province’s perspective are as follows:

**Hospital**: Ontario Case Costing Initiative (OCCI) cost data is used for all program costs when there are 10 or more hospital separations, or one-third or more of hospital separations in the ministry’s data warehouse are for the designated International Classification of Diseases-10 diagnosis codes and Canadian Classification of Health Interventions procedure codes. Where appropriate, costs are adjusted for hospital-specific or peer-specific effects. In cases where the technology under review falls outside the hospitals that report to the OCCI, Program Assignment Code (PAC)-10 weights converted into monetary units are used. Adjustments may need to be made to ensure the relevant case mix group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, MAS normally defaults to considering direct treatment costs only. Historical costs have been adjusted upward by 3% per annum, representing a 5% inflation rate assumption less a 2% implicit expectation of efficiency gains by hospitals.

**Non-Hospital**: These include physician services costs obtained from the Provider Services Branch of the Ontario Ministry of Health and Long-Term Care, device costs from the perspective of local health care institutions, and drug costs from the Ontario Drug Benefit formulary list price.

**Discounting**: For all cost-effective analyses, discount rates of 5% and 3% are used as per the CCOHTA and the Washington Panel of Cost-Effectiveness, respectively.

**Downstream Cost Savings**: All cost avoidance and cost savings are based on assumptions of utilization, care patterns, funding, and other factors. These may or may not be realized by the system or individual institutions.

In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the assumptions, and the revised approach.

The economic analysis represents an estimate only, based on assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied for the purpose of developing implementation plans for the technology.
Diffusion of Sleep Laboratories

The objective of this analysis was to address the second research question: What is the diffusion of sleep laboratory technology in Ontario?

A list of sleep laboratories licensed under the Independent Health Facilities Act was obtained. In addition, the annual number of sleep studies per 100,000 individuals in Ontario from 2000 to 2004 was estimated using administrative databases.

Currently, there are 97 licensed sleep laboratories in Ontario in independent health facilities and several in Ontario hospitals. In 2000, the number of sleep studies performed in Ontario was 376/100,000 people. Since then, there has been a steady rise in the annual volume of studies, such that in 2004, 769 per 100,000 people were performed, for a total of 96,134 sleep studies. Based on prevalence estimates of the Wisconsin Sleep Cohort Study, it is estimated that in Ontario, 927,105 people aged 30 to 60 years have sleep disordered breathing. Thus, there may be a 10-fold rise in the rate of sleep tests over the next few years.

Of the 72,941 patients (mean age = 48 years) who underwent sleep studies between 2000 and 2004, the number of studies/patients ranged from two (quartile 1) to four (quartile 3). In 60,822 (83%) patients, PSG was performed. Many patients had multiple diagnoses. Of 83,254 patient diagnoses, 38,383 (46%) were unknown, 31,273 (37%) were related to psychiatric conditions (e.g., anxiety, depression), 11,827 (14%) were related to congenital conditions, and the rest were related to other systems.

In 2004, at least one PSG (level 1) was done in 62,498 patients. Of these, 10,702 (17%) patients underwent CPAP titration study (which indicates that they were diagnosed with OSA), 12 (0.02%) patients had level 2 PSG, 2,677 (4%) patients had multiple sleep latency tests (indicated when narcolepsy is suspected), and 762 (1.2%) patients had maintenance of sleep wakefulness tests (indicated to determine the ability to stay awake in select cases, for example, factory workers/truck drivers). Thus, the utility of PSG in 48,345 (77%) patients is unclear. This raises the question whether PSG is being appropriately utilized in Ontario.

Budget Impact Analysis

In 2004, approximately 96,000 sleep studies were conducted in Ontario at a total cost of ~$47 million (Cdn). The cost of bariatric surgery is $17,350 (Cdn) per patient. In 2004, Ontario spent $4.7 million (Cdn) per year for 270 patients to undergo bariatric surgery in the province, and $8.2 million (Cdn) for 225 patients to seek out-of-country treatment. Shifting costs from sleep studies to bariatric surgery would benefit more patients with OSA and may also prevent health consequences related to diabetes, hypertension, and hyperlipidemia. It is estimated that the annual cost of treating comorbid conditions in morbidly obese patients often exceeds $10,000 (Cdn) per patient. Thus, the downstream cost savings could be substantial.

