Impact of Treating Depression on Associated Comorbidities: A Systematic Literature Review

Alix M. Arnaud, MSc[a]; Teri S. Brister, PhD[b]; Ken Duckworth, MD[b]; Phyllis Foxworth, BSc[c]; Tonya Fulwider, BA[d]; Ellison D. Suthoff, MBA[a,*]; Brian Werneburg, PhD[a]; Izabela Aleksanderek, PhD[e]; and Marcia L. Reinhart, DPhil[e]

ABSTRACT

Objective: To identify and summarize data that describe the impact of effectively treating major depressive disorder (MDD) on the severity or risk of serious comorbidities.

Data Sources: MEDLINE, Embase, PsycINFO, Cochrane Database of Systematic Reviews, and several congresses were searched. Searches included terms related to MDD, randomized controlled trials (RCTs), and physical comorbidities and were restricted to English-language publications. Searches were conducted in November 2019 for the previous 2 years for conference proceedings; no date restriction was applied to the database searches.

Study Selection: Included studies were RCTs or meta-analyses that assessed depression therapies. Studies were required to report a statistically significant improvement in depression scores as well as the concurrent impact on comorbidities. A total of 1,997 articles were initially identified for screening.

Data Extraction: Two investigators extracted data and assessed study quality.

Results: A total of 30 studies, including 24 RCTs (N = 6,333) and 6 meta/pooled analyses of RCTs, were included. Findings in several comorbidity categories were mixed; for example, in half (4 of 8) of the identified studies in people with cardiovascular disease and depression, individuals who received treatment leading to reduced depressive symptoms compared with a control arm also had a significantly decreased incidence of cardiovascular events or significantly improved cardiac disease symptom/severity scores compared with controls. Significant improvements in comorbid disease severity observed alongside improvements in depressive symptoms were also noted in studies of comorbid Parkinson's disease, multiple sclerosis, chronic pain and fibromyalgia, and chronic obstructive pulmonary disease.

Conclusions: Effective treatment of MDD may lead to a reduction in the severity of certain serious comorbidities. These results highlight the importance of appropriate and timely treatment of MDD.

Prim Care Companion CNS Disord 2023;25(1):22r03330

To cite: Arnaud AM, Brister TS, Duckworth K, et al. Impact of treating depression on associated comorbidities: a systematic literature review. *Prim Care Companion CNS Disord.* 2023;25(1):22r03330.

To share: https://doi.org/10.4088/PCC.22r03330

[a]Sage Therapeutics, Inc, Cambridge, Massachusetts
[b]National Alliance on Mental Illness, Arlington, Virginia
[c]Depression and Bipolar Support Alliance, Chicago, Illinois
[d]Mental Health America of Ohio, Columbus, Ohio
[e]Tantalus Medical Communications Ltd, Victoria, British Columbia, Canada
**Corresponding author:* Ellison D. Suthoff, MBA, 215 First St, Cambridge, MA 02142 (Ellison.Suthoff@sagerx.com).

Many physical and psychiatric comorbidities have been associated with major depressive disorder (MDD).[1] The association between mental health and physical health is often described as bidirectional in nature; while in certain cases depression may develop following an initial underlying disease,[2] there is also evidence that individuals may be at a greater risk of developing various comorbidities because of depression (or existing comorbidities may be worsened by the existence of comorbid depression).[1] Recent research identified significant associations between depression and the incidence and/or worsening of a broad range of comorbidities in a systematic review of observational studies.[3] Furthermore, an analysis of over 9 million commercially insured people in the United States who were diagnosed with MDD in 2016 showed that 85% had at least 1 comorbidity, and nearly 30% had 4 or more comorbidities.[4]

The humanistic and economic burden of comorbidities associated with depression is considerable. An analysis of US Medical Expenditure Panel Survey data (2010–2015) found that approximately 60% of individuals with MDD and/or any anxiety disorder had at least 1 comorbid chronic noncommunicable disease, which led to increased annual health care costs of up to nearly $4,000 per person with MDD that was driven primarily by cardiovascular disease (CVD) and pain conditions.[5] The presence of comorbid disease also led to significant decreases in measures of physical patient-reported quality of life among these affected individuals.[5]

Although several studies have demonstrated that depression is often accompanied by the presence of comorbidities or worsening of existing comorbidities, it remains unclear whether effective treatment of MDD could improve the incidence risk or severity of comorbid diseases. The objective of this systematic literature review was to identify and summarize data that evaluates the impact of effectively treating MDD on the risk or severity of comorbidities known to be associated with depression.

METHODS

A systematic literature search for studies that examined the association between improvement in MDD and the concurrent impact on comorbidities was conducted using methods consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[6]

Clinical Points

- Although there are many well-studied comorbidities among people with depression, the impact of treating depression on the severity or risk of serious comorbidities has not been widely tested.
- Effective treatment of depression may have a positive impact on the severity of certain comorbidities and thus overall patient health.
- Integration of general and mental health care through routine screening for mental health disorders should be considered in a primary care environment along with appropriate and timely treatment of MDD.

The methods of determining comorbidities have been described previously.[3] Briefly, categories of comorbidities were determined from preliminary research, advocacy group reports, medical claims data, and expert opinion. The final list of comorbidity categories included cancer, central nervous system (CNS) disorders, CVD, metabolic and endocrine diseases, autoimmune and gastrointestinal diseases, pain-related conditions, respiratory disorders, and substance abuse disorders.

Databases searched included Embase, MEDLINE (including MEDLINE In-Process), Cochrane Database of Systematic Reviews, Cochrane Controlled Register of Trials, and PsycINFO, and the search used terms for MDD, comorbidity categories, and randomized controlled trials (RCTs; the full search strategy is provided in Supplementary Table 1). In addition, abstracts from several relevant congresses were reviewed, and hand searches of referenced publications were undertaken. Searches were conducted in November 2019 for the previous 2 years for conference proceedings; no date restriction was applied to the database searches.

Included studies were required to report a statistically significant improvement (ie, reduction) in depressive symptoms following any depression treatment intervention compared with another treatment or control arm. Studies were also required to assess change in either comorbidity incidence (ie, risk of developing a downstream comorbidity) or the disease severity of existing comorbidities over the same treatment period. Included studies were required to be RCTs (including meta-analyses of randomized trials), and only English-language records were searched; a complete list of criteria is provided in Supplementary Table 2.

Search results were screened by 2 separate reviewers (M.L.R. and I.A.) initially by titles and abstracts, followed by a review of the full text; any disputes were resolved through discussion between reviewers or consultation with a third reviewer. Data from included studies were extracted by 2 independent reviewers (M.L.R. and I.A.), and any discrepancies between extractions were verified for accuracy by an independent third reviewer. Data describing the study methodology, participant demographic and clinical characteristics, and changes in MDD and comorbidity outcomes were extracted. The quality of included studies was assessed by reviewers using the checklists recommended by the National Institute for Health and Care Excellence for RCTs and meta-analyses (see Supplementary Tables 3–5).[7,8]

RESULTS

In total, 1,992 articles were identified for screening from the database searches for initial screening, which were combined with another 5 relevant articles from conference abstracts and hand searches. The systematic review included 30 studies from 35 publications, including 24 RCTs (N = 6,333) and 6 meta-analyses or pooled analyses of RCTs (Figure 1). Included studies included treatment with several nondrug interventions, such as cognitive-behavioral therapy (CBT), as well as various pharmacologic therapies. Most studies were under 1 year in duration, with many less than 6 months. A description of included studies is provided in Table 1,[9–43] and a summary of findings for changes in comorbidity severity is shown in Figure 2.

Cancer

A total of 2 RCTs were identified that assessed the impact of improving depressive symptoms on outcomes in people with cancer: the Symptom Management Research Trials (SMaRT) Oncology-2 and -3 studies.[9,10] In general, changes in participant survival or pain scores were not observed alongside improvements in depressive symptoms.

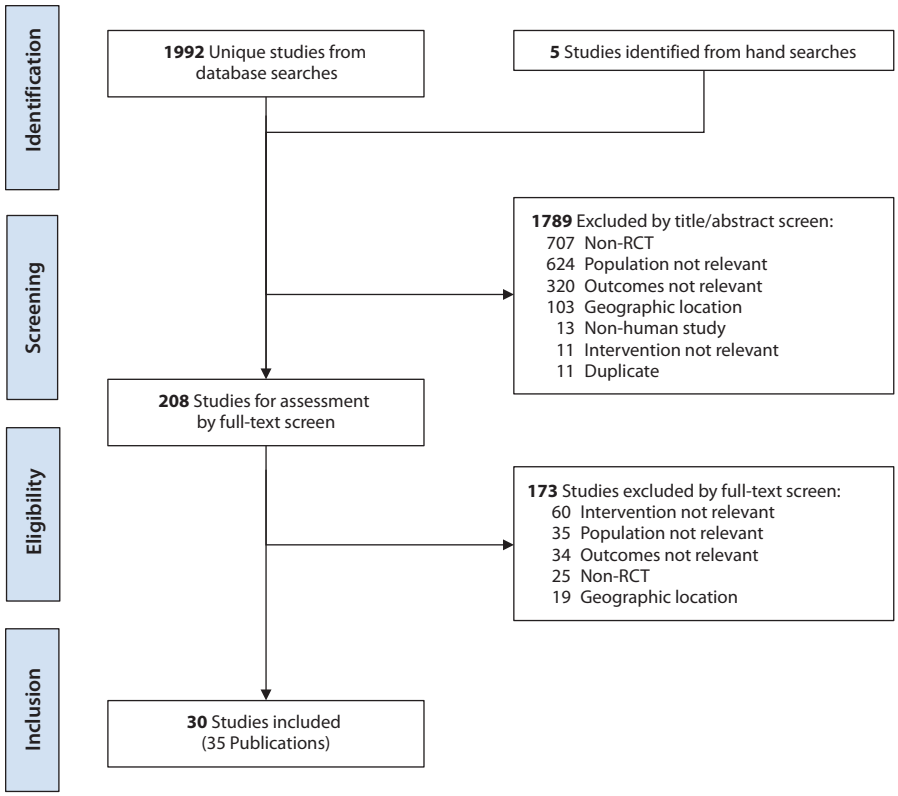
The included studies[9,10] were both UK-based trials that compared a novel depression care program (Depression Care for People with Cancer; DCPC) to usual care among 2 cohorts: those with a good prognosis (SMaRT Oncology-2; any cancer [N = 500]) or poor prognosis (SMaRT Oncology-3; lung cancer only [N = 142]). Although the DCPC program led to a significantly greater proportion of individuals with a depression treatment response compared with usual care in both cohorts (62% vs 17%; $P < .0001$ for SMaRT Oncology-2; odds ratio [OR]: 5.88; 95% confidence interval [CI], 2.42–14.33; $P < .0001$ for SMaRT Oncology-3), there were no significant changes observed between groups in overall survival or pain symptoms on a 100-point visual analog scale (VAS; reported in SMaRT Oncology-3 only).[9,10] Between-group changes in mean fatigue symptoms, measured using a 100-point VAS, were numerically lower in the DCPC group compared with usual care in an analysis that approached significance (59.3 vs 64.1; $P = .058$; SMaRT Oncology-3 only).[9]

