State of the art

Epidemiology and treatment of depression in patients with chronic medical illness

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There is a bidirectional relationship between depression and chronic medical disorders. The adverse health risk behaviors and psychobiological changes associated with depression increase the risk for chronic medical disorders, and biological changes and complications associated with chronic medical disorders may precipitate depressive episodes. Comorbid depression is associated with increased medical symptom burden, functional impairment, medical costs, poor adherence to self-care regimens, and increased risk of morbidity and mortality in patients with chronic medical disorders. Depression may worsen the course of medical disorders because of its effect on proinflammatory factors, hypothalamic-pituitary axis, autonomic nervous system, and metabolic factors, in addition to being associated with a higher risk of obesity, sedentary lifestyle, smoking, and poor adherence to medical regimens. Both evidence-based psychotherapies and antidepressant medication are efficacious treatments for depression. Collaborative depression care has been shown to be an effective way to deliver these treatments to large primary care populations with depression and chronic medical illness.

There is increasing recognition that patients with major depression and bipolar disorder are dying prematurely due to medical illnesses. Evidence suggests that patients with depression die 5 to 10 years earlier and those with bipolar illness die 10 to 20 years earlier than patients without these psychiatric disorders.[1,2] They die from medical disorders such as vascular disease, diabetes, chronic obstructive pulmonary disease (COPD)/asthma and cancer, which account for most mortality in the general population. However, patients with depression and other psychiatric illnesses often develop these illnesses at an earlier age due to both maladaptive health risk behaviors as well as the physiologic effects of their psychiatric illnesses. There is also emerging evidence that the distress, symptom burden, and functional impairment and physiologic changes associated with chronic medical disorders often worsen the course of affective illness.[3,4] This article will review the bidirectional relationship between depression and chronic medical illness and the association of depression with problems in the physician-patient relationship, health risk behaviors, medical symptom burden, functional impairment, adherence to self-care regimens, medical complications, and mortality. The maladaptive psychophysiologic effects of depression on hypothalamic-pituitary axis, autonomic nervous system,

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metabolism, and immune system will also be reviewed. Studies that have tested whether evidence-based depression psychotherapies and pharmacological treatments are efficacious in patients with comorbid depression and chronic medical illness will be described. The evidence in this review will focus on the complex interaction between depression and two of the most common medical disorders: diabetes and cardiovascular disease.

Epidemiology of depression and chronic medical illness

Patients with chronic medical illnesses have been found to have two- to threefold higher rates of major depression compared with age- and gender-matched primary care patients.[5-7] Rates of depression in primary care patients are between 5% and 10%,[8] whereas prevalence rates of depression in patients with diabetes and coronary heart disease (CHD) have been estimated to be 12% to 18%[5] and 15% to 23%[6,7] respectively.

Patten and colleagues found in a large, prospective Canadian community-based study that there was an increased risk of development of major depression in subjects with chronic medical disorders compared with those without such disorders.[9] A total of 4% of those with one or more medical conditions versus 2.8% of those without medical conditions developed major depression over a 2-year period.[9] Wells and colleagues in the Epidemiologic Catchment Area Study found that respondents suffering from one or more of eight chronic medical conditions had a 41% increase in the risk of having any recent psychiatric disorder (depression, anxiety, or substance abuse).[10] Von Korff and colleagues have shown that childhood adversity and depression occurring in adolescence to early adulthood were independent risk factors for development in adulthood of a range of medical disorders, including diabetes, coronary heart disease, asthma, osteoarthritis, epilepsy, and hypertension.[11]

Studies have suggested that the relationship between depression and diabetes and/or heart disease is bidirectional. A recent meta-analysis of 13 studies that included 6916 subjects examined whether depression predicted subsequent development of diabetes.[12] This systematic review found that the pooled relative risk (RR) of depression predicting diabetes was 1.60 (95% CI 1.37, 1.88).[12] This meta-analysis also found 7 studies representing 6414 subjects that examined whether type 2 diabetes increased the subsequent risk of depression. There was modest evidence to support the hypotheses that diabetes was a risk factor for subsequent depression [RR = 1.15 (95% CI 1.02, 1.30)].[12] A recent 5-year prospective study examined factors associated with major depression at 5-year follow-up in approximately 3000 patients with diabetes. Baseline minor and major depression, the number of diabetes symptoms, and having one or more cardiac procedures during the 5-year follow-up (OR=1.92, 95% CI 1.10, 3.35) were independent predictors of major depression at this 5-year time-point.[3]

A systematic review found 8 studies that examined the risk of depression for subsequent onset of myocardial infarction. Clinically diagnosed major depressive disorder was identified as an important risk factor for subsequent development of cardiovascular disease (CVD, RR =1.60 [95% CI 1.34, 1.92]).[13] Depression following myocardial infarction is also very common, occurring in up to 25% of patients.[6,7] Recent data suggests that about half of these patients who developed depression post-MI had recurrent depressive episodes, and half had their first depressive episode post-MI.[7] Those with a first episode post-MI had more severe ventricular damage and had shorter duration of depression.

