Mood disorders: cardiovascular and diabetes comorbidity
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Purpose of review
Depression is often associated with medical comorbidity. New research quantifies patterns of mood disorder in illnesses such as cardiovascular disease and diabetes, evaluates the prognostic significance of mood symptoms, and seeks to identify common mechanisms for both mood and medical disease. This review provides recent findings on comorbidity, summarizes mechanistic hypotheses, and outlines developments in treatment and services.

Recent findings
Depression occurs in up to one-quarter of patients with cardiovascular disease and diabetes. Depressed patients with heart disease have poorer medical outcomes including increased risk of reinfarction and all-cause mortality. Patients with diabetes and depression have poorer glycemic control, more diabetes symptoms, and greater all-cause mortality. Depression is associated with both biological (hypothalamic−pituitary−adrenal axis dysregulation) and psychosocial processes (adherence, poorer diet, and exercise) that may mediate adverse medical outcomes. Antidepressant treatments are effective in treating depression in medically ill patients, but their impact on medical outcomes remains to be quantified.

Summary
Depression, cardiovascular disease, and diabetes are among the most common chronic illnesses affecting an aging population. Depression is treatable in patients with medical illnesses, and collaborative care models can yield better detection and depression treatment in primary care settings in which most patients with depression are seen.

Keywords
cardiovascular disease, collaborative care, comorbidity, depression, diabetes

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Introduction
Depression is among the leading global causes of years lived with disability and is often associated with medical comorbidity. Depressed individuals are more likely to suffer from medical illnesses such as heart disease and diabetes, and as depression increases morbidity and mortality in these and other medical disorders, depression and medical comorbidity are of considerable public health importance. Although the rates of mood disorder in specific medical illnesses are fairly well established, questions concerning shared pathophysiology and the relationship between biological and psychological processes that manifest together in comorbid disorders are unclear. Nevertheless, the complexity of this relationship is recognized as increasingly significant for improving both psychiatric and medical outcomes. This review synthesizes what is currently known and offers future directions.

Depression and medical diagnoses
Eaton *et al*. [1••] summarized findings from the Baltimore, Maryland Epidemiological Catchment Area (ECA), a 13-year follow-up of a representative US community sample assessed for common psychiatric illness. A diagnosis of depression at index evaluation was associated with increased odds ratio (OR) for type II diabetes (OR = 2.2), myocardial infarction (MI) (OR = 4.5), stroke (OR = 2.7), and arthritis (OR = 1.3). Although few other data quantify the proportion of individuals with mood disorder who concurrently suffer from a major medical illness, many studies evaluate the prevalence of depression in medically ill populations. In the first study [2••] of a nationally representative US sample to evaluate the risk of depression after onset of a range medical illnesses

(cancer, diabetes, hypertension, heart disease, arthritis, and stroke) followed up 8387 adults age 51–61 years from 1994 to 2000. The risk of depression was greatest in participants following the onset of cancer, arthritis, chronic lung disease, and heart disease. The peak time of risk varied by illness, but participants with heart disease showed elevated risk up to 8 years after medical diagnosis. Relative to an estimated 10% major depression prevalence in the general population, prevalence ranges for depression in clinical samples are estimated to be 17–27% for cardiac disease, 14–19% for cerebrovascular disease, 30–50% for Alzheimer's disease, 20–55% for recurrent epilepsy, 9–26% for diabetes, 22–29% for cancer, and 5–20% for human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS) [3••].

Substantial evidence supports antidepressant treatment efficacy (in treating depression) in many medical conditions. Evans et al. [3••] and Bogner et al. [4] found little impact of specific co-occurring medical diagnoses on the rate of depression treatment response to enhanced intervention among 324 adults meeting criteria for major depression with co-occurring medical illnesses. Similarly, Simon et al. [5•] reported significant improvement in mood, and social and emotional functioning in patients with heart disease, diabetes, and chronic obstructive pulmonary disease (COPD) treated with antidepressant therapy. Krishnan [6] reports that one or more of the selective serotonin reuptake inhibitors (SSRIs) are effective in treating depression in patients with ischemic heart disease (IHD), diabetes, dementia, and Parkinson's disease. The effect of depression treatment on medical outcomes in these disorders, however, has not been firmly established.