Cost-Effectiveness Analysis

The objective of this analysis was to address the third research question: Are sleep laboratory studies cost-effective?

The analysis focused on OSA, the predominant type of sleep disorder, which, in contrast to literature-based estimates, is diagnosed in approximately 23% of all patients tested with PSG in Ontario. The mean age of OSA patients is 50 ± 10 years and mean BMI is 29 ± 4.5 kg/m². Using cumulative
density function and assuming that BMI are normally distributed, it was estimated that out of these 23%, 11% have a BMI greater than 35 kg/m² (morbid obesity). The treatment of choice for OSA patients is CPAP and the treatment of choice for morbidly obese patients is bariatric surgery. The treatment of comorbid conditions is usually via pharmacological measures.

Three strategies were compared:

1) The current practice of referring all sleepy patients to a sleep laboratory for PSG. Patients in whom OSA is diagnosed are followed up with a CPAP titration test and life-long CPAP therapy with yearly sleep tests and CPAP device replacement every 5 years.

2) An alternate strategy that links the current practice with obesity control strategy: 8% of OSA patients who are also morbidly obese are offered bariatric surgery each year as per current capacity.

3) A new strategy in which sleep tests are not offered but a CPAP trial is offered. Patients diagnosed with OSA are treated with CPAP therapy and 90% of OSA patients who are also morbidly obese are offered bariatric surgery each year.

Using a Markov model (Figure 2), a cohort (mean age = 50 years) was followed for its entire life span, i.e., from 50 to 85 years of age (a total follow-up of 35 years). It was assumed that:

- CPAP trial is as accurate as PSG in diagnosing OSA;
- Patients who are treated with CPAP would have improved quality of life but would require lifelong CPAP therapy;
- 1% to 5% of patients on CPAP may be cured of OSA through lifestyle modification (diet and exercise);
- 87% of patients who would undergo bariatric surgery would be cured of OSA and would no longer require CPAP (they would also no longer require morbid obesity-related care); and
- All patients would be alive during 35 years of follow-up.

The costs of sleep tests ($506/test), CPAP devices ($817/device), and of bariatric surgery ($17,000/patient) are all expressed in Canadian dollars. Annual costs related to morbid obesity ($10,000/patient) were also included; however, the model was run both with and without morbid obesity-related costs. The outcome was QALY, which was computed using the Tufts-New England Medical Center, Institute for Clinical Research and Health Policy Studies Catalog of Preference Scores. (40) Thus, the utility value of untreated OSA was 0.63, CPAP-treated OSA was 0.87, and cured OSA or no OSA was 1.00.
Figure 2: Markov Model

M indicates Markov nodes; MO, morbidly obese; squares (□), decision nodes; circles (O), chance nodes; triangles (Δ), terminal nodes. The # signs represent complementary probabilities, that is, probabilities complementary to those on the above branches. For example, complementary probability for “No CPAP” is 0.01 (1 − 0.99). The plus sign (+) denotes that the subtree is pruned but has a structure identical to its counterpart node.
The model evaluated three strategies in a sleepy patient (age = 50 years) in a Markov process of time cycle. Each cycle was of 1-year duration. In the first strategy, the patient went through standard sleep laboratory testing, following which the patient could transit into one of two Markov states: “OSA” or “No OSA.” The probability of entering an OSA state was 23%, and the probability of entering “No OSA” was 77% (a complementary probability denoted by the ‘#’ sign). “No OSA” was an absorbing state; the patient could not return from that state. If the patient had OSA, then the patient could get CPAP therapy with 99% probability. There was a 1% chance that the patient would not receive therapy (e.g., in case the patient refused). There was a 1% chance that the patient might be cured of OSA (through lifestyle modification). If the patient was cured, the patient began the next time cycle in the “No OSA” state. If the patient was not cured, the patient began the next time cycle in the OSA state and went through the same process. At the end of each time cycle, the patient accumulated some value for QALY depending upon the course the patient took during that cycle.