Using survival as a surrogate endpoint for disease severity, both trials reported that 6-year survival was not significantly different between groups (72% for DCPC vs 69% for usual care in SMaRT Oncology-2; 23% vs 15% in SMaRT Oncology-3).[10]

CNS Disorders

The review identified 1 RCT that met inclusion criteria, the Depression in Alzheimer's Disease Study (DIADS),[11,12] and 1 meta-analysis of 5 RCTs,[13] which collectively assessed depressive symptom improvement in conjunction with changes in Alzheimer's disease severity. Overall, these studies did not demonstrate changes in measures of Alzheimer's

Figure 1. PRISMA Flowchart of Search and Screen Results



Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized controlled trial.

disease severity in conjunction with depressive symptom improvement. In addition, a single RCT was identified that assessed improvement in depressive symptoms following CBT alongside changes in Parkinson's disease severity; this study showed that many improvements in disease severity scores occurred alongside improvements in depressive symptoms.[14,15]

In DIADS, 44 people with Alzheimer's disease and major depressive episode were randomized to 12 weeks of treatment with sertraline or placebo.[11] Overall, a significantly greater proportion of participants achieved depression response criteria following treatment with sertraline compared with placebo (38% full and 46% partial vs 20% full and 15% partial, respectively; $P = .007$).[11] Mean 12-week scores for the Cornell Scale for Depression in Dementia (10.3 vs 14.9) and Hamilton Depression Rating Scale (HDRS) (13.2 vs 17.3) were also significantly improved in the sertraline-treated group compared with placebo ($P = .011$).[11] However, mean Alzheimer's disease severity scores at week 12, including daily living impairment, behavior disturbance, and cognition, were not significantly different in sertraline-treated individuals compared with those who received placebo.[11] A further analysis of changes in mean scores from various cognitive tests similarly showed no differences between the sertraline and placebo groups.[12] When participants were analyzed based on depression treatment response (regardless of randomized treatment group), those with improved mood did not show a significant change in cognitive scores compared with participants who did not have an improved mood.[12]

Similar to the findings from DIADS, the meta-analysis[13] (N = 165) reported significant improvements in antidepressant-treated participants compared with placebo for depression response (OR: 2.32; 95% CI, 1.04–5.16; $P = .04$) and remission (OR: 2.75; 95% CI, 1.13–6.65; $P = .03$), whereas the weighted mean difference in Mini-Mental State Examination (MMSE) score was not significant between groups (−0.71; 95% CI, −3.20 to 1.79; $P = .58$).

The impact of 10-week treatment with CBT and clinical monitoring compared with clinical monitoring alone was evaluated in an RCT of 80 people with Parkinson's disease and comorbid MDD.[14,15] In this study, participants randomized to CBT showed significant improvements in HDRS score (mean score: 13.58 vs 19.33; $P < .0001$) and Beck Depression Inventory (BDI) score (mean score: 9.74 vs 17.45; $P = .001$) compared with those who received clinical monitoring only at end of treatment (week 10) and also demonstrated an improvement in mean Unified Parkinson's Disease Rating Scale scores in the same comparison (40.11 vs 49.59; $P = .001$).[14] The study additionally examined the impact of depression treatment (regardless of intervention group) on various neuropsychological tests, showing that participants who experienced significant depressive symptom

Table 1. Summary of Included RCTs Evaluating Interventions for Depression and the Concomitant Impact on Comorbidities

Study	Country (N), Duration	Depression Treatment	Comorbidity	Comorbidity Outcomes Assessed	Study Population
Cancer					
Walker 2014[9] (SMaRT Oncology-3)	UK (N = 142), 48 wk	DCPC vs UC	Lung cancer	Disease severity (pain, fatigue)	Adults; primary lung cancer; predicted survival ≥ 3 mo; comorbid MDD ≥ 4 wk
Mulick 2018[10] (SMaRT Oncology-2 and -3)	Pooled analysis of 2 RCTs; UK (N = 642), 32–48 wk	DCPC vs UC	Cancer	Disease severity (survival/mortality)	SMaRT Oncology-2: adults; any cancer; predicted survival ≥ 12 mo; comorbid MDD ≥ 4 wk SMaRT Oncology-3: adults; primary lung cancer; predicted survival ≥ 3 months; comorbid MDD of ≥ 4 wk duration
CNS					
Lyketsos 2003[11] Munro 2004[12] (DIADS)	US (N = 44), 12 wk	Sertraline vs placebo	Alzheimer's disease	Disease severity (cognitive function)	Probable Alzheimer's disease; MDE; residing at home or in assisted living
Thompson 2007[13]	Meta-analysis of 5 RCTs (N = 165)	Antidepressant vs placebo	Alzheimer's disease	Disease severity (cognitive function)	Adults; diagnosed with depression and Alzheimer's disease
Dobkin 2011[14] Dobkin 2014[15]	US (N = 80), 14 wk	CBT + clinical monitoring vs clinical monitoring	Parkinson's disease	Disease severity (symptom scale)	Age 35–85 y; Parkinson's disease; primary MDD receiving stable treatment for ≥ 6 wk
CVD					
Stewart 2014[16] (IMPACT)	US (N = 235), 12 mo	IMPACT algorithm vs UC	CVD events, fatal or nonfatal MI, fatal or nonfatal stroke	Incidence	Age ≥ 60 y; current MDD or dysthymia
Sherwood 2016[17] (SMILE-II)	US (N = 202), 16 wk	Sertraline vs exercise vs placebo	CHD	Incidence	Age ≥ 40 y; MDD; no current psychiatric treatment or exercise program
Raskin 2008[18]	US (N = 311), 8 wk	Duloxetine vs placebo	Hypertension	Disease severity (sustained elevated BP, orthostatic hypotension)	Age ≥ 65 y; MDD; hypertension (subgroup)
Berkman 2003[19] (ENRICHD)	US (N = 2,481), 6 mo	CBT vs UC	Acute MI	Disease severity (mortality, recurrent MI, other markers)	Admitted to hospital with acute MI; met criteria for depression
de Jonge 2007[20] (MIND-IT)	Netherlands (N = 331), 24 wk	Mirtazapine vs UC	Acute MI	Disease severity (post-MI cardiac events)	Admitted to hospital with acute MI; developed post-MI depression
Glassman 2002[22] Glassman 2007[21] (SADHART)	7 countries[a] (N = 369), 24 wk	Sertraline vs placebo	Acute MI or unstable angina	Disease severity (CVD rehospitalizations, heart rate variability)	Admitted to hospital with acute MI or unstable angina; current episode of MDD
Huffman 2011[23]	US (N = 175), 12 wk	Collaborative care vs UC	ACS, arrhythmia, or HF	Disease severity (cardiac events/ readmissions)	Admitted to hospital for acute cardiac disease; clinical depression
Wiart 2000[24]	France (N = 31), 45 d	Fluoxetine vs placebo	Stroke	Disease severity (functional status)	Hospitalized with recent single ischemic or hemorrhagic stroke; developed post-stroke depression
Metabolic and endocrine disorders					
Baumeister 2014[25]	Meta-analysis of 18 RCTs (N = NR)	Intervention vs control/ placebo	Diabetes	Disease severity (glycemic control)	Adults; diabetes; depressive disorder
Ell 2010[26] Ell 2011[27] (MDDP trial)	US (N = 387), 12 mo	MDDP vs enhanced UC	T1DM, T2DM	Disease severity (diabetes symptoms, glycemic control, functional impairment)	Adults; Hispanic; T1DM or T2DM; depression
Lustman 1997[28]	US (N = 79), 8 wk	Nortriptyline vs placebo	T1DM, T2DM	Disease severity (glycemic control)	Age 21–65 y; poorly controlled T1DM or T2DM
Lustman 1998[29]	US (N = 51), 10 wk	CBT vs control	T2DM	Disease severity (glycemic control)	Age 21–70 y; T2DM; depression

