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Screening and Management of Depression for Adults With Chronic Diseases: An Evidence-Based Analysis

Health Quality Ontario

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About Health Quality Ontario

Health Quality Ontario (HQO) is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. HQO works with clinical experts, scientific collaborators and field evaluation partners to develop and publish research that evaluates the effectiveness and cost-effectiveness of health technologies and services in Ontario.

Based on the research conducted by HQO and its partners, the Ontario Health Technology Advisory Committee (OHTAC) — a standing advisory sub-committee of the HQO Board — makes recommendations about the uptake, diffusion, distribution or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders and policy-makers.

This research is published as part of Ontario Health Technology Assessment Series, which is indexed in CINAHL, EMBASE, MEDLINE, and the Centre for Reviews and Dissemination. Corresponding OHTAC recommendations and other associated reports are also published on the HQO website. Visit http://www.hqontario.ca for more information.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, HQO and/or its research partners 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, HQO collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario add an important dimension to the review. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social, and legal issues relating to the intervention assist in making timely and relevant decisions to optimize patient outcomes.

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

Disclaimer

This report was prepared by HQO or one of its research partners for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research. It also incorporates, when available, Ontario data and information provided by experts and applicants to HQO. It is possible that relevant scientific findings may have been reported since completion of the review. This report is current to the date of the literature review specified in the methods section, if available. This analysis may be superseded by an updated publication on the same topic. Please check the HQO website for a list of all publications: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Abstract

Background

Depression is the leading cause of disability and the fourth leading contributor to the global burden of disease. In Canada, the 1-year prevalence of major depressive disorder was approximately 6% in Canadians 18 and older. A large prospective Canadian study reported an increased risk of developing depression in people with chronic diseases compared with those without such diseases.

Objectives

To systematically review the literature regarding the effectiveness of screening for depression and/or anxiety in adults with chronic diseases in the community setting.

To conduct a non-systematic, post-hoc analysis to evaluate whether a screen-and-treat strategy for depression is associated with an improvement in chronic disease outcomes.

Data Sources

A literature search was performed on January 29, 2012, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, OVID PsycINFO, 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, 2002 until January 29, 2012.

Review Methods

No citations were identified for the first objective. For the second, systematic reviews and randomized controlled trials that compared depression management for adults with chronic disease with usual care/placebo were included. Where possible, the results of randomized controlled trials were pooled using a random-effects model.

Results

Eight primary randomized controlled trials and 1 systematic review were included in the post-hoc analysis (objective 2)—1 in people with diabetes, 2 in people with heart failure, and 5 in people with coronary artery disease. Across all studies, there was no evidence that managing depression improved chronic disease outcomes. The quality of evidence (GRADE) ranged from low to moderate. Some of the study results (specifically in coronary artery disease populations) were suggestive of benefit, but the differences were not significant.

Limitations

The included studies varied in duration of treatment and follow-up, as well as in included forms of depression. In most of the trials, the authors noted a significant placebo response rate that could be attributed to spontaneous resolution of depression or mild disease. In some studies, placebo groups may have had access to care as a result of screening, since it would be unethical to withhold all care.

Conclusions

There was no evidence to suggest that a screen-and-treat strategy for depression among adults with chronic diseases resulted in improved chronic disease outcomes.

Plain Language Summary

People with chronic diseases are more likely to have depression than people without chronic diseases. This is a problem because depression may make the chronic disease worse or affect how a person manages it. Discovering depression earlier may make it easier for people to cope with their condition, leading to better health and quality of life. We reviewed studies that looked at screening and treating for depression in people with chronic diseases. In people with diabetes, treatment of depression did not affect clinical measures of diabetes management. In people with heart failure and coronary artery disease, treatment of depression did not improve heart failure management or reduce rates of heart attacks or death. At present, there is no evidence that screening and treating for depression improves the symptoms of chronic diseases or lead to use of fewer health care services.

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List of Abbreviations

BDI	Beck Depression Inventory
CAD	Coronary artery disease
CBT	Cognitive behavioural therapy
CHF	Congestive heart failure
CI	Confidence interval(s)
CIDI	Composite International Diagnostic Interview
COPD	Chronic obstructive pulmonary disease
DISH	Depression Interview and Structured Hamilton
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
ECG	Electrocardiogram
GAD	Generalized anxiety disorder
HADS	Hospital Anxiety and Depression Scale
HbA1c	Hemoglobin A1c
HRSD	Hamilton Rating Scale for Depression
ITT	Intention-to-treat
LOCF	Last observation carried forward
LVEF	Left ventricular ejection fraction
M-H	Mantel-Haenszel
MI	Myocardial infarction
NR	Not reported
NYHA	New York Heart Association
PRIME-MD	Primary Care Evaluation of Mental Disorders
RCT	Randomized controlled trial
SSRI	Selective serotonin reuptake inhibitor

Background

In July 2011, the Evidence Development and Standards (EDS) branch of Health Quality Ontario (HQO) began developing an evidentiary framework for avoidable hospitalizations. The focus was on adults with at least 1 of the following high-burden chronic conditions: chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), atrial fibrillation, heart failure, stroke, diabetes, and chronic wounds. This project emerged from a request by the Ministry of Health and Long-Term Care for an evidentiary platform on strategies to reduce avoidable hospitalizations.

After an initial review of research on chronic disease management and hospitalization rates, consultation with experts, and presentation to the Ontario Health Technology Advisory Committee (OHTAC), the review was refocused on optimizing chronic disease management in the outpatient (community) setting to reflect the reality that much of chronic disease management occurs in the community. Inadequate or ineffective care in the outpatient setting is an important factor in adverse outcomes (including hospitalizations) for these populations. While this did not substantially alter the scope or topics for the review, it did focus the reviews on outpatient care. HQO identified the following topics for analysis: discharge planning, in-home care, continuity of care, advanced access scheduling, screening for depression/anxiety, self-management support interventions, specialized nursing practice, and electronic tools for health information exchange. Evidence-based analyses were prepared for each of these topics. In addition, this synthesis incorporates previous EDS work, including Aging in the Community (2008) and a review of recent (within the previous 5 years) EDS health technology assessments, to identify technologies that can improve chronic disease management.

HQO partnered with the Programs for Assessment of Technology in Health (PATH) Research Institute and the Toronto Health Economics and Technology Assessment (THETA) Collaborative to evaluate the cost-effectiveness of the selected interventions in Ontario populations with at least 1 of the identified chronic conditions. The economic models used administrative data to identify disease cohorts, incorporate the effect of each intervention, and estimate costs and savings where costing data were available and estimates of effect were significant. For more information on the economic analysis, please contact either Murray Krahn at murray.krahn@theta.utoronto.ca or Ron Goeree at goereer@mcmaster.ca.

HQO also partnered with the Centre for Health Economics and Policy Analysis (CHEPA) to conduct a series of reviews of the qualitative literature on “patient centredness” and “vulnerability” as these concepts relate to the included chronic conditions and interventions under review. For more information on the qualitative reviews, please contact Mita Giacomini at giacomin@mcmaster.ca.

The Optimizing Chronic Disease Management in the Outpatient (Community) Setting mega-analysis series is made up of the following reports, which can be publicly accessed at http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ohtas-reports-and-ohtac-recommendations.

- Optimizing Chronic Disease Management in the Outpatient (Community) Setting: An Evidentiary Framework
- Discharge Planning in Chronic Conditions: An Evidence-Based Analysis
- In-Home Care for Optimizing Chronic Disease Management in the Community: An Evidence-Based Analysis
- Continuity of Care: An Evidence-Based Analysis
- Advanced (Open) Access Scheduling for Patients With Chronic Diseases: An Evidence-Based Analysis
- Screening and Management of Depression for Adults With Chronic Diseases: An Evidence-Based Analysis
- Self-Management Support Interventions for Persons With Chronic Diseases: An Evidence-Based Analysis
- Specialized Nursing Practice for Chronic Disease Management in the Primary Care Setting: An Evidence-Based Analysis
- Electronic Tools for Health Information Exchange: An Evidence-Based Analysis
- Health Technologies for the Improvement of Chronic Disease Management: A Review of the Medical Advisory Secretariat Evidence-Based Analyses Between 2006 and 2011
- Optimizing Chronic Disease Management Mega-Analysis: Economic Evaluation
- How Diet Modification Challenges Are Magnified in Vulnerable or Marginalized People With Diabetes and Heart Disease: A Systematic Review and Qualitative Meta-Synthesis
- Chronic Disease Patients’ Experiences With Accessing Health Care in Rural and Remote Areas: A Systematic Review and Qualitative Meta-Synthesis
- Patient Experiences of Depression and Anxiety With Chronic Disease: A Systematic Review and Qualitative Meta-Synthesis
- Experiences of Patient-Centredness With Specialized Community-Based Care: A Systematic Review and Qualitative Meta-Synthesis

Objective of Analysis

1. To systematically review the literature regarding the effectiveness of screening for depression and/or anxiety in adults with chronic diseases in the community setting.
2. To conduct a non-systematic, post-hoc analysis to evaluate whether a screen-and-treat strategy for depression is associated with an improvement in chronic disease outcomes.