Conceptual model

Figure 1 describes a conceptual model for the complex interactions between depression and chronic medical illness.[14] Both genetic predisposition and exposure to childhood adversity, such as physical or sexual abuse, have been shown to be vulnerability factors for development of depression.[15] Stressful life events are more likely to precipitate initial episodes of depression in patients with one or more of these vulnerability factors.[16] In addition, exposure to childhood adversity may lead to maladaptive attachment patterns which may result in lack of social support and problems with interpersonal relationships. This lack of support can also precipitate or worsen depressive episodes.[17,18] Maladaptive attachment may also affect the quality of the doctor-patient relationship—as reviewed below. Both childhood adversity and development of depression in adolescent or early adult years are also associated with adverse health behaviors such as poor diet, obesity, sedentary lifestyle, and smoking, which increase the risk of development of diabetes and CVD.[11,19,20] These behaviors add to biological factors that have been shown to be associated with both depression

and childhood adversity, such as high cortisol levels or increased proinflammatory factors that may lead to early development of chronic medical disorders such as diabetes or CHD. Once people develop chronic medical illness, comorbid depression is associated with increased symptom burden[21] and additive functional impairment.[22] The aversive symptoms and functional impairments associated with chronic medical illness may also precipitate or worsen major depression. Comorbid depression may also worsen the course of chronic medical illness because of its adverse effect on adherence to self-care regimens (diet, exercise, cessation of smoking, taking medications as prescribed)[23] and direct pathophysiological effects on inflammatory and metabolic factors, hypothalamic pituitary axis and autonomic nervous system.[24] The effects of these risk factors may be buffered by social and environmental support and access to quality mental health and physical health care.

Patient-physician relationship

Managing chronic illness often requires close collaboration between patients and physicians as well as patients and family members. Primary care physicians rate patients with depression as more difficult to evaluate and treat compared with patients without affective disorders.[25] Patients with depression make approximately twice as many health care visits—often for vague physical symptoms—but also miss more visits.[26] These visits by depressed patients take longer for primary care physicians often because of multiple competing demands such as discussion of life stressors, problems with nonadherence to self-care of chronic medical conditions (diet, exercise, taking medications as prescribed), acute medical complaints such as headaches or abdominal pain, and poor control of chronic medical illnesses.[27] Compared with nondepressed controls, patients with depression are less satisfied with primary care physicians[28] perhaps due to maladaptive attachment patterns such as either fear of leaning on others (including physicians) or anxious attachment.[29] These maladaptive attachment patterns likely occur more often in patients with depression due to higher rates of childhood adversity.[17,18] Patients with depression may delay visits for important medical problems or adhere poorly to medical recommendations due to fears of becoming depen-
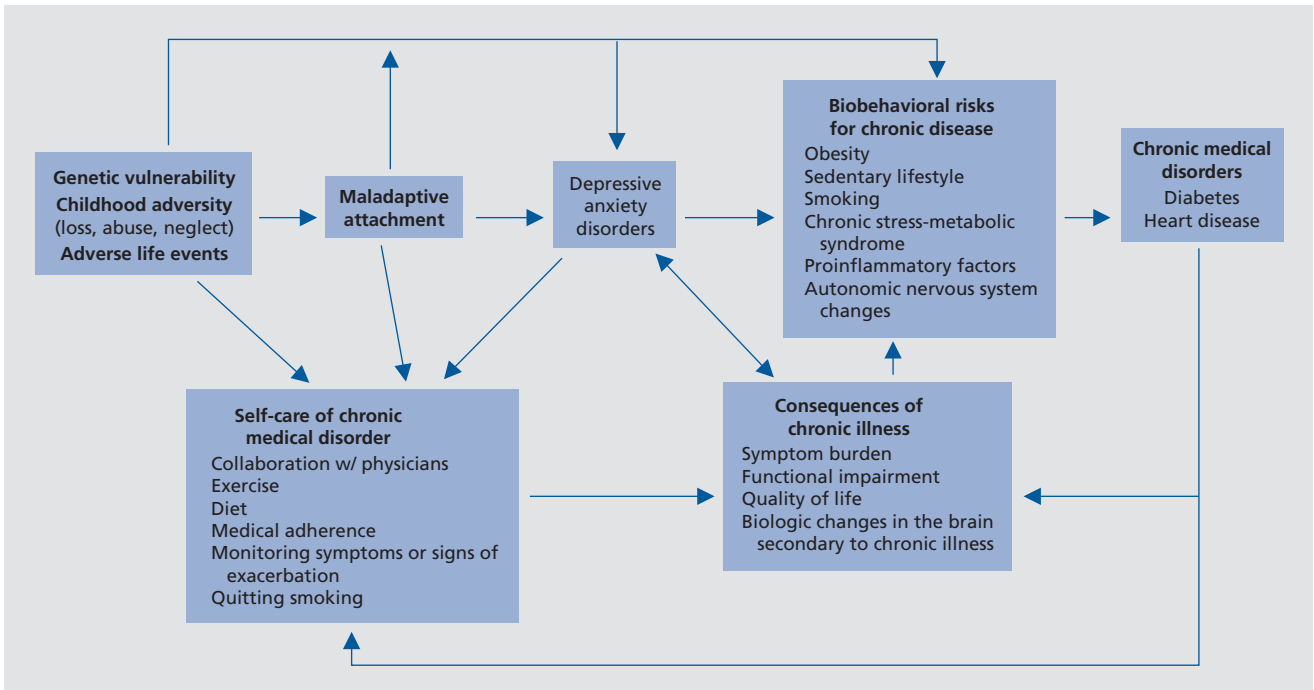