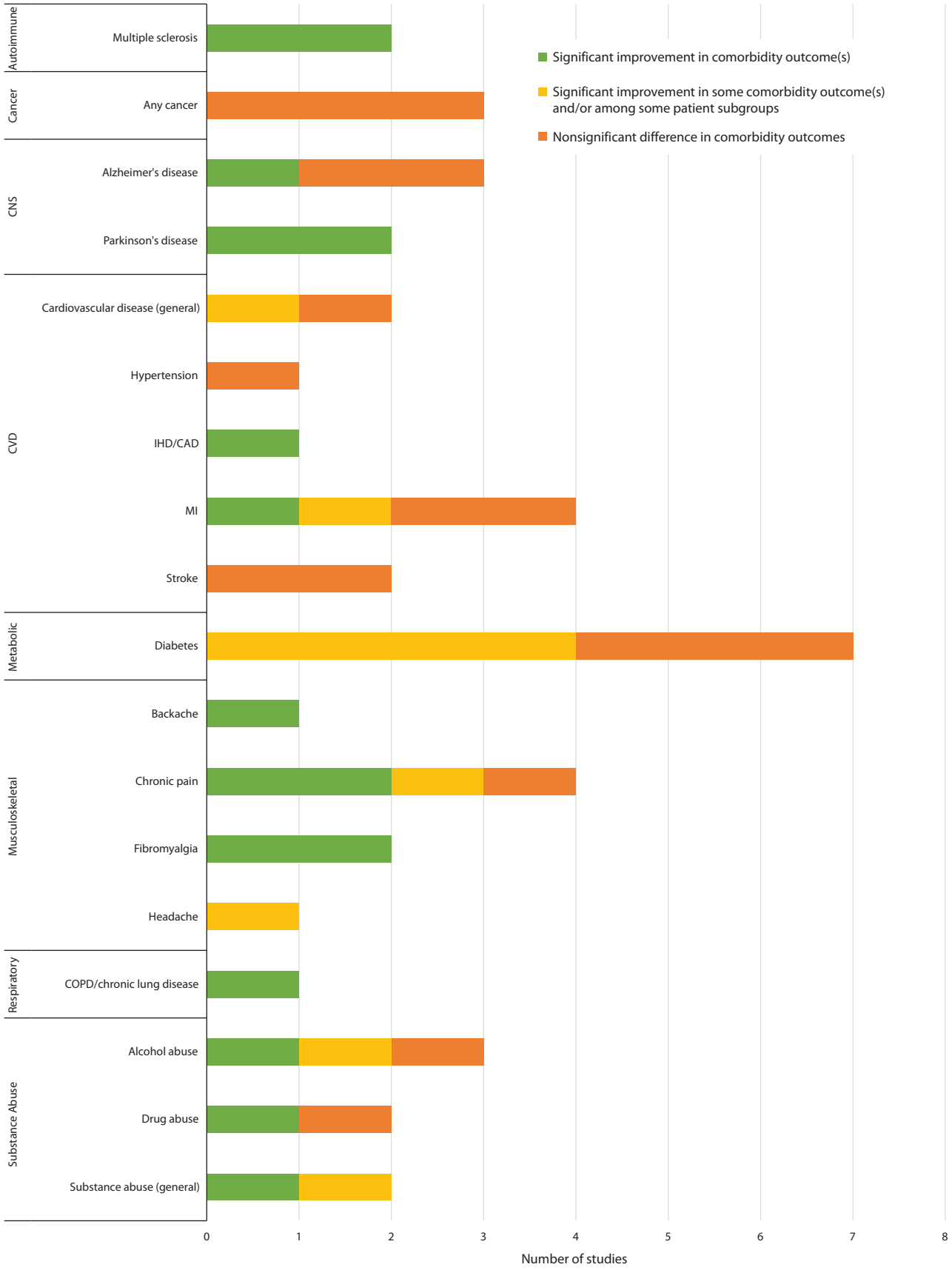
(continued)

Table 1 (continued).

Study	Country (N), Duration	Depression Treatment	Comorbidity	Comorbidity Outcomes Assessed	Study Population
Lustman 2000[30]	US (N = 60), 8 wk	Fluoxetine vs placebo	T1DM, T2DM	Disease severity (glycemic control)	Age 21–65 y; T1DM or T2DM; MDD
Petrak 2015[31] (DAD study)	Germany (N = 251), 12 wk	Sertraline vs CBT	T1DM, T2DM	Disease severity (glycemic control)	Age 21–69 y; T1DM or T2DM; MDD; HbA_{1c} > 7.5%
Autoimmune, gastrointestinal, and musculoskeletal/pain conditions					
Mohr 2007[33] Kinsinger 2010[32]	US (N = 127), 16 wk	Telephone-administered CBT vs EFT	Multiple sclerosis	Disease severity (disability, fatigue)	Adults; multiple sclerosis; depression
Fava 2004[34]	Pooled analysis of 2 RCTs, US (N = 512), 9 wk	Duloxetine vs placebo	Overall pain, headache, back pain, shoulder pain, pain while awake	Disease severity (pain severity)	Adults; MDD
Poleshuck 2014[35]	US (N = 62), 36 wk	Interpersonal psychotherapy vs enhanced UC	Chronic pelvic pain	Disease severity (pain severity, function)	Women; age 18–50 y; MDD; pelvic pain
Marangell 2011[36]	Pooled analysis of 4 RCTs, (N = 350), 12–28 wk	Duloxetine vs placebo	Fibromyalgia	Disease severity (pain severity)	Adults; fibromyalgia; MDD
McIntyre 2014[37]	Canada (N = 120), 8 wk	Quetiapine ER vs placebo	Fibromyalgia	Disease severity (pain severity, function)	Age 18–65 y; fibromyalgia; MDD
Respiratory disorders					
Borson 1992[38]	US (N = 36), 12 wk	Nortriptyline vs placebo	COPD	Disease severity (dyspnea)	Moderate-to-severe COPD; depression
Substance abuse disorders					
Cornelius 1997[39]	US (N = 51), 12 wk	Fluoxetine vs placebo	Alcohol dependence	Disease severity (drinking behavior)	Age 18–65 y; primary MDD; alcohol dependence
Mason 1996[40]	US (N = 71), 6 mo	Desipramine vs placebo	Alcohol abuse	Disease severity (abstinence)	Age 18–65 y; alcohol dependence
Torrens 2005[41]	Meta-analysis[b]	Antidepressant vs placebo	Alcohol, cocaine, or opioid dependence	Disease severity (quantity of use)	Depression; substance use disorder
Nunes 2004[42]	Meta-analysis of 15 RCTs (N = 848)	Antidepressant vs placebo	Substance use disorder	Disease severity (quantity of use)	Depressive disorder; current drug or alcohol use disorder
Nunes 1998[43]	US (N = 137),[c] 12 wk	Imipramine vs placebo	Substance use disorder	Disease severity (craving, use, and abstinence)	Depression; were newly admitted to methadone treatment

[a]7 countries include United States, Canada, Australia, Sweden, Italy, other European countries (details not reported).
[b]Number of studies and total number of participants unclear.
[c]84 participants completed the minimum requirement of 6 weeks.
Abbreviations: ACS = acute coronary syndrome, BP = blood pressure, CBT = cognitive-behavioral therapy, CHD = coronary heart disease, CNS = central nervous system, COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease, DAD = Diabetes and Depression study, DCPC = Depression Care for People with Cancer, DIADS = Depression in Alzheimer's Disease Study, EFT = emotion-focused therapy, ENRICHD = Enhancing Recovery in Coronary Heart Disease, ER = extended release, HbA_{1c} = hemoglobin A_{1c}, HF = heart failure, IMPACT = Improving Mood-Promoting Access to Collaborative Treatment, MDD = major depressive disorder, MDDP = Multifaceted Diabetes and Depression Program, MDE = major depressive episode, MI = myocardial infarction, MIND-IT = Myocardial Infarction and Depression–Intervention Trial, NR = not reported, RCT = randomized controlled trial, SADHART = Sertraline Antidepressant Heart Attack Randomized Trial, SMaRT = Symptom Management Research Trials, SMILE-II = Standard Medical Intervention versus Long-term Exercise, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus, UC = usual care, UK = United Kingdom, US = United States.

Figure 2. Summary of Improvements in Measures of Comorbidity Severity Observed With Concurrent Improvements in Depressive Symptoms Between Treatment Arms of RCTs



Abbreviations: CAD = coronary artery disease, CNS = central nervous system, COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease, IHD = ischemic heart disease, MI = myocardial infarction, RCT = randomized controlled trial.

improvement also had concurrent improvements in verbal memory (assessed with total recall [$P = .009$] and recognition tests [$P = .007$]) and executive functioning based on inhibition score ($P = .02$).[15] Furthermore, a stepwise regression model controlling for baseline scores of Parkinson's disease severity, education, and age showed that depressive symptom improvement contributed unique variance to verbal memory measures of total recall (6%; $P = .009$) and recognition (11%; $P = .001$) and to the executive functioning measure of inhibition (2%; $P = .021$).[15]

Cardiovascular Disease

A total of 8 RCTs (9 references) were identified that assessed the impact of depression interventions on improvement in depressive symptoms and the concurrent change in CVD-associated comorbidities. These included 2 RCTs assessing the risk of incident CVD or changes in coronary artery disease/coronary heart disease (CHD) risk factors,[16,17] 1 RCT assessing the impact on existing hypertension,[18] 4 RCTs assessing the impact on subsequent cardiac events in people admitted to the hospital with acute cardiac disease,[19–23] and 1 RCT assessing disease severity in people with stroke who developed poststroke depression.[24] Many studies showed that people with cardiac disease who experienced improvements in depressive symptoms also had significantly fewer cardiovascular events and improvements in disease severity scores; however, results were not consistent across all trials.

The 2 studies assessing how CVD incidence/risk factors were affected when depressive symptoms improved included the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) study (N = 235) and the Standard Medical Intervention versus Long-term Exercise (SMILE-II) study (N = 202).[16,17] In IMPACT, participants were randomized to receive a stepped-care algorithm using both antidepressant and behavioral therapy (IMPACT group) or usual care for 12 months, with a follow-up period for CVD events of 8 years. Among people without baseline CVD, the IMPACT group showed a significant improvement in the 20-item Symptom Checklist Depression Scale (SCL-20) depression scores compared with usual care (mean change from baseline: −0.4 vs 0.1; $P < .001$) as well as lower rates of combined CVD events (28% vs 47%; $P = .010$; HR: 0.52; 95% CI, 0.31–0.86; $P < .05$).[16] When individual events were examined among participants with no baseline CVD, there was no significant association between treatment effect and risk of myocardial infarction (MI) events; however, there was a significantly lower risk of fatal or nonfatal stroke (HR: 0.25; 95% CI, 0.08–0.75; $P < .01$).[16] In a separate subgroup of individuals with preexisting CVD at baseline, treatment did not lead to a significant change in depression severity or CVD events between groups.[16] In SMILE-II, people with MDD were randomized to sertraline, 2 different exercise regimens, or placebo for 16 weeks.[17,44] When all active treatment groups (home-based exercise, supervised exercise, and sertraline) were pooled, a numeric improvement in MDD remission was observed compared with placebo, although this did not reach statistical significance (OR: 2.0; 95% CI, 0.97–4.2).[44] When changes in CHD risk factors were assessed, all active treatments pooled were significantly associated with an improved composite measure of CHD risk ($P = .001$), reduced carotid intima-media thickness ($P = .037$), improved brachial artery flow–mediated dilation ($P = .032$), a reduction in the 10-year atherosclerotic CVD risk ($P = .049$), and a reduction in systolic blood pressure (SBP; $P = .012$) compared with placebo.[17] There were no differences in serum lipid (total cholesterol [$P = .159$] or high-density lipoprotein [$P = .894$]) risk factors.[17] Although this study[17] did not identify CHD events per se, and provided only pooled data from both pharmacologic and exercise-based interventions, it provides evidence that MDD symptom improvement can occur alongside a reduction in CHD risk factors.