Clinical Need and Target Population

Description of Disease/Condition

Depression

Depressive illness can have a variety of presentations, ranging in both severity and chronicity. (1) According to criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, (2) major depressive disorder is the most severe form, and it consists of an episode of at least 2 weeks in which an individual has 5 of 9 specific depressive symptoms. One of these symptoms must be depressed mood or anhedonia (loss of interest or pleasure). (1) Also, these symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning—a requirement that emphasizes the marked disability resulting from depressive illness.

Depression is recognized by the World Health Organization as the leading cause of disability and the fourth leading contributor to the global burden of disease. (3) Projections suggest that by 2020, depression will be second only to cardiovascular disease as a public health concern. (4) Despite this, depression continues to be under-recognized and undertreated. (4)

Anxiety

Anxiety disorders are usually characterized by excessive fear and subsequent avoidance, typically in response to a specific object or situation and in the absence of true danger. (5;6) Anxiety, like all emotions, has cognitive, neurobiological, and behavioural components. Although it is often comorbid with depressive mood, anxiety is a distinct emotion. (5) Anxiety becomes alarming and burdensome when it increases or persists to such a degree that the individual can no longer function effectively in everyday life; at this stage, anxiety can have negative consequences. Anxiety disorders include panic disorder, phobic anxiety, generalized anxiety disorder, anxiety reactions, and chronic anxiety. (5)

Prevalence

Depression and anxiety are frequently encountered in primary care. The 1994/95 National Population Health Survey (a Canadian longitudinal study that included household residents from all provinces) reported that the 1-year prevalence of major depressive disorder was about 6% for Canadians aged 18 and older. (7) In the United States, point prevalence estimates of major depression range from 4.8% to 8.6% in primary care settings. (1) Anxiety disorders have a high prevalence as well; in the United States, the 12-month rate is 17.2%, and the lifetime rate is about 25%. (8)

In a large prospective Canadian community-based study, (9) Patten and colleagues found an increased risk of major depression in subjects with chronic medical disorders compared to those without such disorders. A total of 4% (95% confidence interval [CI] 3.3–4.7) of those with 1 or more medical conditions developed major depression over a 2-year period, compared to 2.8% (95% CI 2.2–3.4) of those without medical conditions. (9)

The 2005 Canadian Community Health Survey, cycle 3.1, (10) measured the prevalence of comorbid mood disorders among individuals with various chronic medical conditions in Ontario. The highest prevalence was seen among those who had had a stroke (15.5%), followed by those with cardiovascular disease (9.8%) and diabetes mellitus (9.3%). (10)

The estimated prevalence of anxiety and/or depression varies by the type and severity of chronic disease, and by the setting and methodology of screening and diagnosis. Nevertheless, rates are consistently higher across most chronic disease populations compared to the general population, especially for people with stroke, cardiovascular disease, and diabetes. Table 1 provides a range of prevalence estimates based on the literature and survey data.

Table 1: Depression and Anxiety Associated With Selected Chronic Diseases in Ontario

Comorbid Medical Illness	Prevalence, % Canadian Survey Data, Mood Disorders	Prevalence, % Literature	
		Depression	Anxiety
General population	6%[a] (7)	10.3%[a] (8)	17.2%[a] (8)
Stroke	15.5% (10)	5–44% (11) 6–34% (12) 30–36% (13)	GAD: 6–13% (12)
CAD	9.8% (10)	15–20% (14) 20–28% (15)	Panic disorder: 10–50% (16)
Diabetes	9.3% (10)	Self-reported: 26% (17) Diagnostic interview: 9% (17)	GAD: 14% (18)
Heart failure	—	14–26% (19) 25–30% (15)	—
COPD	—	Stable: 10–42% (20) Severe: 37–71% (20)	Stable: 10–19% (20) Severe: 50–75% (20)
Chronic wounds[b]	—	27% (21)	26% (21)

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GAD, generalized anxiety disorder.
[a]1-year prevalence rate.
[b]Chronic venous ulceration.

Technology/Technique

Depression Screening Instruments

Screening is defined as the systematic testing of asymptomatic individuals to detect a potential disease or condition. (22) The purpose of screening is to prevent or delay the development of advanced disease by promoting early detection and treatment in people with preclinical disease. (22)

Screening for depression identifies patients with these conditions, allowing them to access care earlier in the course of their illness. However, despite the potential benefit of screening, it is infrequently conducted; primary care physicians fail to identify an estimated 30% to 50% of patients with depression. (1)

Several depression screening instruments are available for use in the primary care setting; they differ with respect to the time frame they are applied to, the time it takes to administer them, and the discernment of

levels of depression, (23) but most have an adequate level of sensitivity and specificity. They are composed of standardized questions that assess the number and severity depression symptoms and they have been designed for administration in a variety of ways by a range of healthcare providers. A positive screening result requires further diagnostic questioning to establish an appropriate diagnosis and initiate treatment and follow-up. (24)

Depression Screening for Adults With Chronic Diseases

Given the prevalence of depression, a number of clinical groups have developed recommendations for screening practices, for both the general population and disease-specific groups: diabetes, chronic obstructive pulmonary disease (COPD), stroke, and coronary artery disease (CAD) (see Existing Guidelines for Depression Screening, page 26).

Evidence-Based Analysis

Research Questions

Question 1 (Initial Review)

What is the effectiveness of screening for depression and/or anxiety in adults with chronic diseases in the community setting?

Question 2 (Post-Hoc Review)

In a chronic disease population, is a screen-and-treat strategy for depression associated with an improvement in chronic disease outcomes?

Research Methods

Literature Search (Initial Review)

Search Strategy

A literature search was performed on January 29, 2012, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, OVID PsycINFO, 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, 2002, until January 29, 2012. A 10-year interval was selected to better reflect current screening and treatment protocols. Titles and 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

English language full-reports

- addressing 1 or more chronic illnesses:
  - atrial fibrillation
  - CAD
  - chronic wounds
  - COPD
  - diabetes
  - heart failure
  - stroke
- community or outpatient setting
- adult population (aged 18 and older)
- published between January 1, 2002, and January 29, 2012 (10-year interval)
- randomized controlled trials (RCTs), systematic reviews, meta-analyses, and observational studies

Exclusion Criteria

- psychiatric conditions: bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, psychotic symptoms, active substance abuse, and active suicidal ideation
- developmental or acquired neuropsychological impairment
- child and adolescent populations
- abstracts, letters, editorials, case series, case reports, comments

Outcomes of Interest

Patient-Specific Outcomes

- disease-specific clinical outcomes (e.g., hemoglobin A1c [HbA1c], cholesterol)
- health-related quality of life
- functional status
- patient satisfaction
- survival/mortality

Health System Outcomes

- acute care hospital admissions and readmissions
- emergency department visits
- length of stay in hospital long-term care admissions

Revised Search (Post-Hoc Review)

For the post-hoc review, the initial search strategy was used, but it was limited to a 5-year publication interval (January 1, 2007, to January 29, 2012). A 5-year interval was chosen because of recent developments and enhancements in screening tools for depression, and because of the substantial body of literature on depression management.

RCTs, systematic reviews, and meta-analyses were included in which participants were screened using a validated tool; deemed to have to have significant levels of depression; and then received some form of depression treatment.

Statistical Analysis

Question 1 (Initial Review)

No studies were found that addressed question 1.

Question 2 (Post-Hoc Review)

Data from clinical trials were available for 3 disease populations: adults with diabetes (1 study), adults with heart failure (2 studies), and adults with CAD (5 studies and 1 systematic review). Outcomes were analyzed by disease-specific subpopulation. Descriptive analyses were reported for clinical outcomes in the diabetes and heart failure populations and for some outcomes in the CAD population. Rates of recurrent myocardial infarction (MI) and death in the CAD population underwent meta-analysis. Meta-analyses were performed using Review Manager 5.1.7 (25) and a random-effects model.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (26) The overall quality was determined to be very low, low, moderate, or high using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that RCTs are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations or serious limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose response gradient, and accounting for all residual confounding factors. (26) For more detailed information, please refer to the latest series of GRADE articles. (26)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	Very confident that the true effect lies close to the estimate of the effect
Moderate	Moderately confident in the effect estimate—the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Confidence in the effect estimate is limited—the true effect may be substantially different from the estimate of the effect
Very Low	Very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Evidence-Based Analysis

Question 1 (Initial Review)

Eligible articles assessing the effect of depression and/or anxiety screening on chronic disease outcomes included RCTs and observational studies that compared chronic disease outcomes between patients who underwent depression and/or anxiety screening and patients who did not undergo screening.

The database search yielded 6,267 citations published between January 1, 2002, and January 29, 2012 (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.

No articles met the eligibility criteria, and no unpublished studies were identified.

Studies were excluded because of population, intervention, study outcomes, lack of use of a validated screening tool, and study type.