Figure 1. Bidirectional interaction between depression and chronic medical disorders.
Reproduced from ref 14: Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry*. 2003;54:216-226. Copyright © Elsevier, 2003

dent on others.[30] Ciechanowski and colleagues have shown that patients with diabetes with fear of leaning on others (ie, insecure attachment) have poorer adherence to self care, miss more regularly scheduled visits,[26] and have poorer disease control compared with patients with diabetes with normal attachment styles.[30] Patients with anxious attachment may be overly dependent on physicians, leading to increased medical utilization for minor somatic symptoms, multiple phone calls, and ensuing physician frustration.[31]

Recent studies have evaluated the effect of comorbid depression in patients with chronic medical illness on patient perception of physician communication. The presence of comorbid depressive symptoms in patients with diabetes has shown to be associated with patients reporting poor communication, including: elicitation of patient problems, concerns, and expectations, explanations about their condition, and patient empowerment and decision-making.[32] In patients with CHD, each additional standard deviation increase in depression symptoms was found to be associated with 50% greater odds of patients reporting poor explanations about their medical condition, and 30% greater odds of patients reporting physicians responding poorly to their preferences for treatment.[33]

Adherence to self-care

Caring for chronic illness takes patient planning, time, and motivation. Depression may impair self-care of chronic illness by adversely effecting memory, energy, and executive function.[14] Moreover, the sense of helplessness and hopelessness associated with depression may decrease motivation to care for chronic illness. A systematic review by Dimatteo and colleagues found that comorbid depression in patients with chronic medical illness decreased adherence to self-care regimens by threefold.[34]

Studies in patients with diabetes have shown that depression adversely effects adherence to diet, exercise regimens, cessation of smoking, and taking the three key diabetes control medications as prescribed; oral hypoglycemics, antihypertensives, and lipid control medications.[23] On the other hand, comorbid depression in patients with diabetes did not affect the quality of the types of care that physicians have more control over, such as annual retinal or foot exams, ordering HbA_{1C} levels at least twice a year,[23] or increasing intensity of

pharmacological care based on poor control of HbA_{1C}, LDL cholesterol, and blood pressure.[35]

In patients hospitalized after an acute myocardial infarction (MI), those with at least mild-to-moderate depressive symptoms were found to have lower adherence 4 months later to a low-fat diet, regular exercise, reducing stress, and increasing social support.[36] Those with comorbid major depression or dysthymia and CHD compared with those with CHD alone also reported taking medications as prescribed less often than those without comorbid affective illnesses.[36] In the Heart and Soul Study, which followed a large cohort of patients with CHD over time, twice as many depressed patients as nondepressed patients reported both forgetting to take their medications as prescribed and deciding to skip their medications.[37] Several studies have also shown that patients with depression and CHD versus those with CHD alone are less likely to adhere to taking daily low-dose aspirin.[38,39] Patients with comorbid depression and CHD compared with those with CHD alone have also been found to be more likely to drop out of cardiac exercise rehabilitation programs.[40]