In the second strategy, there were three Markov states, the third of which arose from a subdivision of “OSA” state into “OSA (without morbid obesity)” state and “OSA_MO” state to distinguish morbidly obese patients from non-morbidly obese OSA patients. The morbidly obese patient could get bariatric surgery, which would cure or not cure the condition. If cured, the patient began the next cycle in the “No OSA state,” otherwise in the “OSA” state or “OSA_MO” state, depending upon the patient’s current state. In the third strategy, the patient went through the same branching cascade as in the second strategy.

To account for uncertainty in parameter estimates, probabilistic sensitivity analyses were performed by carrying out 10,000 Monte Carlo simulations upon the Markov model. In this process, values were simultaneously sampled for all uncertain parameters from appropriate distributions. All future costs and QALYs were discounted at a 3% annual rate. The software package used for these analyses was Tree Age Pro 2005. The results are summarized in Table 6 and graphically presented in Figure 3.

### Table 6: Results of the Cost-Effectiveness Analyses*

<table>
<thead>
<tr>
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<th>Including Morbid Obesity-Related Costs</th>
<th>Excluding Morbid Obesity-Related Costs</th>
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<tbody>
<tr>
<td><strong>Current standard</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean cost (Cdn)</td>
<td>$10,404</td>
<td>$5,734</td>
</tr>
<tr>
<td>Mean QALY</td>
<td>32.9</td>
<td>32.9</td>
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<tr>
<td><strong>Current standard + bariatric surgery</strong></td>
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<td>Mean cost (Cdn)</td>
<td>$7,236</td>
<td>$5,593</td>
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<tr>
<td>Mean QALY</td>
<td>33.1</td>
<td>33.1</td>
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<tr>
<td><strong>CPAP trial + bariatric surgery</strong></td>
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<td></td>
</tr>
<tr>
<td>Mean cost (Cdn)</td>
<td>$3,496</td>
<td>$3,221</td>
</tr>
<tr>
<td>Mean QALY</td>
<td>33.2</td>
<td>33.2</td>
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*CPAP indicates continuous positive airway pressure; QALY, quality-adjusted life year. Cost represents cumulative cost per patient including costs of sleep tests, CPAP device, bariatric surgery, and costs related to comorbid conditions.
The results show that when morbidity costs were included, the mean incremental cost (Cdn) of the second strategy compared with the first was -$3,168 (95% probability interval = -$2,570 to -$3,761), and the mean incremental cost of the third strategy compared with the first strategy was -$6,908 (-$6,038 to -$7,765). When morbidity costs were excluded, the corresponding mean incremental costs were -$142 (-$116 to -$168) and -$2,513 (-$2,465 to -$2,563). Thus, both the second and third strategies are cost-saving compared with the first strategy (current practice) and this conclusion does not change by inclusion or exclusion of morbid obesity costs, although cost savings are greater when these costs are included.

The results also show that the mean incremental QALYs for the second strategy compared with the first was 0.26 (0.24–0.27), and the mean incremental QALYs for the third strategy compared with the first strategy was 0.28 (0.27–0.30). Hence, linking sleep clinics to obesity clinics would not only result in gains in QALYs but also cost-saving.
Comparison of Ontario-Based Economic Analysis With Other Economic Studies

The Ontario results are not directly comparable to previous economic analyses because of differences in analytic approaches. That said, both Pelletier-Fleury et al. (37) and Albarrak et al. (38) found that costs were higher in OSA patients partly due to higher utilization of health care resources secondary to comorbid conditions. It was demonstrated that these costs could be minimized by linking sleep clinics to obesity clinics. Ayas et al. (39) examined the effect of CPAP therapy on accident rates compared with no therapy. Accident rates were not modeled in the MAS model because in the three examined strategies, patients received CPAP therapy. Thus, in this model all patients had a similar attention span.