Question 2 (Post-Hoc Review)

Eligible articles assessed the effect of a screen-and-treat strategy for depression on chronic disease outcomes in a chronic disease population. RCTs were included where all patients were screened for

depression using a validated instrument and then randomized to depression treatment or placebo/usual care. Since the intention behind the review was to determine whether management of depression could affect chronic disease outcomes in a chronic disease population, outcomes that could have been directly improved with management of depression (e.g., quality of life) were excluded from the analysis.

The revised database search yielded 1,588 citations published between January 1, 2007, and January 29, 2012 (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.

Seven studies (6 RCTs and 1 systematic review) met the inclusion criteria. The reference lists of the included studies and health technology assessment websites were hand searched to identify any additional potentially relevant studies, and 2 additional studies (RCTs) were included, for a total of 9 included citations.

The 2 additional studies came from the systematic review on depression management in a CAD population. These studies preceded the early cut-off date but were included because they were considered to be seminal studies in the area.

Studies were excluded because of population, setting, intervention, study outcomes, study type, lack of initial screening for depression, and treatment for chronic disease (not for depression).

The remainder of this report focuses on the findings of the post-hoc analysis. For each included study, the study design was identified and is summarized below in Table 2, which is a modified version of a hierarchy of study design by Goodman. (27)

Table 2: Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	1
Large RCT[a]	5
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	9

Abbreviation: RCT, randomized controlled trial.
[a]Large RCT was defined as a trial with more than 100 patients.

Study Descriptions

One systematic review (28) and 8 primary studies (29-36) evaluated the impact of depression management on chronic disease outcomes.

The systematic review (28) evaluated the potential benefits of depression screening in patients with CAD. The authors assessed the accuracy of screening instruments and the effect of depression screening and treatment on cardiac outcomes.

Of the 8 primary studies, 1 was in a diabetes population, (29) 2 were in heart failure populations, (30;31) and 5 were in CAD populations. (32-36) Four of the studies explored changes in depression status, (30;31;35;36) and the other 4 evaluated the effect of depression management on chronic disease measures (including clinical measures and event rates). (29;32-34) Appendix 2 presents a full description of the included primary studies.

Study Results

Diabetes

One study evaluated the effect on glycemic control (HbA1c) of depression management using paroxetine. (29) Three months after commencing treatment, there was a significantly greater improvement in glycemic control in the treated group compared to the control group, but the difference between groups was not significant at 6 months (Table 3). The between-group difference at 3 months was not adjusted for baseline differences.

The authors also measured changes in depression status from baseline (using the Hospital Anxiety and Depression Scale [HADS]). Differences between the treatment and placebo groups at 3 and 6 months were not significant, suggesting that treatment with paroxetine was not better than placebo at improving depression status. (29)

Table 3: Diabetes and Depression Outcomes at Baseline, 3, and 6 Months

Follow-up Interval	Mean Difference, Placebo vs. Treatment (*P* value)	
	Glycemic Control, HbA1c	Depression Outcome, HADS score
Baseline	0.5 (0.17)	1.8 (0.33)
3 months	0.6 (0.02)	2.8 (0.07)
6 months	0.1 (0.70)	1.9 (0.35)

Abbreviations: HbA1c, hemoglobin A1c; HADS, Hospital Anxiety and Depression Scale.
Source: Paile-Hyvarinen et al, 2003(29).

For patients with diabetes and mild depression, medication management of depression did not significantly improve clinical measures of either diabetes or depression (quality of evidence: low).

Heart Failure

Two studies evaluated the safety and efficacy of depression management in patients with heart failure. One measured the safety and tolerability of citalopram using changes in cardiopulmonary performance and oxygen consumption. (31) The other used a composite measure of cardiac status[1] and evaluated change in status from baseline as well as reporting individual event rates for participants. (30) Both measured change in depression status using the Hamilton Rating Scale for Depression (HRSD).

Neither study was able to demonstrate that depression treatment had a significant effect on either heart failure or depression outcomes (Table 4). Both reported significant improvements in depression scores compared to baseline in both the treatment and control arms (suggestive of high placebo response rates).

Table 4: Heart Failure and Depression Outcomes

Study	Heart Failure Outcomes	Depression Outcome
Fraguas et al, 2009 (31)[a]	No difference between treatment and placebo arms at baseline or end of treatment in terms of cardiopulmonary performance on exercise test or peak oxygen consumption (*P* = NR)	HRSD scores improved for treatment (–9.7) and control (–9.2), but the between-group difference was not significant (*P* = 0.80) 68% of patients in the treatment arm and 56% of patients in the placebo arm were in remission; remission status did not differ between arms (*P* = 0.46)
O'Conner et al, 2010 (30)	Change in cardiac status did not differ between arms (*P* = 0.78) Cardiovascular events: • End of treatment (12 weeks) o All-cause mortality: treatment 7.7%, placebo 6.8% (*P* = 0.58) o Nonfatal cardiovascular event: treatment 20.1%, placebo 23.0% (*P* = 0.39) • Long-term follow-up (minimum 6 months) o All cause mortality: treatment 29.1%, placebo 26% (*P* = NR)	HRSD scores improved significantly for treatment (–7.1) and control (–6.8) (*P* < 0.001), but the between-group difference was not significant (*P* = 0.89)

Abbreviations: HRSD, Hamilton Rating Scale for Depression; NR, not reported.
[a]This was a safety study; heart failure outcomes were assessed to identify adverse events. (31)

Both studies offered some form of counselling support to the treatment and control arms, and both studies reported high placebo response rates, which may have been due to accompanying counselling or suggestive of tractable illness. Both studies included patients with mild depression; their depression may have not been severe enough to respond to pharmacotherapy, or their acute episode may have resolved more readily.

For patients with heart failure and depression (including mild depression), medication management of depression did not significantly improve clinical measures of heart failure or reduce mortality or morbidity rates (quality of evidence for hospitalization or death: moderate; quality of evidence for cardiopulmonary performance: low).

[1]Composite cardiovascular status measured as (30):

- worsened (any of): all-cause death, occurrence of a primary cardiovascular event, complications of cardiac medications or procedures, discontinuation of trial drugs for cardiovascular reasons, or increase (worsening) in New York Heart Association functional class
- improved: no worsening and at least 1 of improvement in New York Heart Association functional class or improvement in heart failure status based on Clinical Global Impression scale
- unchanged

Coronary Artery Disease

Systematic Review

Thombs et al (28) published a systematic review of depression screening and patient outcomes in a CAD population. Their objective was to evaluate the potential benefits of screening in patients with CAD by assessing the following:

- the accuracy of depression screening instruments
- the effect of depression screening on both depression and cardiac outcomes
- the effect of depression treatment on both depression and cardiac outcomes

The review did not report findings related to the sensitivity of depression screening instruments.

The authors identified 6 depression treatment trials in a CAD population, but no studies that evaluated the effects of depression screening on cardiac outcomes. They found that depression treatment with medication or cognitive behavioural therapy resulted in modest reductions in depressive symptoms (effect size 0.20–0.38; r^2 1%–4%), but there was no evidence that depression treatment improved cardiac outcomes. (28)

Primary Studies

Five studies evaluated the effect of depression management on CAD outcomes (Table 5).

Table 5: CAD Outcomes Reported in Primary Studies

Author, Year	LVEF	Composite Cardiac Outcome[a]	Death	MI	ECG
ENRICHD, 2003 (34)		X	X	X	
Glassman et al, 2002 (32)	X	X	X	X	
Honig et al, 2007 (35)					X
Lesperance et al, 2007 (36)		X		X	X
Van Melle et al, 2007 (33)		X			

Abbreviations: CAD, coronary artery disease; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

[a]The ENRICHD study included a composite outcome measure of death or nonfatal MI; Glassman et al included a composite measure of death, MI, heart failure, stroke, and angina; Lesperance et al included a composite measure of serious adverse events, including MI, heart failure, worsening angina, stroke, and other CAD-related events; van Melle et al included a comparison of composite cardiac event rates, including cardiac death, recurrent MI, revascularization, heart failure, ischemia, and arrhythmia.

One study measured changes in left ventricular ejection fraction (LVEF) as the primary cardiac outcome. (32) After 16 weeks of treatment with sertraline or placebo, the authors reported no significant difference in either change in LVEF from baseline or the proportion of patients with an LVEF < 30% (*P* values not reported) (quality of evidence: moderate). (32)

Two studies measured changes in electrocardiogram (ECG) findings from baseline as the primary cardiac outcome. (35;36) Lesperance et al (36) evaluated the safety of citalopram versus placebo for patients with CAD and reported the change in ECG findings after 12 weeks of treatment. The authors included a number of measures of cardiac safety and reported no significant differences between the treatment and placebo groups (*P* values ranged from 0.15 to 0.80) (quality of evidence: low). Similarly, Honig et al, (35) in their evaluation of the safety of mirtazapine, included ECG safety measures and also reported no significant changes from baseline (*P* values not reported) (quality of evidence: low).