Medical utilization and costs

Studies have shown that patients with major depression tend to be high utilizers of general medical services. In the Epidemiologic Catchment Area Study, Simon and colleagues showed that males with depression had a 50% greater risk and females with depression had an over threefold greater risk of being high utilizers of general medical services (defined as >6 visits in 6 months) compared with controls without psychiatric illness.[41] Katon and colleagues found that in a large primary care population, patients in the highest 10% of utilization of primary care services used 29% of primary care visits, 52% of specialty visits, 40% of hospital days, and 26% of prescriptions.[42] Approximately 50% of the over 1000 high utilizers screened were psychologically distressed (based on SCL-90 depression, anxiety, or somatization scales) and two thirds of these distressed patients met DSM-IV criteria for recurrent major depression and 40% for dysthymia based on structured psychiatric interview.[42] Two thirds also had one or more chronic medical illnesses. Primary care patients with major depression have been found to have 50% to 100% greater medical costs than nondepressed controls after controlling for sociodemographic factors and severity of medical illness.[43,44] Patients

with comorbid depression and diabetes have been found to have 50%[45] greater total medical costs, and those with comorbid depression and congestive heart failure have been found to have 30%[46] greater total medical costs after controlling for sociodemographic factors and severity of medical illness. Moreover, the mean costs of patients with diabetes or heart disease are up to fourfold higher than age-matched controls without these illnesses, which places these patients in an extremely high cost bracket. For instance, research at a large health maintenance organization has shown that a middle-aged adult with minimal medical illness has a mean of about $1500 annual health care costs, a middle-aged depressed patient with minimal medical illness has a mean of approximately $3000 annual health care costs, a middle-aged adult with diabetes has about $6000 in mean annual health care costs, and a middle-aged adult with comorbid depression and diabetes has about $9000 in annual health care costs.[45,47]

The increase in total medical costs is not explained by an increase in mental health utilization, which has been found to explain only about 10% of the increase in medical costs.[43,44,47] Multiple studies have shown that depression is associated with increased costs in every cost component that is measured including primary care, pharmacy, medical specialty, emergency or urgent care, laboratory, inpatient medical, inpatient psychiatric, and outpatient mental health.

Two studies that evaluated the cost–effectiveness of collaborative depression care interventions in patients with comorbid major depression and/or dysthymia and diabetes have shown that the intervention was not only associated with improved quality of depression care and depression outcomes, but that the increased mental health costs associated with the interventions were offset by greater savings in medical costs, especially at year 2.[48,49] A recent study extended the follow-up of patients in one of these intervention studies of patients with depression and diabetes for 5 years.[50] The same savings in total medical costs that were found in intervention versus usual care patients over the first 2 years continued during years 3 to 5.[50] When compared with usual care, the collaborative care intervention was associated with trends for a decrease in every cost component (ie, primary care, medical specialty, pharmacy, laboratory, and inpatient costs).[48-50] Thus, effective depression treatment is associated with decreases in many different types of health care costs.

Medical symptom perception

Patients with depression have been found to have two- to threefold more medical symptoms on a medical review of symptoms compared with controls without depression, after controlling for sociodemographic factors and severity of medical illness.[51] *Table I* shows the results of a study by Kroenke and colleagues in which 1000 primary care patients filled out the Patient Health Questionnaire depression and anxiety scales (generalized anxiety disorder and panic disorder) and a 15-item somatic symptom scale before they saw their primary

No of symptoms	No of patients	No (%) with psychiatric disorder		
		DSM-IV anxiety disorder N(%)	DSM-IV mood disorder N(%)	Any anxiety/DSM-IV depressive disorder (N%)
Physical (n=1000)				
0-1	215	2 (1)	5 (2)	16 (7)
2-3	225	17 (7)	27 (12)	50 (22)
4-5	191	25 (13)	44 (23)	67 (35)
6-8	230	68 (30)	100 (44)	140 (61)
≥9	139	66 (48)	84 (60)	113 (81)
Somatoform (n=933)				
0	654	68 (10)	107 (16)	162 (25)
1-2	143	42 (29)	60 (42)	74 (52)
3-5	87	35 (40)	40 (46)	77 (89)
≥6	49	27 (55)	34 (69)	46 (94)

Table I. Number of physical symptoms and association with DSM-IV anxiety and depressive disorders.
Reproduced from ref 52: Kroenke K, Spitzer RL, Williams JB, et al. Physical symptoms in primary care. Predictors of psychiatric disorders and functional impairment. *Arch Fam Med*. 1994;3:774-779. Copyright © Americal Medical Association 1994

care physician.[52] Primary care physicians were then asked to rate the patient's somatic symptoms as potentially due to a physical illness or unexplained (the authors describe these latter symptoms as somatoform). As seen in *Table I*, whether the physician describes the patients' symptoms as due to a medical illness or as unexplained or somatoform did not change the relationship to depressive and anxiety conditions.[52] Increased somatic symptoms of either type were associated with a higher likelihood that the patient suffered from a DSM-IV depressive or anxiety disorder.