Cardiovascular disease
Epidemiological evidence supports the conclusion that (a) depression, even in mild forms, is an independent risk factor for future IHD including cardiac death, fatal and nonfatal MIs; (b) the prevalence of depression in patients with IHD [MI, unstable angina, congestive heart failure (CHF), coronary artery bypass graft] is between two to three times greater than that in the general population; and (c) depression is a powerful prognostic factor for patients with IHD (post-MI and unstable angina) increasing the relative risk (RR) of readmission, a second MI, and/or cardiac death between twofold and 7.5-fold [7••]. In a case–control study [8] of 2228 outpatients enrolled in a health maintenance organization (HMO) who experienced cardiac arrest during a 15-year period, depressed patients of both sexes had higher OR of cardiac arrest that persisted after adjustment for confounders [1.88; 95% confidence interval (CI), 1.59–2.23]. A smaller case–control study [9] found recurrent major depression associated with a twofold to threefold increased risk of coronary and/or aortic calcification in a group of depressed women.

Pathophysiology and mechanism
Hypotheses regarding the mechanistic link between depression and cardiovascular focus on biological and/or psychosocial correlates of depression and poor cardiac outcome including (a) increased sympathetic nervous system (SNS) or hypothalamic–pituitary–adrenal (HPA) function, (b) SNS-related decreased heart rate variability (HRV), (c) dysregulation of inflammatory and immune functioning, (d) increased platelet/endothelial aggregation, (e) poor treatment compliance and/or unhealthy lifestyles, and (f) a cardio-toxic effect of antidepressant medications [10•].

Using data from 2627 participants in the Women's Health Initiative Observational Study, Kim et al. [11] reported that postmenopausal women with depression had greater heart rate and lower HRV than nondepressed women. Decreased HRV is associated with coronary artery disease (CAD), increased mortality after MI, future ventricular arrhythmia, and sudden death. A report from Heart and Soul [12•], a study of 873 outpatients selected on the basis of history of coronary heart disease (CHD) found no association between depression and HRV in 195/873 (22%) of participants with depression and stable CHD. The authors suggest that decreased HRV may only be associated with unstable CHD (e.g., post-MI, unstable angina) and note that in contrast to other studies, their sample included relatively few women. Depressed patients in this study, however, were more likely to report not taking their medications as prescribed (OR = 2.8; 95% CI, 1.7–4.7; $P < 0.001$); forgetting to take medication (OR = 2.4; 95% CI, 1.6–3.8; $P < 0.001$), and deciding to skip their medication (OR = 2.2; 95% CI, 1.2–4.2; $P = 0.01$), suggesting that medication nonadherence may be an important mediator of CHD mortality in depression, particularly in more representative community samples. In support of this hypothesis, Katon et al. [13] used a managed care database and found that among patients with CAD, dyslipidemia, and/or diabetes who were prescribed an antidepressant, adherence to antidepressant drug therapy was associated with increased adherence to comorbid disease medication and reduced costs for care of CAD, dyslipidemia, and diabetes. A review of smoking, another potential behavioral mediator of the depression–CHD mortality link [14], concluded that there is modest evidence for mediation (depressed individuals are more likely to smoke), but as most studies control for smoking, there is no evidence that smoking moderates this relationship.

Animal studies [15•] indicate that administration of endotoxin or interleukin-1 induces sickness behavior that overlaps with depression. Mice carrying deletions of the proinflammatory cytokine receptor, tumor necrosis factor-alpha receptor 1 (TNFR1) demonstrate antidepressant-like responses and decreased fear conditioning and

mice with TNFR2 receptor deletion show increased hedonic tone [16]. Shimbo *et al*. [17•] review studies establishing that depressive symptoms are significantly associated with higher levels of C-reactive protein (CRP) and that CRP levels predict future coronary events independent of other risk factors. Similar relationships have been found for other inflammatory biomarkers such as interleukin-6, soluble intercellular adhesion molecule-1, and P-selectin. In humans, interleukin-2, interferon-alpha (IFN-α), and endotoxin administration induce a syndrome that includes two components: general malaise and cognitive deficits and sleep disturbance, loss of appetite, and mood symptoms. Available studies preclude clarification of causal pathways involved in the association between inflammatory cytokines, depression, and CHD events. Although no prospective trial has yet assessed whether targeting inflammatory cytokines will reduce the symptoms of major depression, several recent studies demonstrate that SSRI antidepressants effectively treat the mood and anxiety component of IFN-α-induced depressive syndrome [18].

Bruce and Musselman [19] review studies that indicate increased platelet activation (GPIIb/IIIa receptor binding, change in platelet shape, degranulation, secretion of contents, and aggregation; e.g., 'stickiness') among patients with depression at risk for IHD. Brydon *et al*. [20] note that these studies have been inconsistent, but that links between stress, catecholamine release, and serotonergic control of the HPA axis render platelet activation a plausible mechanism linking stress and/or depression and CHD mortality. In a substudy of the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART), Serebruany *et al*. [21••] found that plasma levels of the antidepressant sertraline and its metabolite *N*-desmethylsertraline were strongly negatively correlated with the release of platelet/endothelial biomarkers, providing evidence that this SSRI in therapeutic concentrations exhibits antiplatelet and endothelium-protective properties.