Hypertension is another risk factor for CVD, and 1 RCT included in the review (N = 311) assessed people with and without hypertension and diagnosed with depression who were randomized to treatment with duloxetine or matching placebo for 8 weeks.[18] Participants receiving duloxetine reported significant improvements in HDRS (−6.49 vs −3.72; $P < .001$) and Geriatric Depression Scale (GDS; −4.07 vs −1.34; $P < .001$) scores compared with placebo after 8 weeks of treatment.[18] However, among the subgroups with hypertension, there were no significant differences in the rate of treatment-emergent orthostatic hypotension between treatment groups.[18] Additionally, there were no statically significant treatment-by-subgroup interactions for change from baseline to endpoint in supine and standing SBP, diastolic blood pressure (DBP), pulse pressure, or orthostatic changes in SBP and DBP for any subgroups with prerandomization hypertension.[18]

Findings from 4 RCTs (5 publications) that assessed depressive symptom improvement and the potential impact on disease severity in people with cardiac disease are summarized in Table 2.[19–23] In conjunction with improvements in depressive symptoms, participants in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study[19] (N = 2,481) demonstrated no significant differences in occurrence of recurrent MI or death between treatment groups (CBT vs usual care). People in the Myocardial Infarction and Depression–Intervention Trial (MIND-IT) study[20] (N = 331) showed no increased risk of cardiac events for people with MDD who did not respond to mirtazapine after 24 weeks of treatment compared with responders and between mirtazapine responders and untreated controls. Individuals who participated in a collaborative care program for depression or usual care for 12 weeks (N = 175) had the same likelihood of 6-month cardiac readmissions, although the change in the number of cardiac symptoms and total score on the cardiac symptom list was significantly different between collaborative care and usual care at the 6-month follow-up.[23] Furthermore, participants in the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART; N = 369) treated with sertraline demonstrated a significant improvement in change in ultra low-frequency power (an indication of functional improvement) compared with placebo.[21,22] It is also notable that when study participants

Table 2. Cardiac Outcomes in People With Recent Cardiac Hospitalization Who Underwent Treatment for Depression[a]

Study, N	Depression Treatment; Duration	Depression Outcomes, Treatment vs Comparator	Changes in Comorbidity Measures
Berkman 2003[19] (ENRICHD) (N = 2,481)	CBT vs UC; 6 mo	Mean difference (95% CI): BDI: −2.7 (−3.7 to −1.7) HDRS: −1.7 (−2.5 to −0.9)	Recurrent MI or death (P = NS; data not reported) Subgroup comparison with vs without additional antidepressant: Nonfatal MI: HR = 0.63 (95% CI, 0.46 to 0.87) Death: HR = 0.57 (95% CI, 0.38 to 0.85)
de Jonge 2007[20] (MIND-IT) (N = 331)	Mirtazapine vs UC; 24 wk	Number of participants[b]: Responders: 27 Nonresponders: 43	Risk of cardiac events: Nonresponders vs responders: HR = 4.47 (95% CI, 0.51 to 39.77); P = .18 Responders vs UC: HR = 0.41 (95% CI, 0.05 to 3.58); P = .42 Nonresponders vs UC: HR = 2.92 (95% CI, 1.08 to 7.87); P = .03
Glassman 2002,[22] Glassman 2007[21] (SADHART) (N = 369)	Sertraline vs placebo; 24 wk	CGI score response: 67% vs 53%; P = .01	Week 16 heart rate variability[c]: Treatment vs placebo: 0.086 ± 9.1 vs −0.113 ± −10.7; P = .02 Responders vs nonresponders: −0.012 ± 1.2 vs −0.220 ± 19.7; P = .05 Post-MI cardiovascular events: All combined: RR = 0.77 (95% CI, 0.51 to 1.16) MI: RR = 0.70 (95% CI, 0.23 to 2.16) CHF: RR = 0.70 (95% CI, 0.23 to 2.16) Stroke: RR = 0.98 (95% CI, 0.14 to 6.93) Angina: RR = 0.85 (95% CI, 0.53 to 1.38)
Huffman 2011[23] (N = 175)	Collaborative care vs UC; 12 wk	PHQ-9 score change from baseline: 6 wk: −8.98 vs −5.95; P = .002 12 wk: −8.73 vs −5.30; P < .001	Month 6 outcomes: Change in number of cardiac symptoms: −2.46 vs −1.66; P = .047 Change in total cardiac symptoms score: −6.29 vs −4.15; P = .011 Cardiac readmissions: 39.5% vs 40.5%; OR = 0.96; P = .90

[a]Data are presented as mean ± SD unless otherwise specified.
[b]Data not reported for individual treatment groups; participants were divided into responders and nonresponders to antidepressant therapy.
[c]Measured with ultra low-frequency power.
Abbreviations: BDI = Beck Depression Inventory, CBT = cognitive-behavioral therapy, CGI = Clinical Global Impressions scale, CHF = congestive heart failure, CI = confidence interval, ENRICHD = Enhancing Recovery in Coronary Heart Disease, HDRS = Hamilton Depression Rating Scale, HR = hazard ratio, MI = myocardial infarction, MIND-IT = Myocardial Infarction and Depression—Intervention Trial, NS = not significant, OR = odds ratio, PHQ = Patient Health Questionnaire, RR = risk ratio, SADHART = Sertraline Antidepressant Heart Attack Randomized Trial, SD = standard deviation, UC = usual care.

with improved mood, regardless of treatment group, were compared with those who did not have improved mood, there was a borderline significant difference in change in low-frequency power in SADHART (P = .05).[21] However, not all findings from SADHART were different between groups as, similar to the observations from ENRICHD, there were no significant differences between groups treated with sertraline or placebo for post-MI cardiovascular events combined and separately for MI, CHF, stroke, or angina.[21]

One small RCT (N = 31) reported data for the impact of depression treatment on functional status in people recently hospitalized with stroke.[24] This study showed borderline significant improvements in Montgomery-Asberg Depression Rating Scale scores in participants randomized to fluoxetine compared with placebo for 45 days (mean score: 11.8 vs 18.7; P = .05).[24] However, there were no significant differences in mean ± SD scores of poststroke functional recovery (Motricity Index: 48.5 vs 55.3; MMSE: 24.8 vs 26.2) or Functional Independence Measure (87.4 vs 88.7) at the 45-day time point between treatment groups.[24]

Metabolic and Endocrine Disorders

The review identified 5 individual RCTs and 1 meta-analysis that met inclusion criteria,[25–31] all of which randomized people with diabetes and depression to receive either antidepressants (sertraline, fluoxetine, or nortriptyline) or CBT/behavioral interventions in the intervention arms and evaluated the impact of the intervention or control treatment on both depressive symptoms and diabetes severity (most frequently evaluated using different measures of glycemic control). In general, all studies demonstrated a significant improvement in depression symptoms in the intervention arm compared with the control arm, but few showed evidence of concurrent between-group changes in glycemic control (Table 3).[25–31] However, the meta-analysis[25] showed that among studies assessing treatment with selective serotonin reuptake inhibitors (SSRIs) specifically, the standardized mean difference in glycemic control compared with control/placebo groups was significant (−0.38; 95% CI, −0.64 to −0.12). In a study[26,27] that tested the Multifaceted Diabetes and Depression Program compared with usual care in 387 Hispanic adults with type 1 or type 2 diabetes and depression, the difference in glycemic control measures was not significant between treatment groups; however, there were significant time by group interactions for other measures of diabetes symptoms, functional impairment, and pain.

Autoimmune/Gastrointestinal Disorders and Musculoskeletal/Pain Conditions

This review identified 1 study in people with multiple sclerosis[32,33] and 4 studies assessing the impact of depressive symptom improvement on musculoskeletal and pain outcomes,[34–37] 2 of which were pooled analyses of multiple RCTs.[34,36] Many of these studies showed that pain outcomes and other markers of disease severity improved alongside improvements in depressive symptoms, although results were not consistent across all analyses, and it has been shown that some antidepressant therapies used (duloxetine and quetiapine) have potential analgesic effects.[45,46]

Table 3. Glycemic Control and Other Outcomes in People With Diabetes Who Underwent Treatment for Depression