Pain symptoms are particularly common in patients with depression.[51] Longitudinal data suggest a bidirectional association between pain and depression.[9,53] Community-based studies have found that respondents with depression have a higher likelihood than nondepressed respondents to develop an incident pain symptom.[53] Persistent pain symptoms in community respondents without depression are also associated with a higher likelihood of developing subsequent depression.[9,53] Recent data from the Health Care for Communities study have shown that depression at baseline survey was one of the strongest predictors of subsequent development of regular opiate use at a 5-year follow-up (presumably for treatment of chronic pain).[54] Multifocal pain is especially likely to be associated with depression and with opiate use.[55]

Many patients with chronic illness must learn to adapt and habituate to chronic aversive symptoms, such as pain or fatigue. When patients are not depressed, most patients with chronic medical illness are able to successfully adapt to their chronic aversive disease symptoms.[51] However, there is now extensive data to suggest that having comorbid anxiety and depressive disorders in patients with chronic medical illness interferes with this adaptation process, and is associated with heightened awareness and focus on both symptoms of that physical illness as well as physical symptoms associated with other organ systems.[51]

The lack of adaptation to aversive symptoms may be explained by dysregulation of the endogenous pain modulatory system.[56,57] The periaqueductal gray (PAG) is a key anatomic structure in this modulatory system. The PAG is an important source of endogenous opioids and an anatomic relay station from limbic forebrain and midbrain structures to the brain stem. The amygdala, hypothalamus, and frontal neocortex all send fibers to the PAG, which, in turn, connects with relay stations in the

pons and medulla.[57] These relay stations contain serotonergic neurons such as those in the rostral-ventromedial medulla (RVM) as well as noradrenergic neurons such as those in the dorsolateral pontine tegmentum (DLPT).[58] The RVM sends projections to the dorsal horn of the spinal cord directly, whereas the DLPT affects the dorsal horn neurons indirectly by its projection to the RVM as well as by having direct connections to the dorsal horn. The RVM has "on cells," which facilitate transmission of spinal nociception to the brain, and "off cells" that inhibit this transmission.[56]

The above on and off cells, through data transmitted from the limbic forebrain and other structures transmitted through the RVM, may dampen or amplify pain impulses transmitted from the periphery.[56,59] Activation of the RVM off neurons or DLPT neurons via electrical stimulation dampens activity of nociceptive neurons in the dorsal horn.[56,58] These bidirectional on/off systems determine vigilance to external threats as well as sensations coming from inside the body.[56,59] Decrease of serotonin and/or norepinephrine neurotransmission as occurs in depression may lead this descending system to decrease its inhibitory effect so that nociceptive signals from the body are considered stronger and more salient.[59] This may explain the clinical experience of patients with depression being quite focused on the bothersomeness of many physical symptoms.

A recent systematic review of 31 studies found that comorbid depression in patients with chronic medical illnesses such as diabetes, congestive heart failure, CHD, osteoarthritis, rheumatoid arthritis, asthma, or COPD was associated with a significantly higher number of medical symptoms after controlling for severity of medical illness.[21] Across these medical conditions, depression was at least as strongly associated with the number of medical symptoms as were objective physiological measures.[21] *Figure 2* shows the relationship of both comorbid depression and number of diabetes complications with a 10-item diabetes symptom scale.[60] After controlling for socioeconomic factors and severity of medical illness, depression was more highly associated with each of these 10 symptoms than was the number of diabetes complications.

Three randomized controlled studies that tested depression interventions in patients with a specific chronic medical illness (COPD,[61] osteoarthritis,[62] or diabetes[63]) have also shown that, compared with controls, greater improvement in comorbid depressive symptoms in

patients with chronic medical illness with the depression intervention was associated with improvement in medical symptoms without improvement in physiologic measures. For instance, Ell and colleagues tested a collaborative care intervention versus usual care in 387 patients with comorbid depression and diabetes. Compared with usual primary care, collaborative care was associated with improvements in quality of depression care, severity of depressive symptoms, and number of diabetes symptoms, but lack of change in HbA_{1c} levels.[63] Lin and colleagues showed that a collaborative care intervention that improved quality of depression care and depression

Comparison of patients with comorbid major depression and diabetes with those with diabetes alone: odds ratios and 95% CIs