Treatment and medical outcome
Three large-scale studies of depression-related interventions in post-MI patients have been reported. The Canadian Montreal Heart Attack Readjustment Trial (MHART) randomized 1376 post-MI patients not selected for preexisting depression to usual care or an intervention to reduce psychological distress. With the exception of a possible negative effect on women, no reduction in 1-year or 5-year cardiac mortality was found [22,23]. The National Institutes of Health (NIH)-funded Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial randomized 2481 post-MI patients who met criteria for major depression or low social support to 6 months of usual care or a 6-month cognitive-behavioral intervention. During a 5-year follow-up (mean

29 months), the treatment groups did not differ in survival without a nonfatal MI, the primary study endpoint [24] and women had poorer outcome than men. The multisite industry-sponsored SADHART study randomized 369 post-MI or patients with unstable angina with major depression to sertraline (50–200 mg) or placebo for 24 weeks. Sertraline was effective in treatment of depression and was not associated with worsening of cardiovascular parameters. Although not reaching statistical significance, the RR for at least one cardiac event (death, MI, stroke, worsened angina, CHF) was reduced for the sertraline group (RR = 0.68; 95% CI, 0.43–1.09) [25].

Post-hoc analyses from the ENRICHD trial [26•] indicate reduced mortality and reinfarction among the subgroup of depressed patients nonrandomly treated with antidepressant medications, most often, sertraline. Joynt and O'Connor [27] point out that SADHART was underpowered to detect changes in cardiovascular mortality but does provide strong evidence for the safety of sertraline for depression in patients with cardiovascular disease. A comprehensive review of clinical trial data [28••] on the cardiac safety profile of antidepressant medication concludes that tricyclic antidepressants are effective against depression but associated with adverse cardiovascular side effects, that SSRIs have benign cardiovascular profiles and are well tolerated in patients with cardiac disease, and that the safety of dual action [serotonin and norepinepherine reuptake inhibitors; e.g., serotonin–norepinephrine reuptake inhibitors (SNRIs)] require further study. Clinicians should note that individual SSRIs differ with regard to drug–drug interactions with commonly prescribed cardiac medications based on inhibition of cytochrome P (CYP450) enzymes. A Cochrane Collaboration [29] review failed to find a single well designed randomized controlled trial (RCT) assessing the effects of psychological interventions for depression in people with heart failure. In summary, the impact of depression treatment on morbidity and mortality in patients with cardiovascular disease has yet to be demonstrated in adequately powered trials. Even absent definitive cardiac benefit, however, depression screening and treatment is advocated because of its consistent positive impact on quality of life [30•].

Diabetes
During the past 25 years, the number of people in the United States diagnosed with diabetes has more than doubled from 5.8 to 14.7 million [31]; 90–95% of cases are type II diabetes and diabetes prevalence is greatest in ethnic minorities and in those older than 60 years of age [32]. Epidemiological data [33] indicate both that depression is an independent risk factor for onset of type II diabetes and that future depression risk is increased by a factor of two in patients with diabetes [34]. A comprehensive review [35••] notes that depression probably

affects one-quarter of the diabetic population and is associated with decreased metabolic control, poor medication and diet adherence, reduced quality of life, and higher healthcare expenditures. Likewise, poor diabetes control may worsen depression and impair antidepressant treatment response.

Gross *et al.* [36] studied diabetic patients of Hispanic ancestry in an urban medical practice and reported that the probability of poor glycemic control (HbA(1c) > 8.0) increased with depression severity: 55.7% of 70 patients with major depression had HbA(1c) $\geq$ 8%, compared with 39/92 (42.4%) in the minimal-to-mild depression group, and 15/47 (31.9%) in the no depression group (P = 0.01; OR = 3.27; 95% CI, 1.23–8.64 for moderate or severe depression vs. no-depression). Less than half of the depressed patients received mental healthcare in the past year.