Study, N	Depression Treatment	Depression Outcomes, Treatment vs Comparator	Changes in Comorbidity Measures
Baumeister 2014[25] Meta-analysis (N = NR)	Intervention vs control/placebo	Depression severity SMD: −0.61 (95% CI, −0.94 to −0.27) SSRI subgroup SMD: −0.39 (95% CI, −0.64 to −0.13)	SMD glycemic control, end of treatment: Range among all included studies: −0.97 to 0.47 SMD, SSRIs vs placebo: −0.38 (95% CI, −0.64 to −0.12)
Ell 2010,[26] Ell 2011[27] (MDDP trial) (N = 387)	MDDP vs enhanced UC; 12 mo	Response, by month, mean: 6: 86 (57.0%) vs 55 (36.4%); $P < .001$ 12: 88 (62.0%) vs 59 (42.4%); $P < .001$ 18: 89 (61.8%) vs 60 (43.8%); $P < .001$	Time-by-group interaction: HbA_{1c}: $P = .93$ Whitty-9 diabetes symptoms: $P < .001$ Sheehan Disability Scale of functional impairment: $P = .04$ Pain impact: $P < .001$
Lustman 1997[28] (N = 79)	Nortriptyline vs placebo; 8 wk	Change from baseline, mean BDI score: −10.2 vs −5.8; $P = .03$	Change from baseline in glycemic control: $P = .54$ vs placebo (data NR)
Lustman 1998[29] (N = 51)	CBT vs control; 10 wk	Remission, mean: 17 (70.8%) vs 6 (22.2%); $P < .001$ Clinical improvement, mean: 16 (66.6%) vs 8 (29.6%); $P = .01$	Post-treatment gHb levels, mean: CBT vs control: 10.2% vs 9.9%; $P = .17$ Responders vs nonresponders: 8.5% vs 10.9%; $P = .003$
Lustman 2000[30] (N = 60)	Fluoxetine vs placebo; 8 wk	Mean change from baseline: BDI: −14.0; $P = .03$ HDRS: −10.7; $P = .01$	Improvement in gHb, mean: −0.40% vs −0.07%; $P = .13$ vs placebo
Petrak 2015[31] (DAD study) (N = 251)	Sertraline vs CBT; 12 wk	Between-group difference HDRS: 2.59 (95% CI, 1.15 to 4.04); $P < .05$	Between-group difference, HbA_{1c}: −0.27 (95% CI, −0.62 to 0.08) HbA_{1c} decrease ≥ 1%: OR = 1.43 (95% CI, 0.28 to 7.65)

Abbreviations: BDI = Beck Depression Inventory, CBT = cognitive-behavioral therapy, CI = confidence interval, DAD = Diabetes and Depression study, gHb = glycosylated hemoglobin, HDRS = Hamilton Depression Rating Scale, HbA_{1c} = hemoglobin A_{1c}, MDDP = Multifaceted Diabetes and Depression Program, NR = not reported, OR = odds ratio, SMD = standardized mean difference, SSRI = selective serotonin reuptake inhibitor, UC = usual care.

In the single RCT of people with multiple sclerosis (N = 127) and depression who were randomized to 16 weeks of telephone-administered therapy (CBT or supportive emotion-focused therapy),[32,33] telephone CBT led to significant improvements in HDRS score over supportive emotion-focused therapy (treatment by time effect estimate: −0.17; $P = .01$). CBT-treated participants also demonstrated improvements over the comparator in Guy's Neurologic Disability Scale (treatment by time effect estimate: −0.169; $P = .004$) and the Fatigue Impact Scale (treatment by time effect estimate: −0.302; $P = .032$).[32,33]

A pooled analysis of 2 RCTs (N = 512) assessed pain outcomes in people with MDD who were randomized to either duloxetine or placebo for 9 weeks.[34] Duloxetine is an antidepressant but also has analgesic effects; to adjust for this, this study assessed the proportion of overall pain reduction that was independent of changes in depressive symptoms.[34] In this analysis, both depressive symptoms and pain severity were reduced in the duloxetine-treated group compared with the placebo-treated group. This observation was consistent for most pain scores at most weekly time points ($P = .016$ at week 9 for overall pain). To account for the analgesic effects of the intervention, a path analysis for overall pain showed that 50.6% of duloxetine's total effect was independent of changes in depressive symptoms, whereas 49.4% was an indirect effect mediated through change in the HDRS total score.[34] Another study[35] that assessed interpersonal psychotherapy compared with enhanced treatment as usual in 62 women with chronic pelvic pain showed an improvement in HDRS score for interpersonal psychotherapy over enhanced treatment (effect estimate: 2.1533; $P < .05$), whereas the effect on the Multidimensional Pain Inventory score was not significantly different between treatment groups.

Individuals with fibromyalgia and depression were assessed in a pooled analysis of 4 RCTs (N = 350) wherein participants were randomized to duloxetine or placebo for 12–28 weeks.[36] In this analysis, the total effect of treatment on depressive symptoms was statistically significant ($P = .037$). A path analysis showed that changes from baseline in Brief Pain Inventory (BPI) mean pain severity were positively correlated with the changes in HDRS total score, indicating that 68.7% of the reduction in pain was a direct effect of duloxetine, whereas the improvement in mood accounted for 31.3% of pain improvement.[36] In a separate RCT of people with fibromyalgia and depression (N = 120) who were treated with quetiapine extended-release or placebo for 8 weeks,[37] adjusted mean differences for quetiapine compared with placebo were observed for HDRS scores (−3.7; 95% CI, −5.9 to −1.5; $P = .001$), Clinical Global Impression–Severity of Depression scores (−0.6; 95% CI, −1.0 to −0.2; $P = .003$), HDRS response rate (25.9%; 95% CI, 9.9 to 41.9; $P = .002$), and HDRS remission rate (18.0%; 95% CI, 5.8 to 30.1; $P = .004$). At the same time, changes in disease severity measured by adjusted mean difference in pain outcomes were demonstrated for quetiapine over placebo, including for the outcomes of BPI total (−1.6; 95% CI, −2.8 to −0.5; $P = .007$), BPI-Severity (−0.6; 95% CI, −1.2 to 0; $P = .036$), and BPI-Interference (−1.0; 95% CI, −1.7 to −0.2; $P = .008$).[37] Furthermore, symptoms of depression (HDRS scores) were moderately correlated with measures of pain (BPI-Interference) and fibromyalgia (Fibromyalgia Impact Questionnaire).[37]

Infectious Diseases

The review did not identify any studies that met inclusion criteria and assessed infectious disease comorbidities.

Respiratory Disorders

This review identified 1 small RCT in 36 people with chronic obstructive pulmonary disease (COPD) and depression who were randomized to treatment with nortriptyline or placebo for a 12-week period.[38] A significantly greater proportion of participants in the nortriptyline-treated group experienced a depression response (77% vs 12%, $P = .0003$), and the mean end-of-treatment HDRS score was significantly lower (12.6 vs 22.8, $P = .01$) compared with the placebo group (an improvement from baseline of 60% vs 17%).[38] Disease severity was measured using several assessments of dyspnea; overall, the nortriptyline-treated group showed a significantly greater improvement in symptoms associated with breathing (differential treatment effect: 5.4, $P = .04$) and change in Pulmonary Functional Status Instrument (differential treatment effect: 0.71, $P = .002$) compared with placebo-treated participants.[38]

Substance Abuse

In total, 3 RCTs and 2 meta-analyses of RCTs were identified that assessed the impact of interventions for depression in people with both depression and substance use disorder.[39–43] Many, but not all, studies reported improvements in substance use behavior that were concurrent with improvements in depressive symptoms.

In an RCT of people with alcohol dependence (n = 71), median change in HDRS score (−13.00 vs −6.00; $P < .05$) and proportion of participants achieving depression response criteria (81.8% vs 22%; $P = .02$) was significantly improved in desipramine-treated individuals compared with placebo over a 6-month period.[40] There were also fewer alcohol use relapses in the desipramine group compared with the placebo group in the depressed subgroup, but this was not statistically significant (8.3% vs 40%; $P = .14$).[40] In a separate RCT of 51 people with alcohol dependence and MDD, treatment with fluoxetine led to a significantly greater mean change in HDRS score compared with placebo over 12 weeks (−6.0 vs −2.0; $P < .05$).[39] Concurrent improvements were observed in several measures of drinking behavior including cumulative drinks (70.2 vs 215.5; $P < .03$), cumulative number of drinking days (10.6 vs 20.3; $P < .05$), drinks per drinking day (2.4 vs 5.4; $P < .05$), cumulative number of days of heavy drinking (4.8 vs 16.0; $P = .04$), and number of weeks until first heavy drinking (8.0 vs 4.7; $P < .02$).[39]

A meta-analysis assessed quantity of substance use in people with alcohol, cocaine, or opioid dependence who received antidepressant therapy compared with placebo.[41] In this analysis, a pooled improvement in depressive symptoms was noted for participants with alcohol dependence who were treated with antidepressants other than SSRIs (OR: 4.15; 95% CI, 1.35–12.75).[41] These same studies showed no reduced alcohol use among non–SSRI-treated individuals compared with those treated with placebo (OR: 1.99; 95% CI, 0.78–5.08).[41] Studies included in the meta-analysis that assessed either cocaine or opioid dependence showed no significant change in depressive symptoms following antidepressant treatment compared with placebo and therefore were not relevant for this analysis. It is notable, however, that treatment with antidepressants did lead to a significant improvement (ie, reduction) in illicit opioid use compared with placebo in people with depression (OR: 3.65; 95% CI, 1.10–12.16), despite no significant improvement in depressive symptoms.[41]

Another RCT assessed 137 people with depression who were newly admitted to a methadone-based treatment program and randomized to imipramine hydrochloride or placebo.[43] Following 12 weeks of therapy, both the depression response (67% vs 26%; $P = .001$) and HDRS score (8.0 vs 13.6; $P < .001$) were significantly improved in the imipramine group compared with the placebo group.[43] Furthermore, concurrent improvements were observed in some measures of substance abuse in participants treated with imipramine hydrochloride compared with placebo, including days per week craving a substance (2.7 vs 4.5; $P = .003$) and intensity of craving (1.6 vs 2.3; $P = .006$).[43] Although the proportion of study participants with urine-confirmed abstinence also showed a numeric improvement following treatment with imipramine compared with placebo, it was not statistically significant (14% vs 2%; $P = .11$).[43]

A separate meta-analysis of 15 RCTs (N = 848) assessed the impact of antidepressant treatment in people with depression and substance use disorder (both drugs and alcohol).[42] Studies were stratified based on effect of treatment on depressive symptoms. Among studies with a depression effect size > 0.50 (ie, stronger improvement in depressive symptoms for intervention vs placebo), the pooled effect size on the quantity of substance abuse was significantly improved (0.56; 95% CI, 0.33–0.79), whereas no significant difference was observed among studies with a depression effect size < 0.50.[42]

Quality Assessment

According to the risk of bias assessment across RCTs, most studies had a low or unclear risk of selection bias and attrition bias. Nearly all studies were determined to have an unclear risk of detection bias, which was primarily because of a lack of clarity regarding whether investigators were blinded to other important confounding factors. In addition, studies were evenly split between low and high risk of performance bias. Reasons for high risk gradings were typically a lack of blinding to treatment among participants and/or those administering care, although this was often not possible for behavioral intervention studies. Further details of the quality assessment for individual studies are reported in Supplementary Tables 3–5.