Comparison of patients with diabetes with those with diabetes and ≥2 diabetes complications to those with 0 or 1 complication: odds ratios and 95% CIs
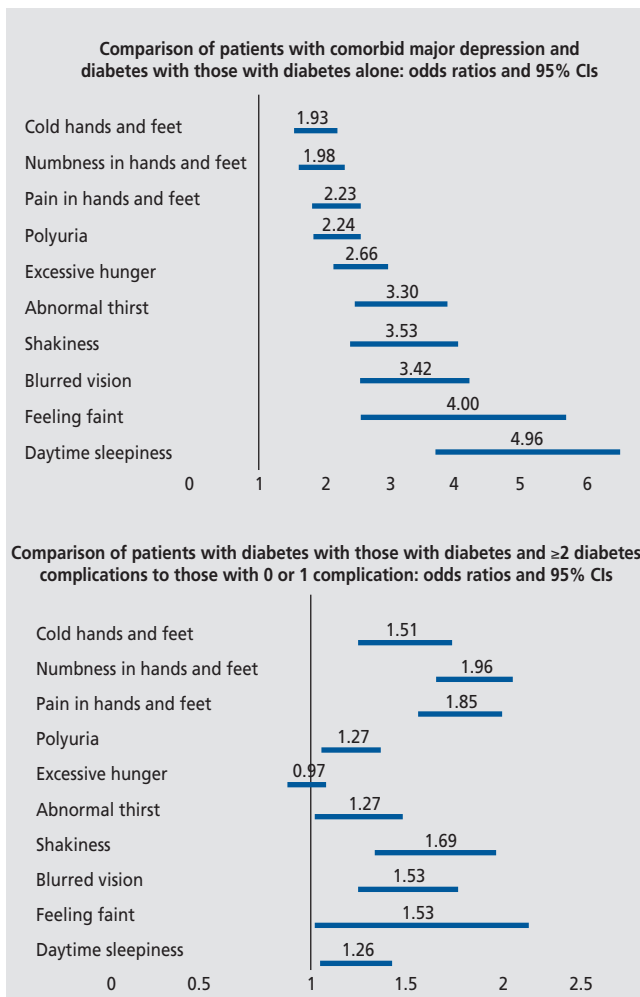
Figure 2. Relationship of depression and diabetes complications to 10 diabetes symptoms.
Reproduced from ref 60: Ludman EJ, Katon W, Russo J, et al. Depression and diabetes symptom burden. *Gen Hosp Psychiatry*. 2004;26:430-436. Copyright © Elsevier 2004

outcomes compared with usual primary care in over 1000 elderly patients with comorbid depression and pain predominantly due to osteoarthritis was associated with improvement in perception of pain intensity and decreased pain interference during regular activities.[62]

Risk of complications and mortality

Multiple large epidemiologic studies have examined whether comorbid depression in patients with CHD or diabetes increases risk of mortality. A recent meta-analysis found 22 papers that examined the association of depression with cardiovascular outcomes of patients experiencing a recent myocardial infarction (MI), defined as mortality or cardiovascular events occurring within 2 years of index MI.[64] Comorbid depression was associated with an approximate 2.4-fold increase in all-cause mortality, a 2.6-fold increase in cardiovascular-related mortality, and an almost 2.0-fold increase in new cardiovascular events.[64] Depression has also been found across multiple studies to be a significant predictor of mortality and cardiac events in patients undergoing coronary artery bypass surgery,[65-67] as well as those with congestive heart failure.[68]

Six prospective epidemiologic studies have shown that after controlling for sociodemographic factors and clinical severity of illness, comorbid depression in patients with diabetes compared with those with diabetes alone was associated with a 33% to 52% increase in risk of all-cause mortality.[69-74] One recent study of over 4000 patients with diabetes examined specific causes of mortality associated with depression documented with both state mortality data and careful chart review. Comorbid depression was associated with an approximately 50% increase in risk of all-cause morbidity, and an over twofold risk of noncancer and nonatherosclerotic associated mortality.[69]

A large prospective study of an aging Hispanic population found that both depression and diabetes were independently associated with an increased risk of all-cause mortality, and when combined they had a greater than additive effect on mortality.[72] Thus, lifetime depression was associated with a 1.64 (95% CI 1.17-2.28) and diabetes a 1.51 (95% CI 1.23, 1.86) hazard ratio for all-cause mortality respectively, compared with those without history of depression or diabetes.[72] Patients with comorbid lifetime depression and diabetes had a hazard ratio of 4.59 (95% CI 2.12, 9.93) of all-cause mortality

compared with controls without history of diabetes or depression.[72] In another study that followed over 10 000 participants for 8 years, compared with those without diabetes or depression, those with depression but no diabetes had a 1.20 (95% CI 1.03, 1.40) increase in all-cause mortality, those with diabetes but no depression had a 1.88 (95% CI 1.55, 2.27) increase, and those with both depression and diabetes a 2.50 (95% CI 2.04, 3.08) increase in all-cause mortality.[73]