Four of the 5 studies (32-34;36) reported a composite measure of cardiac outcomes, but no 2 studies reported the same set of outcomes, precluding meta-analysis. Event rates varied based on differences in

definitions and follow-up intervals, but confidence intervals from the 4 studies overlapped. One study reported an odds ratio that was suggestive of an overall protective effect with depression treatment, (32) and 1 reported an odds ratio indicative of increased risk of adverse events with treatment. (33) The other 2 reported odds ratios of 1.0 for the composite outcomes. (34;36) Table 6 describes the composite outcome measures, follow-up intervals, and event rates from each study.

Table 6: Composite Cardiac Outcome Measures for CAD Patients Screened and Treated for Depression

Author, Year	Composite Measure	Follow-up	Event Rate, % (n)		Odds Ratio
			Treatment	Control	
ENRICHD, 2003 (34)	MI, death	18 months (minimum) 29 months (mean)	24.2 (1,238)	24.1 (1,243)	1.0 (0.9–1.2)
Glassman et al, 2002[a] (32)	MI, heart failure, stroke, angina, death	24 weeks	17.2 (186)	22.4 (183)	0.8 (0.5–1.2)
Lesperance et al, 2007[a] (36)	MI, heart failure, stroke, worsening angina, other CAD-related events	12 weeks	4.2 (142)	4.2 (142)	1.0 (0.3–3.2)
Van Melle et al, 2007[a] (33)	MI, heart failure, ischemia, arrhythmia, revascularization, cardiac death	18 months	13.8 (196)	12.7 (118)	1.1 (0.6–2.2)

Abbreviations: CAD, coronary artery disease; MI, myocardial infarction.
[a]Proportion with at least 1 event.

Data on MI rates were available for 3 studies and a total of 1,566 participants. (32;34;36) The results of the meta-analysis (Figure 1) suggest a protective effect of depression management, but the difference between groups was not significant (quality of evidence: moderate).

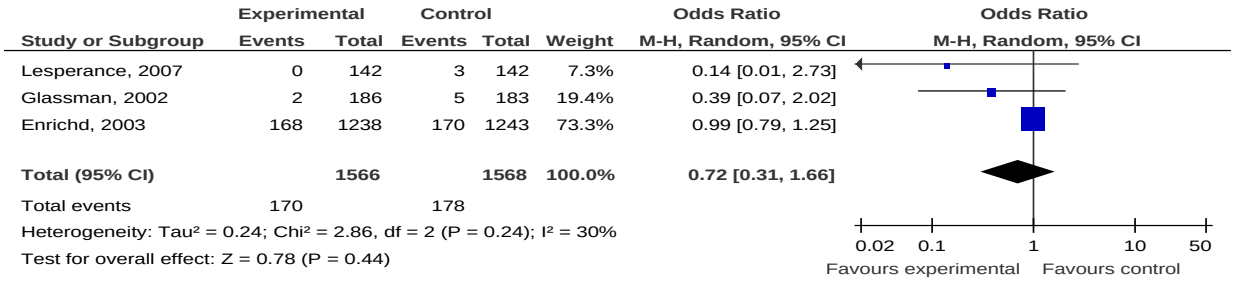

Figure 1: Myocardial Infarction Rates for Treatment Versus Placebo Arms

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Data on mortality were available for 2 studies and a total of 1,424 participants. (32;34) The results of the meta-analysis (Figure 2) suggest a slight protective effect of depression management, but the difference between groups was not significant (quality of evidence: moderate).

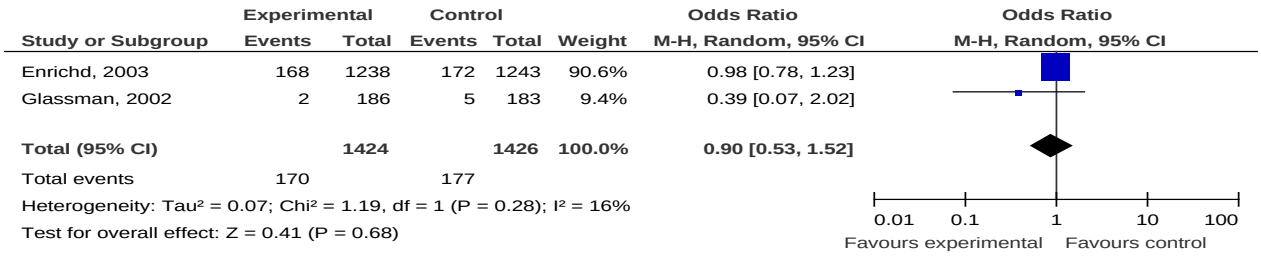

Figure 2: Mortality Rates for Treatment Versus Placebo Arms

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

For patients with CAD and depression (including mild depression), medication management of depression did not significantly affect clinical measures of cardiac status, MI rates, or mortality compared to placebo or usual care (quality of evidence: low to moderate).

Conclusions

Question 1 (Initial Review)

This systematic review did not identify any studies that investigated the effect of depression and/or anxiety screening on chronic disease outcomes in a chronic disease population.

Question 2 (Post-Hoc Review)

- For patients with diabetes and mild depression, medication management of depression did not significantly improve clinical measures (HbA1c) of diabetes; the quality of the evidence was low.
- For patients with heart failure and depression (including mild depression), medication management of depression did not significantly affect (improve or worsen) the following:
    - ECG findings; the quality of the evidence was low
    - cardiac event rates; the quality of the evidence was moderate
    - mortality; the quality of the evidence was moderate
- For patients with CAD and depression (including mild depression), medication management of depression did not significantly affect (improve or worsen) the following:
    - ECG findings; the quality of the evidence was low
    - the percentage of patients with reduced LVEF (< 30%); the quality of the evidence was moderate
- For patients with CAD and depression (including mild depression), medication management of depression appeared to have a potentially protective (although not statistically significant) effect on the following:
    - MI rates; the quality of evidence was moderate
    - mortality; the quality of evidence was moderate

Existing Guidelines for Depression Screening

Population	Organization, Year	Recommendations
Adults in primary care	Canadian Task Force on Preventive Health Care, 2005 (37)	• There is fair evidence to recommend screening adults in the general population for depression in primary care settings that have integrated programs for feedback to patients and access to case management or mental health care • There is insufficient evidence to recommend for or against screening adults in the general population for depression in primary care settings where effective follow-up and treatment are not available
Adults with diabetes	Canadian Diabetes Association, 2008 (38)	• Individuals with diabetes should be regularly screened for subclinical psychological distress and psychiatric disorders (e.g., depressive and anxiety disorders) by interview or with a standardized questionnaire • Patients diagnosed with depression, anxiety, or eating disorders should be referred to mental health professionals who are either part of the diabetes team or are in the community. Those diagnosed with depression should be offered treatment with CBT and/or antidepressant medication • Multidisciplinary team members with required expertise should offer CBT-based techniques, such as stress management strategies and coping skills training, family behaviour therapy, and case management to improve glycemic control and/or psychological outcomes in individuals with suboptimal self-care behaviours, suboptimal glycemic control and/or psychological distress
Adults with COPD	Global Initiative for Chronic Obstructive Lung Disease, 2007 (39)	• New COPD patients should have a detailed medical history including an "assessment of feelings of depression or anxiety"
Adults with stroke	American Heart Association/ American Stroke Association, 2005 (40)	*Assessment* • The Working Group recommends using a structured inventory to assess specific psychiatric symptoms and monitor symptom change over time *Treatment* • The Working Group strongly recommends that patients with a diagnosed depressive disorder be given a trial of antidepressant medication, if no contraindication exists; side effect profiles suggest that SSRIs may be favoured in this patient population. There is insufficient evidence to recommend for or against the use of individual psychotherapy alone in the treatment of post-stroke depression • Routine use of prophylactic antidepressants is not recommended in post-stroke rehabilitation • Recommend that mood disorders causing persistent distress or worsening disability be managed by, or with the advice of, an experienced clinical psychologist or psychiatrist
Adults with CAD or heart failure	American Heart Association, 2008 (41)	• Routine screening for depression in patients with CAD in various settings, including the hospital, physician's office, clinic, and cardiac rehabilitation centre • Patients with positive screening results should be evaluated by a professional qualified in the diagnosis and management of depression

Abbreviations: CAD, coronary artery disease; CBT, cognitive behavioural therapy; COPD, chronic obstructive pulmonary disease; SSRI, selective serotonin reuptake inhibitor.