DISCUSSION

Mental health, including both its improvement and decline, is intricately linked with changes in overall health. For people with certain comorbid disorders and MDD, effective treatment of depression occurred alongside a significant improvement in the severity of their comorbid disease compared to less effective treatment. This trend was demonstrated for people with Parkinson's disease,

multiple sclerosis, diabetes pain and symptom severity (but not glycemic control outcomes), COPD, and certain pain conditions. Effective treatment of depression was also associated with a decrease in the risk of CVD events in otherwise healthy individuals and the risk of cardiac symptoms (but not events) in people with prior cardiac hospitalizations. Findings in people with substance use disorders were somewhat mixed, although several included studies reported decreases in alcohol and substance use alongside improvements in depression symptoms. There were no observed differences in disease severity/course for cancer, Alzheimer's disease, and poststroke recovery in conjunction with improvements in depressive symptoms.

Constraints associated with study designs complicated the identification of clinically meaningful findings. For example, although the included studies demonstrated statistically significant improvements in depression symptoms with treatment compared with controls, the effect sizes observed following depression treatment were often relatively small, which could impact the ability to observe meaningful effects on associated comorbidities. Furthermore, the included studies had heterogeneous designs, with considerably different methods, populations, follow-up durations, and analyses. It should also be noted that the time frames used in many studies (eg, 12 weeks) may not have been a sufficient length to capture the long-term positive impact of these interventions on comorbid outcomes. Some studies[12,20,21,29,30] conducted additional analyses in depression treatment responders compared with nonresponders, regardless of the treatment received. In 2 of 5 studies,[21,29] these analyses led to statistically significant (or borderline significant) changes in comorbidity outcomes that had not been observed between treatment groups.

Similar findings to those of this review have been reported previously. In a literature review of the association between depression and pain, most of the studies that assessed whether antidepressant treatment was effective for pain symptoms (22 in total) reported that participants experienced improvements in both pain and depression symptoms.[47] It should be acknowledged, however, that antidepressants may be directly impacting pain pathways in the brain rather than modulating pain through their effects on depressive symptoms.[48] The inability to distinguish causality is a limitation of this systematic review and is discussed in further detail below. A separate review that examined the relationship between depression and CVD concluded that, although the association between depression and the incidence or worsening of CVD was well established, the question of whether effective depression treatment could lead to subsequent improvement in CVD did not yet have adequate supporting evidence.[49]

This review contains several limitations. Observed results from the included studies demonstrated a correlation between improvements in depressive symptoms and changes in comorbidity outcomes in certain diseases, but this must be interpreted with caution. The mechanism of action of certain antidepressants (including analgesic effects of duloxetine and quetiapine, which were assessed in patients with chronic pain) may have a direct impact on comorbidities, which inherently cannot be controlled for. It therefore remains possible that the comorbidity could be directly improved by the treatment. Alternatively, positive changes resulting from MDD improvement could be weakened by direct negative adverse effects of therapy. One example of such negative treatment impacts is the observation that SSRI therapy is associated with patient-reported weight gain,[50] thus improvements in metabolic and endocrine outcomes that are directly impacted by depression symptoms could be offset by the increased risk of obesity. In a handful of included studies, analyses were conducted to account for the potential direct impact of the antidepressant agent on comorbidity outcomes. Additional studies designed to adjust for appropriate covariates could help to further uncover the causal association between depression improvement and downstream effects on comorbid diseases.

The findings of this review further underscore the need to continue integrating general and mental health care, for example through routine screening for mental health disorders in a primary care environment. Such actions could lead to more rapid identification and coordinated, efficient management of both physical and psychiatric diseases. Findings from programs that piloted an integrated care model have shown that they lead to improvements in participants' access to health care, satisfaction with care, and health outcomes as well as a greater willingness of their providers to address mental health issues within the primary care setting.[51,52]

In conclusion, effective treatment of MDD may lead to an improvement in the incidence and severity of certain serious comorbidities. These results highlight the importance of appropriate and timely treatment of MDD, particularly among those suffering from comorbid conditions.

Submitted: May 31, 2022; accepted August 3, 2022.

Published online: January 5, 2023.

Relevant financial relationships: **Ms Suthoff** is a current employee and **Ms Arnaud** and **Dr Werneburg** are former employees of Sage Therapeutics, Inc and own stock/stock options. **Drs Reinhart** and **Aleksanderek** are current or former employees of Tantalus Medical Communications, Ltd, which received financial support from Sage Therapeutics, Inc and Biogen, Inc for research and medical writing support. During the peer review process, both Sage Therapeutics, Inc and their collaboration partner Biogen, Inc had the opportunity to review and comment on this manuscript; however, the authors had full editorial control of the manuscript and provided final approval on all content. **Ms Fulwider** has received consulting fees from Sage Therapeutics, Inc. **Drs Brister** and **Duckworth** and **Ms Foxworth** have nothing to disclose.

Funding/support: This work was supported by Sage Therapeutics, Inc and Biogen, Inc.

Role of the sponsor: Employees of Sage Therapeutics, Inc contributed to the protocol design and manuscript drafting and review but had no role in the screening and study selection for inclusion in the systematic review.

Previous presentation: This work has not been presented previously.

Acknowledgments: The authors thank Katie Stenson, MSc, a former employee of Sage Therapeutics, Inc, for contributions to the design and interpretation of the systematic review and Shawn Eapen, MSc, and Sara Watchko, MPH, both affiliates of Tantalus Medical Communications (Victoria, British Columbia, Canada), for assistance

with the systematic review. Mr Eapen and Mss Stenson and Watchko have no conflicts of interest to declare. The authors thank Tantalus Medical Communications for providing research and medical writing support, which was funded by Sage Therapeutics, Inc and Biogen, Inc in accordance with Good Publication Practice (GPP3) guidelines.

Supplementary material: See accompanying pages.

REFERENCES

1. Bhattacharya R, Shen C, Sambamoorthi U. Excess risk of chronic physical conditions associated with depression and anxiety. *BMC Psychiatry*. 2014;14(1):10.
2. Kang HJ, Kim SY, Bae KY, et al. Comorbidity of depression with physical disorders: research and clinical implications. *Chonnam Med J*. 2015;51(1):8–18.
3. Arnaud AM, Brister TS, Duckworth K, et al. Impact of major depressive disorder on comorbidities: a systematic literature review. *J Clin Psychiatry*. 2022;83(6):21r14328.
4. Blue Cross Blue Shield Association. Major depression: the impact on overall health. Published 2018. Accessed February 5, 2020. https://www.bcbs.com/sites/default/files/file-attachments/health-of-america-report/HoA_Major_Depression_Report.pdf
5. Armbrecht E, Shah A, Schepman P, et al. Economic and humanistic burden associated with noncommunicable diseases among adults with depression and anxiety in the United States. *J Med Econ*. 2020;23(9):1032–1042.
6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
7. National Institute for Health and Care Excellence. The social care guidance manual Appendix B Methodology checklist: systematic reviews and meta-analyses. Published 2013. Accessed February 5, 2020. https://www.nice.org.uk/process/pmg10/chapter/appendix-b-methodology-checklist-systematic-reviews-and-meta-analyses
8. National Institute for Health and Care Excellence. The social care guidance manual Appendix C Methodology checklist: randomized controlled trials. Published 2012. Accessed February 5, 2020. https://www.nice.org.uk/process/pmg6/resources/the-guidelines-manual-appendices-bi-2549703709/chapter/appendix-c-methodology-checklist-randomised-controlled-trials
9. Walker J, Hansen CH, Martin P, et al; SMaRT (Symptom Management Research Trials) Oncology-3 Team. Integrated collaborative care for major depression comorbid with a poor prognosis cancer (SMaRT Oncology-3): a multicentre randomised controlled trial in patients with lung cancer. *Lancet Oncol*. 2014;15(10):1168–1176.
10. Mulick A, Walker J, Puntis S, et al. Does depression treatment improve the survival of depressed patients with cancer? A long-term follow-up of participants in the SMaRT Oncology-2 and 3 trials. *Lancet Psychiatry*. 2018;5(4):321–326.
11. Lyketsos CG, DelCampo L, Steinberg M, et al. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. *Arch Gen Psychiatry*. 2003;60(7):737–746.
12. Munro CA, Brandt J, Sheppard JM, et al. Cognitive response to pharmacological treatment for depression in Alzheimer disease: secondary outcomes from the depression in Alzheimer's disease study (DIADS). *Am J Geriatr Psychiatry*. 2004;12(5):491–498.
13. Thompson S, Herrmann N, Rapoport MJ, et al. Efficacy and safety of antidepressants for treatment of depression in Alzheimer's disease: a metaanalysis. *Can J Psychiatry*. 2007;52(4):248–255.
14. Dobkin RD, Menza M, Allen LA, et al. Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. *Am J Psychiatry*. 2011;168(10):1066–1074.
15. Dobkin RD, Tröster AI, Rubino JT, et al. Neuropsychological outcomes after psychosocial intervention for depression in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 2014;26(1):57–63.
16. Stewart JC, Perkins AJ, Callahan CM. Effect of collaborative care for depression on risk of cardiovascular events: data from the IMPACT randomized controlled trial. *Psychosom Med*. 2014;76(1):29–37.
17. Sherwood A, Blumenthal JA, Smith PJ, et al. Effects of exercise and sertraline on measures of coronary heart disease risk in patients with major depression: results from the SMILE-II randomized clinical trial. *Psychosom Med*. 2016;78(5):602–609.
18. Raskin J, Wiltse CG, Dinkel JJ, et al. Safety and tolerability of duloxetine at 60 mg once daily in elderly patients with major depressive disorder. *J Clin Psychopharmacol*. 2008;28(1):32–38.
19. Berkman LF, Blumenthal J, Burg M, et al; Enhancing Recovery in Coronary Heart Disease Patients Investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA*. 2003;289(23):3106–3116.
20. de Jonge P, Honig A, van Melle JP, et al; MIND-IT Investigators. Nonresponse to treatment for depression following myocardial infarction: association with subsequent cardiac events. *Am J Psychiatry*. 2007;164(9):1371–1378.
21. Glassman AH, Bigger JT, Gaffney M, et al. Heart rate variability in acute coronary syndrome patients with major depression: influence of sertraline and mood improvement. *Arch Gen Psychiatry*. 2007;64(9):1025–1031.
22. Glassman AH, O'Connor CM, Califf RM, et al; Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288(6):701–709.
23. Huffman JC, Mastromauro CA, Sowden G, et al. Impact of a depression care management program for hospitalized cardiac patients. *Circ Cardiovasc Qual Outcomes*. 2011;4(2):198–205.
24. Wiart L, Petit H, Joseph PA, et al. Fluoxetine in early poststroke depression: a double-blind placebo-controlled study. *Stroke*. 2000;31(8):1829–1832.
25. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus: an abridged Cochrane review. *Diabet Med*. 2014;31(7):773–786.
26. Ell K, Katon W, Xie B, et al. Collaborative care management of major depression among low-income, predominantly Hispanic subjects with diabetes: a randomized controlled trial. *Diabetes Care*. 2010;33(4):706–713.
27. Ell K, Katon W, Xie B, et al. One-year postcollaborative depression care trial outcomes among predominantly Hispanic diabetes safety net patients. *Gen Hosp Psychiatry*. 2011;33(5):436–442.
28. Lustman PJ, Griffith LS, Clouse RE, et al. Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. *Psychosom Med*. 1997;59(3):241–250.
29. Lustman PJ, Griffith LS, Freedland KE, et al. Cognitive behavior therapy for depression in type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med*. 1998;129(8):613–621.
30. Lustman PJ, Freedland KE, Griffith LS, et al. Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care*. 2000;23(5):618–623.
31. Petrak F, Herpertz S, Albus C, et al. Cognitive behavioral therapy versus sertraline in patients with depression and poorly controlled diabetes: the Diabetes and Depression (DAD) study: a randomized controlled multicenter trial. *Diabetes Care*. 2015;38(5):767–775.
32. Kinsinger SW, Lattie E, Mohr DC. Relationship between depression, fatigue, subjective cognitive impairment, and objective neuropsychological functioning in patients with multiple sclerosis. *Neuropsychology*. 2010;24(5):573–580.
33. Mohr DC, Hart S, Vella L. Reduction in disability in a randomized controlled trial of telephone-administered cognitive-behavioral therapy. *Health Psychol*. 2007;26(5):554–563.
34. Fava M, Mallinckrodt CH, Detke MJ, et al. The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher remission rates? *J Clin Psychiatry*. 2004;65(4):521–530.
35. Poleshuck EL, Gamble SA, Bellenger K, et al. Randomized controlled trial of interpersonal psychotherapy versus enhanced treatment as usual for women with co-occurring depression and pelvic pain. *J Psychosom Res*. 2014;77(4):264–272.
36. Marangell LB, Clauw DJ, Choy E, et al. Comparative pain and mood effects in patients with comorbid fibromyalgia and major depressive disorder: secondary analyses of four pooled randomized controlled trials of duloxetine. *Pain*. 2011;152(1):31–37.
37. McIntyre A, Paisley D, Kouassi E, et al. Quetiapine fumarate extended-release for the treatment of major depression with comorbid fibromyalgia syndrome: a double-blind, randomized, placebo-controlled study. *Arthritis Rheumatol*. 2014;66(2):451–461.
38. Borson S, McDonald GJ, Gayle T, et al. Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients with chronic obstructive pulmonary disease. *Psychosomatics*. 1992;33(2):190–201.
39. Cornelius JR, Salloum IM, Ehler JG, et al. Fluoxetine in depressed alcoholics: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 1997;54(8):700–705.
40. Mason BJ, Kocsis JH, Ritvo EC, et al. A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. *JAMA*. 1996;275(10):761–767.