In patients with diabetes, recent prospective studies have examined the association of depression with subsequent development of macrovascular and microvascular complications. Lin and colleagues, in a prospective study of over 4000 patients with diabetes found that comorbid depression was associated with a 36% increased risk of microvascular and 24% risk of macrovascular complications over a 5-year period.[74] A recent large study of 4000 patients with diabetes has also shown that comorbid depression in patients with diabetes was associated with a twofold increased risk of development of foot ulcers.[75] A second large study that included over half a million Veterans with diabetes showed that comorbid depression was associated with a 33% increased risk of having a nontraumatic lower-limb amputation over a 4-year period.[76] Black and colleagues found in the above-described prospective study of aging Hispanic respondents that having diabetes was associated with an increased risk of 1.37 (95% CI 1.16, 1.62) for macrovascular complications and 9.30 (95% CI 7.38, 11.15) for microvascular complications compared with controls without diabetes or depression.[72] Those with depression and diabetes had an increased risk compared with those without history of diabetes or depression of 2.64 (95% CI 1.73, 4.04) for macrovascular complications and 11.32 (95% CI 8.76, 15.43) for microvascular complications.[72] Both depression and diabetes have been found in multiple studies to be independent risk factors for development of dementia.[77] A recent study of over 4000 patients with type 2 diabetes found that patients with comorbid depression compared with those with diabetes alone had a 2.7-fold increase in development of dementia over a 5-year period.[78]

Functional impairment

Interest in the adverse effect of depression on functional impairment was stimulated by findings from the Medical Outcomes survey. This large study showed that patients with depression were at least as functionally impaired as patients with chronic medical illnesses such as diabetes, CHD, and arthritis.[22] Moreover, when depression was comorbid with chronic physical illness, there was additive functional impairment.[22]

One of the methodological challenges in assessing functioning in patients with depression is whether reported impairments result from true deficits or from reporting bias. Methodologists have attempted to understand this problem by comparing more "objective" impairment such as length of time a patient walks on a stress treadmill test to more "subjective" functional measures. Recent data have shown that depressed patients also have significant deficits on these more "objective" measures. For instance, depressed patients whose cardiac function is tested by stress treadmill EKG have been found to be more likely to stop the test due to fatigue prior to an adequate length of time for assessment.[79] Patients with depression with congestive heart failure (CHF) also have been shown to have poorer performance on the standard 6-minute walk compared with those with CHF alone.[80]

A recent study of over 4000 patients with diabetes has shown that patients with comorbid depression and diabetes compared with those with diabetes alone had a 10-fold increased risk of overall functional impairment as well as low social function scores and a fourfold increase in the risk of having 20 or more days of reduced household work in the last 30 days after controlling for medical comorbidity.[81] The number of diabetes complications and the number of diabetes symptoms were also independently associated with increased disability risks, but had less impact compared with comorbid depression.[81]

A second study examined the impact of depression in 1600 patients with diabetes who were still working part- or full-time.[82] Depressive illness and diabetic symptoms were associated with greater work disability, including missing 5 or more days of work in the prior month and severe difficulty performing work tasks.[82]

Cross-sectional studies of patients with CHD and CHF have also shown that comorbid depression is associated with additive functional impairment.[83,84] Because it is unclear whether decreased functioning causes depression or whether this affective illness leads to functional decline, studies have begun to utilize longitudinal designs. Longitudinal studies in aging populations have described a bidirectional relationship between depression and functional impairment.[85-89] Functional impair-

ment in aging populations predicts depression and, conversely, major depression and depressive symptoms have been found to be risk factors for progression of disability.[85-88] Studies by Van Korff and colleagues[90] and Ormel et al[91] have also shown that depressive symptoms and disability measures change synchronously over time—as depression improves, so do measures of functional impairment.