Cohort studies document increased mortality among depressed individuals compared with nondepressed individuals with diabetes. Black *et al.* [37] followed up 2830 Mexican Americans older than age 65 years of age for 7 years and found higher rates of microvascular and macrovascular events and mortality in participants with diabetes and depression compared with those with either condition alone. Comorbidity predicted both earlier and more adverse events. Egede *et al.* [38•] studied 10 025 participants in the population-based National Health and Nutrition Examination who were interviewed in 1982. During 8 years, hazard ratios for all-cause mortality were as follows: depression alone, 1.20 (95% CI, 1.03–1.40); diabetes alone, 1.88 (95% CI, 1.55–2.27); and diabetes–depression co-occurrence, 2.50 (95% CI, 2.04–3.08). Hazard ratios for CHD mortality were depression alone, 1.29 (95% CI, 0.96–1.74); diabetes alone, 2.26 (95% CI, 1.60–3.21); and diabetes–depression co-occurrence, 2.43 (95% CI, 1.66–3.56). Zhang *et al.* [39] noted that in this sample, depression increased mortality only in individuals with diabetes. Katon *et al.* [40] followed up 4154 patients with type II diabetes in the Group Health Diabetes registry-based Pathways Study for 3 years and found 275 (8.3%) deaths among 3303 patients without depression compared with 48 (13.6%) deaths among 354 patients with minor depression and 59 (11.9%) deaths among 497 patients with major depression. Compared with nondepressed patients with diabetes, minor depression was associated with a 1.67-fold increase in mortality (P = 0.003), and major depression a 2.30-fold increase (P < 0.0001). In an Australian community-based study, Bruce *et al.* [41] found higher mortality in depressed patients compared with nondepressed patients with type II diabetes followed up for an average of 7.8 years, but noted that when diabetic microvascular and macrovascular complications were added to the Cox models, depression was not significantly associated with excess mortality. They suggest that depression may contribute to the progression of important prognostic variables in diabetes, particularly vascular changes.

Mechanism

Physiological functions disrupted in depression that influence normal glucose–insulin homeostasis include (a) dysregulation of HPA axis, (b) abnormal sleep physiology, (c) diminished activity levels, (d) inflammatory cytokine activation, (e) diminished central serotonin function associated with hyperphagia, and (f) central mechanisms mediated by depression-induced disruption in the insulin receptor-rich hippocampus [42••].

Health behaviors related to depression also influence medical outcome. Among 6090 patients age 18–64 years studied in a large employee-based pharmacy database, 1-year nonadherence to oral hypoglycemic agents and insulin approached 50% [43]. In the HMO-based Pathways Study [44], almost half (48.9%) of 4463 patients with mostly type II diabetes had a body mass index (BMI) > 30 kg/m^2 and 47.8% exercised less than once a week. Major depression was significantly associated with less physical activity, lower adherence to medications and unhealthy diet [45]. Patients in this cohort with major depression and diabetes with or without evidence of heart disease had a higher number of CHD risk factors [smoking, BMI > 30.0; physical inactivity, hypertension, low-density lipoprotein (LDL) >130, triglyceride > 400, microalbuminuria, HbA(1c) > 8.0] and were more likely to have three or more risk factors [46].

In a study of 1034 adult patients with diabetes enrolled in an HMO, Surwit *et al.* [47] only found a relationship between depression and glycemic control in patients taking three or more insulin shots per day, the most complex treatment regimen. They suggest that depression-induced changes in self-care may be more important in patients with complex regimens or that patients with less endogenous insulin may be more susceptible to depression-related metabolic dysregulation. Sacco *et al.* [48•] reported that diabetic patients who were less adherent with self-care had lower self-efficacy (confidence that they could engage in health behavior) and that low self-efficacy mediated the relationship between poor adherence, high BMI, and depression. Diabetic symptoms can be painful and disabling. Vileikyte *et al.* [49] found that severity of diabetic neuropathy was significantly associated with depression scores and this was partially mediated by perception of symptom unpredictability, lack of symptom control, and restrictions in activities of daily living (ADLs). Unsteadiness was the symptom most strongly associated with depression.

Treatment

Cognitive behavioral therapy (CBT) and SSRIs are effective for the treatment of depression in diabetes

and are weight neutral [35••]. A review of preclinical and clinical data on antidepressant medications and glucose metabolism indicates that some SSRIs (e.g., fluoxetine, paroxetine) reduce hyperglycemia, normalize glucose homeostasis and increase insulin sensitivity, whereas some noradrenergic antidepressants (e.g., desipramine) exert opposite effects. Dual-mechanism antidepressants (e.g., duloxetine and venlafaxine) do not appear to disrupt glucose metabolism, whereas monoamine oxidase inhibitors (e.g., phenelzine) are associated with hypoglycemia and an increased glucose disposal rate [42••].