41. Torrens M, Fonseca F, Mateu G, et al. Efficacy of antidepressants in substance use disorders with and without comorbid depression: a systematic review and meta-analysis. *Drug Alcohol Depend*. 2005;78(1):1–22.
42. Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. *JAMA*. 2004;291(15):1887–1896.
43. Nunes EV, Quitkin FM, Donovan SJ, et al. Imipramine treatment of opiate-dependent patients with depressive disorders: a placebo-controlled trial. *Arch Gen Psychiatry*. 1998;55(2):153–160.
44. Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med*. 2007;69(7):587–596.
45. Enomoto H, Fujikoshi S, Funai J, et al. Assessment of direct analgesic effect of duloxetine for chronic low back pain: post hoc path analysis of double-blind, placebo-controlled studies. *J Pain Res*. 2017;10:1357–1368.
46. Heo MH, Kim JY, Hwang I, et al. Analgesic effect of quetiapine in a mouse model of cancer-induced bone pain. *Korean J Intern Med (Korean Assoc Intern Med)*. 2017;32(6):1069–1074.
47. Bair MJ, Robinson RL, Katon W, et al. Depression and pain comorbidity: a literature review. *Arch Intern Med*. 2003;163(20):2433–2445.
48. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. *J Psychiatry Neurosci*. 2001;26(1):30–36.
49. Glassman AH. Depression and cardiovascular comorbidity. *Dialogues Clin Neurosci*. 2007;9(1):9–17.
50. Cascade E, Kalali AH, Kennedy SH. Real-world data on SSRI antidepressant side effects. *Psychiatry (Edgmont)*. 2009;6(2):16–18.
51. Brawer PA, Martielli R, Pye PL, et al. St. Louis Initiative for Integrated Care Excellence (SLI(2) CE): integrated-collaborative care on a large scale model. *Fam Syst Health*. 2010;28(2):175–187.
52. Reiss-Brennan B. Mental health integration: normalizing team care. *J Prim Care Community Health*. 2014;5(1):55–60.

See supplementary material for this article at PSYCHIATRIST.COM.

THE PRIMARY CARE COMPANION
FOR CNS DISORDERS

Supplementary Material

Article Title: Impact of Treating Depression on Associated Comorbidities: A Systematic Literature Review

Author(s): Alix M. Arnaud, MSc; Teri S. Brister, PhD; Ken Duckworth, MD; Phyllis Foxworth, BSc; Tonya Fulwider, BA; Ellison D. Suthoff, MBA; Brian Werneburg, PhD; Izabela Aleksanderek, PhD; and Marcia L. Reinhart, DPhil

DOI: https://doi.org/10.4088/PCC.22r03330

List of Supplementary Material for the article

1. Supplementary Table 1
2. Supplementary Table 2
3. Supplementary Table 3
4. Supplementary Table 4
5. Supplementary Table 5

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. Search strategies (searches conducted November 28, 2019)

#	MEDLINE	Embase	PsycINFO	Cochrane CCRCT
1	exp Depressive Disorder, Major/	exp major depression/	exp Major Depression/	(major adj2 depress*).ab,ti.
2	(major adj2 depress*).ab,ti.	(major adj2 depress*).ab,ti.	(major adj2 depress*).ab,ti.	(controlled clinical trial or randomized controlled trial).pt.
3	1 or 2	1 or 2	1 or 2	[disease-specific terms, see below]
4	Randomized Controlled Trial/	randomized controlled trial/	Randomized Controlled Trials/	1 and 2 and 3
5	Random Allocation/	controlled clinical trial/	Randomized Clinical Trials/	limit 4 to (case report or comment or editorial or letter or "review")
6	Double-Blind Method/	phase 3 clinical trial/	randomi?ed controlled trial$.tw.	4 not 5
7	Single-Blind Method/	phase 4 clinical trial/	(random$ adj2 allocat$).tw.	limit 6 to english language
8	clinical trial, phase iii.pt.	randomization/	single blind$.tw.	
9	clinical trial, phase iv.pt.	randomi?ed controlled trial$.tw.	double blind$.tw.	
10	controlled clinical trial.pt.	rct.tw.	((treble or triple) adj blind$).tw.	
11	randomized controlled trial.pt.	(random$ adj2 allocat$).tw.	or/4-10	
12	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	single blind$.tw.	[disease-specific terms, see below]	
13	randomly allocated.tw.	double blind$.tw.	3 and 11 and 12	
14	(allocated adj2 random$).tw.	((treble or triple) adj blind$).tw.	limit 13 to ("column/opinion" or "comment/reply" or editorial or letter or reviews)	
15	or/4-14	or/4-14	13 not 14	
16	[disease-specific terms, see below]	[disease-specific terms, see below]	limit 15 to english language	
17	3 and 15 and 16	3 and 15 and 16		
18	(review not systematic review).pt.	limit 17 to (editorial or letter or note or conference abstract or conference paper or "conference review")		
19	17 and 18	17 not 18		
20	17 not 19	limit 19 to english language		
21	limit 20 to (case reports or comment or editorial or letter)			
22	20 not 21			
23	limit 22 to english language			
24	exp Depressive Disorder, Major/			

#	MEDLINE	Embase	PsycINFO	Cochrane CCRCT
25	(major adj2 depress*).ab,ti.			
Disease-specific search terms				
Autimmune/infectious	**Cancer**	**CNS**	**CVD**	**GI**
	(((AIDS or acquired immune deficiency syndrome or acquired immunodeficiency syndrome or HIV or human immunodeficiency virus or human immun* deficiency virus or ankylosing spondylitis or Bechterew* or ((autoimmun* or auto-immun* or auto immune*) adj (disorder or disease)) or c?eliac or Gee-Herter* or crohn* or enteritis) adj region*) or MS or multiple sclerosis or psoriasis or (psoria* adj (skin or derm*)) or ulcerative colitis or (ulcer* adj (colitis or colon))).ab,ti.	(cancer* or (malignan* adj (neoplas* or tumo?r))).ab,ti.	(dementia or Alzheimer* or epilep* or Parkinson* or paralysis agitans).ab,ti.	(((coronary or isch?emic) adj (artery or heart or cardiac) adj (disease or disorder)) or (cardiovascular adj (disease or disorder or lesion or syndrome)) or IHD or CAD or CVD or hypertens* or (high adj2 blood pressure) or MI or ((myocard* or heart) adj infarct*) or heart attack or stroke or cerebrovascular accident or CVA).ab,ti.	(((gastrointestinal or digestive tract) adj (disease or disorder or syndrome or h?emorrhage or bleeding)) or gastroenteropathy or ?esophagitis or ((Escherichia coli or coliform) adj infection*) or "e.coli infection" or ((cardioesophageal or gastr* or ?esophageal) adj (reflux or regurgitation)) or GERD or (irritable adj (bowel or colon)) or IBS or IBD).ab,ti.
Metabolic/endocrine	**Musculoskeletal/pain**	**Respiratory**	**Substance abuse**	
(((metabolic or insulin resistance) adj syndrome) or diabet* or hyperlipid?emi* or lupus or obes* or adipos* or body weight or (polycystic adj ovar*) or PCOS or Stein-Leventhal).ab,ti.	(arthriti* or backache or (chronic adj pain) or fibromyalgia or headache or cephalalgia or cephalgia or migraine or hemicrania or ((back or head) adj2 (ache or pain)) or (joint adj (disease or disorder)) or arthropathy or (joint* adj inflamm*) or osteoporo*).ab,ti.	(asthma or (chronic adj2 (pulmonary or lung or bronchopulmonary) adj (disease or disorder)) or COPD or bronchitis or (bronch* adj (infection or inflammation)) or emphysema).ab,ti.	((substance or drug or alcohol) adj2 abus*).ab,ti.	