Conclusions

Obesity, rather than OSA, leads to cardiovascular consequences. Treating and preventing obesity would substantially reduce the economic burden associated with diabetes, hypertension, hyperlipidemia, and OSA. Promotion of healthy weight may be achieved by a multisectorial approach as recommended by the Chief Medical Officer of Health for Ontario. Bariatric surgery has a major role in morbidly obese individuals (BMI > 35 kg/m² and a comorbid condition, or BMI > 40 kg/m²).

Habitual snorers with excessive daytime sleepiness have a high pretest probability of having OSA. These patients may be offered a therapeutic trial of CPAP to diagnose OSA, rather than a PSG. A majority of these patients are also obese and may benefit from weight loss. Thus, individualized weight loss programs should be offered, and patients who are morbidly obese should be offered bariatric surgery. That said, and in view of the still evolving understanding of the causes, consequences and optimal treatment of OSA, further research is warranted to identify which patients should be screened for OSA.
Appendix

Search date: February 28, 2006
Databases searched: OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Library, INAHTA

Database: Ovid MEDLINE(R) <1996 to February Week 3 2006>
Search Strategy:

1 *Sleep Apnea, Obstructive/ (2566)
2 (sleep adj (apnea or apnoea) adj3 (resistance or obstructi$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4828)
3 1 or 2 (4828)
4 exp Polysomnography/ (4943)
5 3 and 4 (1731)
6 limit 5 to (humans and english language and yr="2004 - 2006") (409)
7 (systematic review$ or metaanalysis or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (22113)
8 6 and 7 (2)
9 6 (409)
10 limit 9 to (case reports or comment or editorial or letter or "review") (80)
11 9 not 10 (329)
12 8 or 11 (330)
13 limit 12 to "diagnosis (sensitivity)" (215)

Database: EMBASE <1980 to 2006 Week 08>
Search Strategy:

1 *Sleep Apnea Syndrome/ (7857)
2 (obstructi$ or resistance).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (408404)
3 1 and 2 (5361)
4 exp POLYSOMNOGRAPHY/ (6187)
5 3 and 4 (1929)
6 limit 5 to (human and english language and yr="2004 - 2006") (405)
7 (systematic review$ or metaanalysis or metaanalys$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (36850)
8 6 and 7 (4)
9 6 (405)
10 limit 9 to (editorial or letter or note or "review") (85)
11 Case Report/ (875351)
12 9 not (10 or 11) (288)
13 limit 12 to "diagnosis (sensitivity)" (153)
## Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Apnea-hypopnea index</td>
<td>The sum of apneas and hypopneas per hour of sleep.</td>
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<td>Body habitus</td>
<td>The physique or body build.</td>
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<tr>
<td>Body mass index</td>
<td>An index that relates body weight to height. The body mass index (BMI) is obtained by dividing a person’s weight in kilograms (kg) by their height in meters (m) squared.</td>
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<tr>
<td>Continuous positive airway pressure</td>
<td>A technique of respiratory therapy in which airway pressure is maintained above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilatory circuit.</td>
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<tr>
<td>Obstructive sleep apnea</td>
<td>The repetitive complete obstruction (apnea) or partial obstruction (hypopnea) of the collapsible part of the upper airway during sleep.</td>
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<tr>
<td>Polysomnography</td>
<td>Simultaneous and continuous monitoring of normal and abnormal physiological activity during sleep, including the apnea-hypopnea index (AHI) and respiratory disturbance index (RDI).</td>
</tr>
<tr>
<td>Respiratory disturbance index</td>
<td>The sum of apneas, hypopneas, and abnormal respiratory events per hour of sleep.</td>
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</tbody>
</table>
References