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Expert Panel for Health Quality Ontario: Optimizing Chronic Disease Management in the Community (Outpatient) Setting

Name	Title	Organization
Shirlee Sharkey (chair)	President & CEO	Saint Elizabeth Health Care
Theresa Agnew	Executive Director	Nurse Practitioners' Association of Ontario
Onil Bhattacharrya	Clinician Scientist	Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto
Arlene Bierman	Ontario Women's Health Council Chair in Women's Health	Department of Medicine, Keenan Research Centre in the Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto
Susan Bronskill	Scientist	Institute for Clinical Evaluative Sciences
Catherine Demers	Associate Professor	Division of Cardiology, Department of Medicine, McMaster University
Alba Dicenso	Professor	School of Nursing, McMaster University
Mita Giacomini	Professor	Centre of Health Economics & Policy Analysis, Department of Clinical Epidemiology & Biostatistics
Ron Goeree	Director	Programs for Assessment of Technology in Health (PATH) Research Institute, St. Joseph's Healthcare Hamilton
Nick Kates	Senior Medical Advisor	Health Quality Ontario – QI McMaster University Hamilton Family Health Team
Murray Krahn	Director	Toronto Health Economics and Technology Assessment (THETA) Collaborative, University of Toronto
Wendy Levinson	Sir John and Lady Eaton Professor and Chair	Department of Medicine, University of Toronto
Raymond Pong	Senior Research Fellow and Professor	Centre for Rural and Northern Health Research and Northern Ontario School of Medicine, Laurentian University
Michael Schull	Deputy CEO & Senior Scientist	Institute for Clinical Evaluative Sciences
Moira Stewart	Director	Centre for Studies in Family Medicine, University of Western Ontario
Walter Wodchis	Associate Professor	Institute of Health Management Policy and Evaluation, University of Toronto

Appendices

Appendix 1: Literature Search Strategies

Search date: January 29th, 2012
Databases searched: OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, OVID PsycINFO, Wiley Cochrane, EBSCO CINAHL, Centre for Reviews and Dissemination

Limits: 2002-current; English; Human; NOT comments, editorials, letters, conference abstracts (Embase)

Database: Ovid MEDLINE(R) <1946 to January Week 3 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 27, 2012>, Embase <1980 to 2012 Week 04>
Search Strategy:

#	Searches	Results
1	exp Coronary Artery Disease/	212075
2	exp Myocardial Infarction/ use mesz	133578
3	exp heart infarction/ use emez	216992
4	(coronary artery disease or cad or heart attack).ti.	44463
5	((myocardi* or heart or cardiac or coronary) adj2 (atheroscleros* or arterioscleros* or infarct*)).ti.	149559
6	or/1-5	539975
7	exp Atrial Fibrillation/ use mesz	28093
8	exp heart atrium fibrillation/ use emez	55522
9	((atrial or atrium or auricular) adj1 fibrillation*).ti,ab.	73540
10	or/7-9	99451
11	exp heart failure/	300981
12	((myocardi* or heart or cardiac) adj2 (failure or decompensation or insufficiency)).ti,ab.	234590
13	11 or 12	381953
14	exp Stroke/	178088
15	exp Ischemic Attack, Transient/ use mesz	16370
16	exp transient ischemic attack/ use emez	19680
17	exp stroke patient/ use emez	5637
18	exp brain infarction/ or exp cerebrovascular accident/ use emez	101006
19	(stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA).ti,ab.	281375
20	or/14-19	391798
21	exp Diabetes Mellitus, Type 2/ use mesz	68223
22	exp non insulin dependent diabetes mellitus/ use emez	101711
23	exp diabetic patient/ use emez	12920
24	(diabetes or diabetic* or niddm or t2dm).ti,ab.	765351
25	or/21-24	790292
26	exp Skin Ulcer/	72073
27	((pressure or bed or skin) adj2 (ulcer* or sore* or wound*)).ti,ab.	28723
28	(decubitus or bedsore*).ti,ab.	8532
29	or/26-28	90816
30	exp Pulmonary Disease, Chronic Obstructive/ use mesz	17049
31	exp chronic obstructive lung disease/ use emez	54779

32	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab.	54491
33	(copd or coad).ti,ab.	45716
34	chronic airflow obstruction.ti,ab.	1063
35	exp Emphysema/	37444
36	exp chronic bronchitis/ use emez	6985
37	((chronic adj2 bronchitis) or emphysema).ti,ab.	50848
38	or/30-37	159366
39	exp Chronic Disease/	340792
40	((chronic* adj2 disease*) or (chronic* adj2 ill*)).ti,ab.	220217
41	39 or 40	506604
42	exp Comorbidity/	143585
43	(comorbid* or comorbid* or multimorbid* or multi-morbid* or (complex* adj patient*) or "patient* with multiple" or (multiple adj2 (condition* or disease*))).ti.	36006
44	42 or 43	165120
45	6 or 10 or 13 or 20 or 25 or 29 or 38 or 41 or 44	2731842
46	exp *Depression/ use mesz	35805
47	exp *Depressive Disorder/ use mesz	53384
48	exp *Depression/ use emez	135637
49	(depression* or depressive*).ti.	161961
50	exp *Anxiety/ use mesz	22426
51	exp *Anxiety Disorders/ use mesz	44663
52	exp *Anxiety/ or exp *Anxiety Disorder/ use emez	112134
53	anxiety.ti.	56051
54	or/46-53	388835
55	*Mass Screening/ use mesz	36995
56	exp *Psychological Tests/ use mesz	50572
57	exp *Psychiatric Status Rating Scales/ use mesz	7863
58	exp *Interview, Psychological/ use mesz	2348
59	*Severity of Illness Index/ use mesz	9347
60	*Diagnostic Self Evaluation/ use mesz	147
61	exp *Screening/ use emez	91617
62	exp *Psychologic Test/ use emez	40337
63	*Self Evaluation/ use emez	3049
64	((depression* or depressive* or anxiety or anxieties) adj2 (assessment? or detect* or diagnos* or inventor* or scale? or screen* or self-assessment? or test*)).ti,ab.	84893
65	case-finding.ti.	1646
66	or/55-65	318547
67	45 and 54 and 66	9461
68	((((cardiovascular or cardio-vascular) adj (care or disease?)) or heart disease?) adj5 (depression* or depressive* or anxiety or anxieties) adj5 (assessment? or detect* or diagnos* or inventor* or scale? or screen* or self-assessment? or test*)).ti,ab.	127
69	67 or 68	9553
70	Case Reports/ or Comment.pt. or Editorial.pt. or Letter.pt. use mesz	2912209
71	Case Report/ or Editorial/ or Letter/ or Conference Abstract.pt. use emez	5806576
72	or/70-71	5911444
73	69 not 72	8769
74	limit 73 to english language	7907
75	limit 74 to human	7706
76	limit 75 to humans	7706

77	from 74 keep 3919-4050	132
78	76 or 77	7838
79	limit 78 to yr="2002 - Current"	5896
80	remove duplicates from 79 Ovid MEDLINE(R) <1946 to January Week 3 2012> (2780) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 27, 2012> (121) Embase <1980 to 2012 Week 04> (1098)	3999

Database: Ovid PsycINFO <2002 to January Week 4 2012>
Search Strategy:

#	Searches	Results
1	exp heart disorders/	5124
2	(coronary artery disease or cad or heart attack).ti.	233
3	((myocardi* or heart or cardiac or coronary) adj2 (atherosclerosis* or arteriosclerosis* or infarct*)).ti.	545
4	or/1-3	5197
5	"fibrillation (heart)"/	203
6	((atrial or atrium or auricular) adj1 fibrillation*).ti,ab.	341
7	or/5-6	407
8	((myocardi* or heart or cardiac) adj2 (failure or decompensation or insufficiency)).ti,ab.	1410
9	cerebrovascular accidents/	7280
10	exp cerebral ischemia/	1853
11	(stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA).ti,ab.	11207
12	or/9-11	12555
13	diabetes mellitus/	1919
14	(diabetes or diabetic* or niddm or t2dm).ti,ab.	10497
15	or/13-14	10530
16	((pressure or bed or skin) adj2 (ulcer* or sore* or wound*)).mp.	312
17	(decubitus or bedsore*).mp.	48
18	or/16-17	354
19	exp chronic obstructive pulmonary disease/	372
20	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab.	781
21	(copd or coad).ti,ab.	556
22	chronic airflow obstruction.ti,ab.	1
23	((chronic adj2 bronchitis) or emphysema).ti,ab.	128
24	or/19-23	1000
25	exp chronic illness/	10726
26	((chronic* adj2 disease*) or (chronic* adj2 ill*)).ti,ab.	8934
27	or/25-26	16734
28	comorbidity/	12514
29	(comorbid* or comorbid* or multimorbid* or multi-morbid* or (complex* adj patient*) or "patient* with multiple" or (multiple adj2 (condition* or disease*))).ti.	4442
30	or/28-29	13151
31	4 or 7 or 8 or 12 or 15 or 18 or 24 or 27 or 30	54577
32	exp "depression (emotion)"/	3561
33	(depression* or depressive*).ti.	30687
34	or/32-33	32592