Clinical studies evaluating the effect of depression treatment on glycemic control have been mixed. Lustman et al. [50] randomized 51 patients with type II diabetes and major depression to 12-week CBT or no specific treatment. A greater percentage of patients receiving CBT achieved remission of depression and 6-month follow-up (but not immediate) Hg1Ac in levels were significantly better in the CBT group (mean 9.5% compared with 10.9%; $P = 0.03$). With respect to antidepressant medications, Lustman et al. [51] observed improvement in depression but worsening of glycemic control in 28 depressed diabetic patients treated with nortriptyline for 8 weeks. A second study from this group [52] randomized 60 patients with type I and type II diabetes to fluoxetine or placebo for 8 weeks. Fluoxetine group showed greater improvement in depression and a nonsignificant improvement in Hg1Ac ($P = 0.13$). In a small single-blind study, Paile-Hyvarinen et al. [53] randomized 15 mildly depressed women with type II diabetes to paroxetine or placebo for 10 weeks. No difference between groups was found in quality of life, but a trend toward superior glycemic control was seen in the paroxetine group ($P = 0.08$). On balance, evidence for improved glycemic control with the treatment of depression in diabetes is not impressive, although studies have been small and underpowered.

Depression detection and care among patients with diabetes is often suboptimal. In the Pathways Study, Katon et al. [54] used data from 9063 HMO Diabetes registry patients and found that only half (51%) of patients with major depression were recognized as depressed by the health system; among these 43% received one or more antidepressant prescriptions and only 6.7% received four or more psychotherapy sessions during a 12-month period. Data from this survey [55] also demonstrated that severity of depression was a greater predictor of diabetic symptom burden than measures of glycemic control and that for individuals with major depression and diabetes, total health service costs during a 6-month period were more than 70% higher than for diabetic patients without depression [56•].

To improve depression treatment in primary care, Katon et al. [44] built upon registries developed in the Pathways project and tested a collaborative care model of service delivery in an RCT that included 329 patients with diabetes and depression. The intervention, delivered by three part-time nurses, offered an initial choice of two evidence-based treatments [medications or the psychosocial problem solving treatment (PST)] with a stepped care progression to four options (switch to the treatment not chosen, a different antidepressant, the combination of medication and PST, or referral for specialty consultation). Patients were seen for an initial 1-h visit, then twice a month for 0–12 weeks. The treatment focused on depression and did not address diabetes care. Compared with usual care, collaborative care patients demonstrated significantly greater improvement in depression at 6 and 12 months. No between-group differences in Hg1Ac were found, and during the 12-month evaluation period, enhanced depression care and outcomes were not associated with improved diabetes self-care behaviors [57••]. The investigators conclude that though depression-focused collaborative care improves depression outcomes, integrated self-care interventions tailored for specific conditions will be required to simultaneously achieve better depression and medical outcomes in comorbid conditions.

In a preplanned substudy of a similar collaborative depression care model delivered in 18 primary care clinics, Katon et al. [58•] identified 418 patients with diabetes and depression. Relative to usual care, those in the intervention group experienced 115 (95% CI, 72–159) more depression-free days during 24 months. Total outpatient costs were only US$25.00 higher for intervention group patients during this same time. The value of the additional depression-free days yielded an incremental net benefit in the intervention group of US$1129 (95% CI, 692–1572).

Depression and diabetes in children and adolescents

Co-occurrence of depression and diabetes in children and adolescents presents unique clinical challenges including difficulties in diagnosis and treatment, the role of family functioning in symptom exacerbation, and the developmental task of transition of diabetes care from the parent to the child [59]. Although effective behaviorally oriented family interventions that target family conflict and better glycemic control have been described, studies focused specifically on depressed children and adolescents have yet to be conducted.

Conclusion

During the period of this review, new studies supported the co-occurrence of depression in CHD and diabetes at a rate that exceeds chance and indicated that depression

adversely affects medical outcome in these disorders. Although the mechanism of these associations is not fully understood, evidence indicates that both biological dysregulation and behavioral impairments in self-care associated with depression may mediate the relationship between depression and poor medical outcome. Both primary care physicians and psychiatrists should be cognizant of the common co-occurrence of depression with heart disease and diabetes and consider the possibility of comorbidity in their patients. Antidepressant medications and cognitive-behavioral therapy are effective in treating depression in patients with CHD and diabetes, but their effect on improving medical outcomes has yet to be convincingly demonstrated. Nonetheless, better detection and treatment of depression will reduce suffering and improve quality of life for patients with cooccurring disorders. The development of collaborative care service models improves depression outcomes in primary care, but new integrated medical–psychiatric approaches will probably be required to achieve better depression and medical outcomes.

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