CNS, central nervous system, CVD, cardiovascular disease, GI, castrointestinal. Supplementary congress abstract searches conducted for 2018 and 2019 in the Academy of Managed Care Pharmacy (AMCP) Annual Meeting and Nexus, American Psychological Association (APA) annual congress, European Psychological Association (EPA) annual congress, European College of Neuropsychopharmacology (ECNP) annual congress, and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) annual congresses.

Supplementary Table 2. Study inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Diagnosis of MDD Adults ≥18 years of age	Mixed population where MDD subgroup is not reported separately Age <18 years
Intervention(s)	Any antidepressant treatment	No restrictions
Comparator(s)	Any comparator, including placebo	No comparator
Outcomes	Improvement in depression outcomes Risk of comorbidity or severity of existing comorbidity	No statistically significant improvement in depression outcomes
Study type	RCTs Meta-analyses of RCTs	Non-human studies Observational studies Commentaries and letters Recommendations/guidelines Methods articles/protocols Hypothetical models Narrative reviews
Other	English language only Located in Europe and North America	Non-English language Local studies in countries outside of Europe and North America

MDD, major depressive disorder; RCT, randomized controlled trial.

List of congresses searched

- Academy of Managed Care Pharmacy (AMCP) – Annual Meeting and Nexus
- American Psychological Association (APA)
- European Psychological Association (EPA)
- European College of Neuropsychopharmacology (ECNP)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – all conferences

Supplementary Table 3. Quality assessment of RCTs—part 1

	Selection bias				Performance bias				Attrition bias			
Reference(s)	A1	A2	A3	Risk of bias	B1	B2	B3	Risk of bias	C1	C2	C3	Risk of bias
Berkman 2003	Unclear	Yes	Yes	Unclear	Yes	No	No	High	Yes	Yes	Yes	Low
Borson 1992	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Yes	Unclear	Low
Cornelius 1997	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Yes	Unclear	Unclear
de Jonge 2007	Yes	Unclear	Yes	Unclear	No	Yes	Yes	Low	Yes	Yes	Unclear	Low
Dobkin 2011; Dobkin 2014	Yes	Yes	Yes	Low	Yes	No	No	High	Yes	Yes	Yes	Low
Ell 2010; Ell 2011	Yes	Yes	Unclear	Unclear	No	No	No	High	Yes	Yes	Yes	Low
Fava 2004	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Unclear	Unclear	Unclear
Glassman 2002; Glassman 2007	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear	Low	Yes	Unclear	Unclear	High
Huffman 2011	Yes	Unclear	Yes	Low	Yes	No	No	High	Yes	Yes	Yes	Low
Lustman 1997	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Yes	Yes	Low
Lustman 1998	Unclear	Yes	Yes	Low	Yes	No	No	High	Yes	Yes	Yes	Low
Lustman 2000	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Yes	Unclear	Unclear
Lyketsos 2003; Munro 2004	Yes	Yes	Yes	Low	Yes	Yes	Yes	Low	Yes	Yes	Yes	Low
Marangell 2011	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Unclear	Unclear	Unclear
Mason 1996	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Yes	Unclear	Unclear
McIntyre 2014	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Yes	Yes	Low
Mohr 2007; Kinsinger 2010	Unclear	Unclear	Yes	Unclear	Yes	No	No	High	Yes	Yes	Unclear	Low
Mulick 2018	Yes	Yes	Yes	Low	No	No	No	High	Yes	Yes	Yes	Low
Nunes 1998	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Low	Yes	Yes	Yes	Low

	Selection bias				Performance bias				Attrition bias			
Reference(s)	A1	A2	A3	Risk of bias	B1	B2	B3	Risk of bias	C1	C2	C3	Risk of bias
Petrak 2015	Yes	Unclear	Yes	Unclear	Yes	No	No	High	Yes	Yes	Unclear	Unclear
Poleshuck 2014	Yes	Yes	Yes	Low	Yes	No	No	High	Yes	Yes	Yes	Low
Raskin 2008	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear	Low	Yes	Yes	Unclear	Low
Sherwood 2016	Yes	Yes	Yes	Low	Yes	Unclear	Unclear	Low	Yes	Yes	Yes	Low
Stewart 2014	Yes	Unclear	Yes	Unclear	Yes	No	No	High	Yes	Yes	Unclear	Low
Walker 2014; Mulick 2018	Yes	Yes	Yes	Low	No	No	No	High	Yes	Yes	Yes	Low
Wiart 2000	Unclear	Unclear	Yes	High	Yes	Yes	Unclear	Low	Yes	Yes	Yes	Low

A1, appropriate method of randomization was used; A2, adequate concealment of allocation; A3, groups were comparable at baseline; B1, groups received the same care and support apart from the intervention(s) studied; B2, participants were kept 'blind' to intervention allocation; B3, individuals administering care and support were kept 'blind' to intervention allocation; C1, all groups were followed up for an equal length of time; C2, groups were comparable for intervention completion; C3, groups were comparable with respect to the availability of outcome data.

Supplementary Table 4. Quality assessment of RCTs—part 2

	Detection bias					Overall		
Reference(s)	D1	D2	D3	D4	D5	Risk of bias	Internal validity	External validity
Berkman 2003	Yes	Yes	Yes	No	Unclear	Unclear	+	++
Borson 1992	Yes	Yes	Yes	Yes	Unclear	Unclear	+	++
Cornelius 1997	Yes	Yes	Yes	Unclear	Unclear	Unclear	+	++
de Jonge 2007	Yes	Yes	Yes	Yes	Unclear	Unclear	+	++
Dobkin 2011; Dobkin 2014	Yes	Yes	Yes	No	Unclear	Unclear	++	++
Ell 2010; Ell 2011	Yes	Yes	Yes	Yes	Unclear	Unclear	+	+
Fava 2004	Yes	Yes	Yes	Unclear	Unclear	Unclear	+	++
Glassman 2002; Glassman 2007	Yes	Yes	Yes	Yes	Unclear	Low	+	++
Huffman 2011	Yes	Yes	Yes	Yes	Unclear	Unclear	++	++
Lustman 1997	No	Yes	Yes	Yes	Unclear	Unclear	+	++
Lustman 1998	Yes	Yes	Yes	Yes	Unclear	Unclear	++	++
Lustman 2000	No	Yes	Yes	Yes	Unclear	Unclear	+	++
Lyketsos 2003; Munro 2004	Yes	Yes	Unclear	Yes	Unclear	Unclear	++	++
Marangell 2011	Yes	Yes	Yes	Unclear	Unclear	Unclear	+	++
Mason 1996	Yes	Yes	Yes	Yes	Unclear	Unclear	+	++
McIntyre 2014	Yes	Yes	Yes	Yes	Unclear	Unclear	+	++
Mohr 2007; Kinsinger 2010	Yes	Unclear	Yes	Yes	Unclear	Unclear	+	++
Mulick 2018	Yes	Yes	Yes	No	Unclear	Unclear	++	++
Nunes 1998	No	Yes	Yes	Yes	Unclear	Unclear	+	++
Petrak 2015	Yes	Yes	Yes	Yes	Unclear	Unclear	+	++
Poleshuck 2014	Yes	Yes	Yes	Yes	Unclear	Unclear	++	+
Raskin 2008	Yes	Yes	Yes	Yes	Unclear	Unclear	+	++
Sherwood 2016	Yes	Yes	Yes	Yes	Unclear	Unclear	++	++
Stewart 2014	Yes	Yes	Yes	No	Unclear	Unclear	+	++
Walker 2014; Mulick 2018	Yes	Yes	Yes	No	Unclear	Unclear	++	++
Wiart 2000	Unclear	Yes	Yes	Unclear	Unclear	Unclear	+	++

D1, appropriate length of follow-up; D2, used a precise definition of outcome; D3, a valid and reliable method was used to determine the outcome; D4, investigators were kept 'blind' to participants' exposure to the intervention; D5, investigators were kept 'blind' to other important confounding factors.

Supplementary Table 5. Quality assessment of meta-analyses

	Screening questions					Overall assessment	
Reference(s)	1	2	3	4	5	Internal validity	External validity
Baumeister 2014	Yes	Yes	Yes	Yes	Yes	++	++
Nunes 2004	Yes	Yes	Yes	Yes	Yes	++	++
Thompson 2007	Yes	Yes	Yes	Yes	Yes	++	++
Torrens 2005	Yes	Yes	Yes	Yes	Yes	++	+

1, the review addresses an appropriate and clearly focused question that is relevant to the review question; 2, the review collects the type of studies you consider relevant to the guidance review question; 3, the literature search is sufficiently rigorous to identify all the relevant studies; 4, study quality is assessed and reported; 5, an adequate description of the methodology used is included, and the methods used are appropriate to the question.