35	exp anxiety/	18060
36	exp anxiety disorders/	26934
37	anxiety.ti.	13893
38	or/35-37	42510
39	exp screening/	8742
40	exp screening tests/	1707
41	exp psychological screening inventory/	16
42	exp psychological assessment/	14264
43	exp psychiatric evaluation/	2459
44	exp psychodiagnosis/	3503
45	exp psychodiagnostic interview/	588
46	self evaluation/	2247
47	((depression* or depressive* or anxiety or anxieties) adj2 (assessment? or detect* or diagnos* or inventor* or scale? or screen* or self-assessment? or test*)).mp.	56141
48	case-finding.ti.	47
49	or/39-48	84741
50	((((cardiovascular or cardio-vascular) adj (care or disease?)) or heart disease?) adj5 (depression* or depressive* or anxiety or anxieties) adj5 (assessment? or detect* or diagnos* or inventor* or scale? or screen* or self-assessment? or test*)).ti,ab.	30
51	(31 and (34 or 38) and 49) or 50	3131
52	limit 51 to (human and english language)	2880
	limit 52 to yr="2002 -Current"	
53		2877

PsycINFO 2002 to January Week 5 2012

#	Searches	Results
1	exp heart disorders/	5156
2	(coronary artery disease or cad or heart attack).ti.	234
3	((myocardi* or heart or cardiac or coronary) adj2 (atheroscleros* or arterioscleros* or infarct*)).ti.	546
4	or/1-3	5229
5	"fibrillation (heart)"/	208
6	((atrial or atrium or auricular) adj1 fibrillation*).ti,ab.	344
7	or/5-6	413
8	((myocardi* or heart or cardiac) adj2 (failure or decompensation or insufficiency)).ti,ab.	1419
9	cerebrovascular accidents/	7321
10	exp cerebral ischemia/	1867
11	(stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA).ti,ab.	11269
12	or/9-11	12627
13	diabetes mellitus/	1920
14	(diabetes or diabetic* or niddm or t2dm).ti,ab.	10532
15	or/13-14	10565
16	((pressure or bed or skin) adj2 (ulcer* or sore* or wound*)).mp.	313
17	(decubitus or bedsore*).mp.	48
18	or/16-17	355
19	exp chronic obstructive pulmonary disease/	373
20	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab.	782

21	(copd or coad).ti,ab.	556
22	chronic airflow obstruction.ti,ab.	1
23	((chronic adj2 bronchitis) or emphysema).ti,ab.	128
24	or/19-23	1001
25	exp chronic illness/	10757
26	((chronic* adj2 disease*) or (chronic* adj2 ill*)).ti,ab.	8955
27	or/25-26	16783
28	comorbidity/	12556
29	(comorbid* or comorbid* or multimorbid* or multi-morbid* or (complex* adj patient*) or "patient* with multiple" or (multiple adj2 (condition* or disease*))).ti.	4457
30	or/28-29	13198
31	4 or 7 or 8 or 12 or 15 or 18 or 24 or 27 or 30	54791
32	exp "depression (emotion)"/	3565
33	(depression* or depressive*).ti.	30769
34	or/32-33	32677
35	exp anxiety/	18097
36	exp anxiety disorders/	26977
37	anxiety.ti.	13914
38	or/35-37	42585
39	exp screening/	8771
40	exp screening tests/	1708
41	exp psychological screening inventory/	16
42	exp psychological assessment/	14316
43	exp psychiatric evaluation/	2470
44	exp psychodiagnosis/	3506
45	exp psychodiagnostic interview/	590
46	self evaluation/	2256
47	((depression* or depressive* or anxiety or anxieties) adj2 (assessment? or detect* or diagnos* or inventor* or scale? or screen* or self-assessment? or test*)).mp.	56357
48	case-finding.ti.	47
49	or/39-48	85043
50	((((cardiovascular or cardio-vascular) adj (care or disease?)) or heart disease?) adj5 (depression* or depressive* or anxiety or anxieties) adj5 (assessment? or detect* or diagnos* or inventor* or scale? or screen* or self-assessment? or test*)).ti,ab.	30
51	(31 and (34 or 38) and 49) or 50	3138
52	limit 51 to (human and english language)	2887
53	limit 52 to yr="2002 -Current"	2884

CINAHL

#	Query	Limiters/Expanders	Results
S54	S51 or S52	Limiters - Published Date from: 20020101-20121231; English Language; Exclude MEDLINE records; Human Search modes - Boolean/Phrase	343
S53	S51 or S52	Search modes - Boolean/Phrase	4354
S52	((((cardiovascular or cardio-vascular) N1 (care or disease*)) or heart disease*) N5 (depression* or depressive* or anxiety or anxieties) N5 (assessment* or detect* or diagnos* or inventor* or scale* or screen* or self-assessment* or test*))	Search modes - Boolean/Phrase	32

S51	S34 and S40 and S50	Search modes - Boolean/Phrase	4329
S50	S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49	Search modes - Boolean/Phrase	85757
S49	TI case-finding	Search modes - Boolean/Phrase	99
S48	((depression* OR depressive* OR anxiety OR anxieties) N2 (assessment* OR detect* OR diagnos* OR inventor* OR scale* OR screen* OR self-assessment* OR test*))	Search modes - Boolean/Phrase	21939
S47	(MH "Self Assessment")	Search modes - Boolean/Phrase	3943
S46	(MH "Severity of Illness Indices+")	Search modes - Boolean/Phrase	16574
S45	(MH "Hamilton Rating Scale for Depression") OR (MH "Self-Rating Anxiety Scale") OR (MH "Self-Rating Depression Scale")	Search modes - Boolean/Phrase	1281
S44	(MH "Neuropsychological Tests") OR (MH "Psychological Tests")	Search modes - Boolean/Phrase	44945
S43	(MH "Health Screening (Iowa NIC)")	Search modes - Boolean/Phrase	2
S42	(MH "Mental Health Care (Saba CCC)+")	Search modes - Boolean/Phrase	5
S41	(MH "Health Screening")	Search modes - Boolean/Phrase	14895
S40	S35 or S36 or S37 or S38 or S39	Search modes - Boolean/Phrase	57836
S39	TI anxiety	Search modes - Boolean/Phrase	5561
S38	(MH "Anxiety Disorders+")	Search modes - Boolean/Phrase	12833
S37	(MH "Anxiety+")	Search modes - Boolean/Phrase	12572
S36	TI depression* OR depressive*	Search modes - Boolean/Phrase	21304
S35	(MH "Depression+")	Search modes - Boolean/Phrase	36357
S34	S5 OR S8 OR S11 OR S15 OR S19 OR S22 OR S27 OR S30 OR S33	Search modes - Boolean/Phrase	221088
S33	S31 OR S32	Search modes - Boolean/Phrase	28945
S32	comorbid* OR comorbid* OR multimorbid* OR multi-morbid* OR (complex* N1 patient*) OR "patient* with multiple" OR (multiple N2 (condition* OR disease*))	Search modes - Boolean/Phrase	28945
S31	(MH "Comorbidity")	Search modes - Boolean/Phrase	16646
S30	S28 OR S29	Search modes - Boolean/Phrase	43734
S29	(chronic* N2 disease*) OR (chronic* N2 ill*)	Search modes - Boolean/Phrase	43734
S28	(MH "Chronic Disease")	Search modes - Boolean/Phrase	23647
S27	S23 OR S24 OR S25 OR S26	Search modes - Boolean/Phrase	8774
S26	chronic N2 bronchitis OR emphysema	Search modes - Boolean/Phrase	1820
S25	(MH "Emphysema")	Search modes - Boolean/Phrase	885
S24	chronic obstructive N2 disease* OR chronic obstructive N2 disorder* OR copd OR coad	Search modes - Boolean/Phrase	7349
S23	(MH "Pulmonary Disease, Chronic Obstructive+")	Search modes - Boolean/Phrase	5342
S22	S20 OR S21	Search modes - Boolean/Phrase	16179
S21	pressure N1 ulcer* OR bedsore* OR bed N1 sore* OR skin N1 ulcer* OR pressure N1 wound* OR decubitus	Search modes - Boolean/Phrase	9574
S20	(MH "Skin Ulcer+")	Search modes - Boolean/Phrase	14845
S19	S16 OR S17 OR S18	Search modes - Boolean/Phrase	70185
S18	diabetes OR diabetic* OR niddm OR t2dm	Search modes - Boolean/Phrase	70185
S17	(MH "Diabetic Patients")	Search modes - Boolean/Phrase	3536

S16	(MH "Diabetes Mellitus, Type 2")	Search modes - Boolean/Phrase	18233
S15	S12 OR S13 OR S14	Search modes - Boolean/Phrase	38210
S14	stroke OR tia OR transient ischemic attack OR cerebrovascular apoplexy OR cerebrovascular accident OR cerebrovascular infarct* OR brain infarct* OR CVA	Search modes - Boolean/Phrase	37713
S13	(MH "Cerebral Ischemia, Transient")	Search modes - Boolean/Phrase	1903
S12	(MH "Stroke") OR (MH "Stroke Patients")	Search modes - Boolean/Phrase	25676
S11	S9 OR S10	Search modes - Boolean/Phrase	18862
S10	myocardi* failure OR myocardial decompensation OR myocardial insufficiency OR cardiac failure OR cardiac decompensation OR cardiac insufficiency OR heart failure OR heart decompensation OR heart insufficiency	Search modes - Boolean/Phrase	18850
S9	(MH "Heart Failure+")	Search modes - Boolean/Phrase	14393
S8	S6 OR S7	Search modes - Boolean/Phrase	8072
S7	atrial N1 fibrillation* OR atrium N1 fibrillation* OR auricular N1 fibrillation*	Search modes - Boolean/Phrase	8072
S6	(MH "Atrial Fibrillation")	Search modes - Boolean/Phrase	6490
S5	S1 OR S2 OR S3 OR S4	Search modes - Boolean/Phrase	30133
S4	TI myocardi* N2 infarct* OR TI heart N2 infarct* OR TI cardiac N2 infarct* OR TI coronary N2 infarct* OR TI arterioscleros* OR TI atherosclerosis*	Search modes - Boolean/Phrase	9643
S3	coronary artery disease OR cad OR heart attack*	Search modes - Boolean/Phrase	7706
S2	(MH "Myocardial Infarction+")	Search modes - Boolean/Phrase	19219
S1	(MH "Coronary Arteriosclerosis")	Search modes - Boolean/Phrase	4646

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ID	Search	Hits
#1	MeSH descriptor **Coronary Artery Disease** explode all trees	2183
#2	MeSH descriptor **Myocardial Infarction** explode all trees	7746
#3	(myocardi* or heart or cardiac or coronary) NEAR/2 (atherosclerosis* or arterioscleros* or infarct*):ti or (coronary artery disease or cad or heart attack*):ti	8469
#4	MeSH descriptor **Atrial Fibrillation** explode all trees	2102
#5	(atrial NEAR/2 fibrillation* or atrium NEAR/2 fibrillation* or auricular NEAR/2 fibrillation*):ti	2310
#6	MeSH descriptor **Heart Failure** explode all trees	4710
#7	(myocardi* NEAR/2 (failure or decompensation or insufficiency)):ti or (heart NEAR/2 (failure or decompensation or insufficiency)):ti or (cardiac NEAR/2 (failure or decompensation or insufficiency)):ti	5252
#8	MeSH descriptor **Stroke** explode all trees	3899
#9	MeSH descriptor **Ischemic Attack, Transient** explode all trees	466
#10	(stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA):ti	9902
#11	MeSH descriptor **Diabetes Mellitus, Type 2** explode all trees	6993
#12	(diabetes or diabetic* or niddm or t2dm):ti	16585
#13	MeSH descriptor **Skin Ulcer** explode all trees	1572
#14	(pressure or bed or skin) NEAR/2 (ulcer* or sore* or wound*):ti	669

#15	(decubitus or bedsore*):ti	98
#16	MeSH descriptor **Pulmonary Disease, Chronic Obstructive** explode all trees	1754
#17	(chronic obstructive NEAR/2 (lung* or pulmonary or airway* or airflow or respiratory)):ti	2415
#18	(copd or coad):ti	3319
#19	(chronic airflow obstruction):ti	72
#20	MeSH descriptor **Emphysema** explode all trees	91
#21	(chronic NEAR/2 bronchitis) or emphysema:ti	1183
#22	MeSH descriptor **Chronic Disease** explode all trees	9875
#23	(chronic* NEAR/2 disease* or chronic* NEAR/2 ill*):ti	1670
#24	MeSH descriptor **Comorbidity** explode all trees	1941
#25	(comorbid* OR comorbid* OR multimorbid* OR multi-morbid* OR (complex* NEXT patient*) OR "patient* with multiple" OR (multiple NEAR/2 (condition* OR disease*))):ti	649
#26	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)	68126
#27	MeSH descriptor **Depression** explode all trees	4309
#28	MeSH descriptor **Depressive Disorder** explode all trees	6395
#29	MeSH descriptor **Anxiety** explode all trees	4337
#30	MeSH descriptor **Anxiety Disorders** explode all trees	4159
#31	(depression* OR depressive*):ti or (anxiety):ti	15300
#32	(#27 OR #28 OR #29 OR #30 OR #31)	24777
#33	MeSH descriptor **Mass Screening** explode all trees	4120
#34	MeSH descriptor **Psychological Tests** explode all trees	9194
#35	MeSH descriptor **Psychiatric Status Rating Scales** explode all trees	7297
#36	MeSH descriptor **Interview, Psychological** explode all trees	459
#37	MeSH descriptor **Severity of Illness Index** explode all trees	11790
#38	MeSH descriptor **Diagnostic Self Evaluation** explode all trees	15
#39	(depression* OR depressive* OR anxiety OR anxieties) NEAR/2 (assessment* OR detect* OR diagnos* OR inventor* OR scale* OR screen* OR self-assessment* OR test*):ti or (case-finding):ti	486
#40	(#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39)	30235
#41	(((cardiovascular OR cardio-vascular) NEXT (care OR disease*)) OR heart disease*) NEAR/5 (depression* OR depressive* OR anxiety OR anxieties) NEAR/2 (assessment* OR detect* OR diagnos* OR inventor* OR scale* OR screen* OR self-assessment* OR test*):ti	0
#42	(#26 AND #32 AND #40)	670
#43	(#26 AND #32 AND #40), from 2002 to 2012	439

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Line	Search	Hits
1	MeSH DESCRIPTOR coronary artery disease EXPLODE ALL TREES	230
2	(coronary artery disease or cad or heart attack*):TI	213
3	((myocardi* or heart or cardiac or coronary) adj2 (atheroscleros* or arterioscleros* or infarct*)):TI	224
4	MeSH DESCRIPTOR Atrial Fibrillation EXPLODE ALL TREES	225

5	(((atrial or atrium or auricular) adj1 fibrillation*):TI	0
6	((atrial or atrium or auricular) adj1 fibrillation*):TI	168
7	MeSH DESCRIPTOR heart failure EXPLODE ALL TREES	418
8	((myocardi* or heart or cardiac) adj2 (failure or decompensation or insufficiency)):TI	280
9	MeSH DESCRIPTOR stroke EXPLODE ALL TREES	549
10	MeSH DESCRIPTOR Ischemic Attack, Transient EXPLODE ALL TREES	32
11	(stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA):TI	622
12	MeSH DESCRIPTOR Diabetes Mellitus, Type 2 EXPLODE ALL TREES	511
13	(diabetes or diabetic* or niddm or t2dm):TI	1223
14	MeSH DESCRIPTOR Skin Ulcer EXPLODE ALL TREES	253
15	((pressure or bed or skin) adj2 (ulcer* or sore* or wound*)):TI	73
16	(decubitus or bedsore*):TI	0
17	MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive EXPLODE ALL TREES	237
18	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory)):TI	219
19	(copd or coad):TI	108
20	(chronic airflow obstruction):TI	0
21	MeSH DESCRIPTOR Emphysema EXPLODE ALL TREES	10
22	((chronic adj2 bronchitis) or emphysema):TI	47
23	MeSH DESCRIPTOR Chronic Disease EXPLODE ALL TREES	687
24	((chronic* adj2 disease*) or (chronic* adj2 ill*)):TI	252
25	MeSH DESCRIPTOR Comorbidity EXPLODE ALL TREES	146
26	(comorbid* OR comorbid* OR multimorbid* OR multi-morbid* OR (complex* adj1 patient*) OR "patient* with multiple" OR (multiple adj2 (condition* OR disease*))):TI	22
27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	4656
28	MeSH DESCRIPTOR Depression EXPLODE ALL TREES	286
29	MeSH DESCRIPTOR Depressive Disorder EXPLODE ALL TREES	572
30	MeSH DESCRIPTOR Anxiety EXPLODE ALL TREES	134
31	MeSH DESCRIPTOR Anxiety Disorders EXPLODE ALL TREES	255
32	(depression* or depressive*):TI OR (anxiety):TI	869
33	#28 OR #29 OR #30 OR #31 OR #32	1290

34	MeSH DESCRIPTOR Mass Screening EXPLODE ALL TREES	1704
35	MeSH DESCRIPTOR Psychological Tests EXPLODE ALL TREES	139
36	MeSH DESCRIPTOR Psychiatric Status Rating Scales EXPLODE ALL TREES	171
37	MeSH DESCRIPTOR Interview, Psychological EXPLODE ALL TREES	15
38	MeSH DESCRIPTOR Severity of Illness Index EXPLODE ALL TREES	575
39	((depression* or depressive* or anxiety or anxieties) adj2 (assessment? or detect* or diagnos* or inventor* or scale? or screen* or self-assessment? or test*)):TI OR (case-finding):TI	34
40	#34 OR #35 OR #36 OR #37 OR #38 OR #39	2533
41	((((cardiovascular or cardio-vascular) adj (care or disease?)) or heart disease?) adj5 (depression* or depressive* or anxiety or anxieties) adj5 (assessment? or detect* or diagnos* or inventor* or scale? or screen* or self-assessment? or test*)):TI	0
42	#27 AND #33 AND #40	13
43	#41 OR #42	13

Appendix 2: Study Descriptions

Table A1: Study Descriptions

Author, Year, Setting	Objective	Design	Population	Depression Screening	Treatment Period, Follow-up Period	Treatment, Control, n	Depression Measure	Chronic Disease Measures
Diabetes								
Paile-Hyvarinen et al, 2003 (29) Finland	To evaluate whether antidepressant drug therapy (paroxetine) improves metabolic control, quality of life, and mental health in patients (aged 50–70) with diabetes (and depression)	Single-blinded RCT; per-protocol analysis	Primary care population aged 50–70 years with type 2 diabetes, non-optimal glycemic control, and mild depression	HADS	6 months 6 months	Paroxetine (24) Placebo (24)	HADS	HbA1c
Heart Failure								
Fraguas et al, 2009 (31) Brazil	To evaluate the efficacy and safety of citalopram in elderly subjects with CHF and major depressive disorder	Double-blind placebo-controlled RCT; ITT analysis with LOCF	Patients aged 65+ with CHF and LVEF < 50% and with major depressive disorder (HRSD score 18+); onset of depression was post-cardiac symptoms	PRIME-MD	8 weeks 8 weeks	Citalopram (19) Placebo (18)	HRSD-17	Cardiopulmonary performance; maximum oxygen consumption
O'Conner et al, 2012 (30) United States	To evaluate the safety and efficacy of sertraline in patients with heart failure and depression	Double-blind placebo-controlled RCT; ITT analysis with LOCF	Patients aged 45 and older, LVEF ≤ 45%, NYHA class II–IV, and clinical depression	Psychiatric consultation using DSM criteria	12 weeks 6 months (minimum)	Sertraline (234) Placebo (235)	HRSD-17	Change in CAD status (worsened, improved, unchanged) and cardiac event rates
Coronary Artery Disease								
ENRICHD, 2003 (34) United States	To determine whether treating depression and increasing social support as soon as possible after acute MI reduces the risk of recurrent nonfatal MI and death	RCT (blind outcome assessment); ITT analysis with LOCF	Patients with an acute MI admitted to hospital and with clinical depression (and not receiving treatment); protocol changed in 1998 to include patients who were on antidepressants but still depressed	DISH (includes HRSD)	6 months 29 months (mean)	CBT with or without addition of pharmacotherapy (as needed) (1,238) Usual care (could also include pharmacotherapy) (1,243)	BDI, DISH (includes HRSD)	Recurrent MI or death from any cause and cardiac events (revascularization, CAD hospitalizations)

Glassman et al, 2002 (32) Multiple countries	To evaluate the efficacy of sertraline in patients diagnosed with major depression in the immediate period after hospitalization for MI or unstable angina	Double-blind placebo-controlled RCT; stratified by LVEF and depression score; ITT analysis with LOCF	Patients who were hospitalized for MI or unstable angina and had a current episode of major depression	BDI, HRSD	24 weeks 24 weeks	Sertraline (186) Placebo (183)	BDI, HRSD (up to 16 weeks), and CGI (up to 24 weeks)	LVEF and cardiac event rates (MI, stroke, severe angina, heart failure and, death)
Honig et al, 2007 (35) Netherlands	To evaluate the safety and efficacy of mirtazapine treatment for major or minor depression in patients post-MI	Nested RCT in MIND-IT study	Patients post-MI; included patients at least 3 months post-MI diagnosed with a post-MI depressive episode	BDI, CIDI	6 months 6 months	Mirtazapine (47) Placebo (44)	BDI, HRSD	Hospitalization rates, ECG findings
Lesperance et al, 2007 (36) Canada	To evaluate the short-term efficacy and tolerability of 2 depression treatments in patients with CAD: antidepressants and/or interpersonal psychotherapy	2x2 factorial design, parallel-group RCT (medication management was blinded and placebo-controlled); ITT analysis with LOCF	Patients aged 18+ with CAD (based on hospital chart) and current major depression	HRSD	12 weeks 12 weeks	Citalopram (142) Placebo (142)	BDI, HRSD	Cardiac events, ECG findings
Van Melle et al, 2007 (33) Netherlands	To evaluate whether active treatment for depression post-MI improves long-term depression status and cardiovascular prognosis	RCT; per-protocol analysis	Patients hospitalized with an MI and who had a depressive episode at least 3 months post-MI; included patients who were identified as having a current depressive episode on interview	BDI, CIDI	6 months 6 months	Any treatment modality (209) Care as usual; psychiatric treatment outside of study was recorded (122)	HRSD	Cardiac event (cardiac death, recurrent MI, revascularization, heart failure, ischemia, arrhythmia)

Abbreviations: BDI, Beck Depression Inventory; CAD, coronary artery disease; CBT, cognitive behavioural therapy; CGI, Clinical Global Impression; CHF, congestive heart failure; CIDI, Composite International Diagnostic Interview; DISH, Depression Interview and Structured Hamilton; DSM, *Diagnostic and Statistical Manual of Mental Disorders;* ECG, electrocardiogram; HADS, Hospital Anxiety and Depression Scale; HbA1c, hemoglobin A1c; HRSD, Hamilton Rating Scale for Depression; ITT, intention to treat; LOCF, last observation carried forward; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PRIME-MD, Primary Care Evaluation of Mental Disorders; RCT, randomized controlled trial.

Appendix 3: GRADE Tables

Table A2: GRADE Evidence Profile for Comparison of Depression Treatment and Usual Care/Placebo

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Diabetes: HbA1c							
1 (RCT)	Serious limitations (–1)[a]	Not applicable	No serious limitations	Serious limitations (–1)[b]	Undetected	None	⊕⊕ Low
Heart Failure: Hospitalization or Death							
1 (RCT)	No serious limitations	Not applicable	No serious limitations	Serious limitations (–1)[c]	Undetected	None	⊕⊕⊕ Moderate
Heart Failure: Cardiopulmonary Performance							
1 (RCT)	Serious limitations (–1)[d]	Not applicable	No serious limitations	Serious limitations (–1)[b]	Undetected	None	⊕⊕ Low
CAD: Nonfatal MI (Recurrent or MI Post-CAD Diagnosis)							
3 (RCTs)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (–1)[e]	Undetected	None	⊕⊕⊕ Moderate
CAD: Death							
2 (RCTs)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (–1)[e]	Undetected	None	⊕⊕⊕ Moderate
CAD: Change in LVEF							
1 (RCT)	Serious limitations (–1)[f]	Not applicable	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
CAD: Change in ECG Findings							
2 (RCTs)	Serious limitations (–1)[g]	Not applicable[g]	Serious limitations (–1)[h]	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: CAD, coronary artery disease; ECG, electrocardiogram; HbA1c, hemoglobin A1c; LVEF, left ventricular ejection fraction; MI, myocardial infarction; No., number; RCT, randomized controlled trial.
[a]Authors completed a per-protocol analysis with unequal dropout rates (intervention 4%, control 36%).
[b]Study was underpowered based on authors' own power calculations.
[c]Authors reported a high placebo response rate, which reduced power to detect a difference.
[d]Authors completed a per-protocol analysis of patients who were originally randomized; because of a high placebo response rate during the washout period, a number of patients were excluded.
[e]Low event rates leading to wide confidence intervals and potentially reduced power.
[f]Authors conducted a per-protocol analysis for evaluation of LVEF.
[g]Study by Honig et al was assessing safety of treatment and did not report individual findings but rather stated that there were no significant changes.
[h]Both studies were assessing the safety of treatment and so used limited clinical measures to assess CAD outcomes.

Table A3: Risk of Bias Among Randomized Controlled Trials for the Comparison of Depression Treatment and Usual Care/Placebo

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
ENRICHD, 2003 (34)	No limitations	Unclear[a]	No limitations	No limitations	No limitations
Fraguas et al, 2009 (31)	Unclear[b]	No limitations	No limitations	No limitations	No limitations
Glassman et al, 2002 (32)	Unclear[b]	No limitations	No limitations	No limitations	No limitations
Honig et al, 2007 (35)	Unclear[b]	No limitations	No limitations	No limitations	No limitations
Lesperance et al, 2007 (36)	No limitations	No limitations	No limitations	No limitations	No limitations
O'Conner et al, 2010 (30)	Unclear[b]	No limitations	No limitations	No limitations	No limitations
Paile-Hyvarinen et al, 2003 (29)	No limitations	No limitations	Limitations[c]	No limitations	No limitations
Van Melle et al, 2007 (33)	No limitations	No limitations	Limitations[d]	No limitations	No limitations

[a]Intervention was cognitive behavioural therapy, so patients and providers could not be blinded to allocation. Authors indicated that outcome assessors were "blinded as much as possible," but did not clarify what was done to ensure blinding of outcome assessment.

[b]Not reported in paper.

[c]Authors completed a per-protocol analysis with unequal dropout rates (intervention 4%, control 36%).

[d]Authors completed a per protocol analysis, but dropout rates were low (intervention 6.2% [13/209], control 3.3% [4/122]).

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