Prospective studies in both cardiology and primary care settings have shown comorbid depression in patients with CHF and CHD can be more predictive of functional impairment over time than is severity of physical illness. Sullivan and colleagues[80] showed that in 113 patients with CHF in a specialty cardiology clinic that comorbid depression was prospectively associated with decreased distance on the 6-minute walk as well as decreased self-reported functioning on generic and disease-specific measures of function (Kansas City Cardiomyopathy Questionnaire[92]) after controlling for demographic and clinical characteristics (such as left ventricular ejection fraction). A primary care-based study showed that over a 6-month period after controlling for severity of cardiac disease, comorbid depression in 139 patients with CHF was associated with significant and persistent adverse effects on perception of health, impairment on the Kansas City Cardiomyopathy Questionnaire, physical limitations, role function, and quality of life compared with patients with CHF alone.[93] Depression was also shown to be the strongest predictor of functional decline in a prospective study of patients with heart failure.[94]

Sullivan and colleagues demonstrated that symptoms of depression and anxiety at initial diagnosis of coronary artery disease by angiogram were more highly correlated with function impairment at both 1- and 5-year follow-ups than was number of coronary occlusions.[95,96] This study controlled for the number of vessels occluded 70% or more, ejection fraction at baseline, and cardiac procedures over time.[95,96] Mayou et al showed that in patients with recent myocardial infarction, DSM-IV depressive and anxiety disorders predicted poor outcome at 1 year on all dimensions of quality of life.[97]

Studies of patients with comorbid depression and diabetes,[63,98] coronary artery disease,[99] and those post-coronary artery bypass surgery[100] have shown that enhancing quality of care of depression not only improves depressive outcomes but markedly improves functional outcomes compared with control treatments.

Biological factors

Multiple biological links that potentially mediate the adverse effect of comorbid depression on diabetes-related and cardiovascular mortality have been described. These include increased proinflammatory cytokines, abnormalities of the hypothalamic pituitary axis (HPA), changes in homeostasis between the sympathetic and parasympathetic nervous systems and changes in metabolism.[24,101] As described in *Figure 3*, the HPA axis and sympathetic nervous system are both activated by stress.[102] The increased cortisol levels associated with HPA activity and the increased catecholamine and cytokine levels associated with increased sympathetic activation may in turn lead to increased insulin resistance, which is a risk factor for both diabetes and CHD.[101,102]

A recent meta-analysis found 24 studies that examined links between major depression and cytokine levels. Patients with depression were found to have significantly higher concentrations of TNF-alpha ($P<.00001$) and
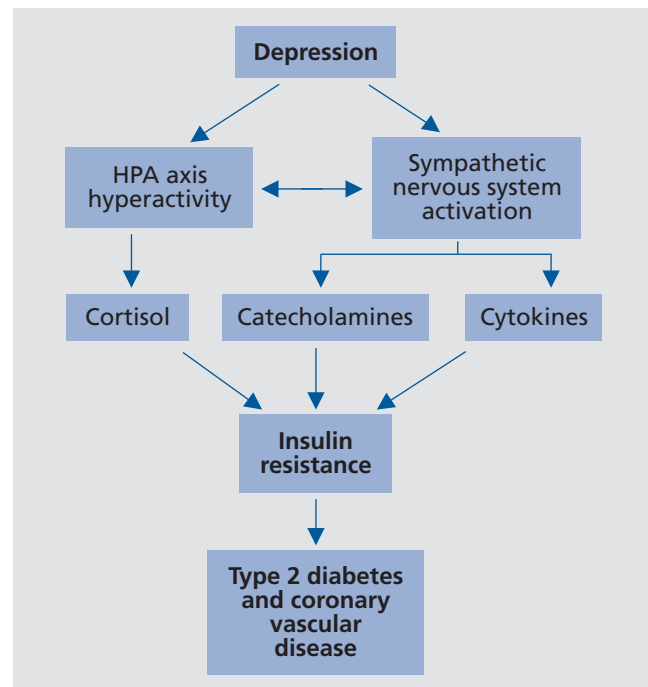

Figure 3. Psychophysiologic effects of depression. HPA, hypothalamic-pituitary-adrenal
Adapted from ref 102: Champaneri S, Wand GS, Malhotra SS, Casagrande SS, Golden SH. Biological basis of depression in adults with diabetes. *Curr Diab Rep*. 2010;10:396-405. Copyright © Current Science 2010

interleukin-6 levels (P<.00001) compared with nondepressed subjects but no significant differences were found in other cytokines that were examined.[103] Studies examining whether depression is associated with higher levels of C-reactive protein have been inconsistent.[104,105]

Depression may also increase the risk of cardiovascular death through increased platelet aggregation.[106-108] A recent study showed that mean plasma levels of factor 4 and β-thromboglobulin were higher in depressed patients with ischemic heart disease than those with ischemic heart disease alone or normal controls.[106] Other studies have shown that patients with depression and stable CHD compared with those with CHD alone have increased β-thromboglobulin, fibrinogen, and d-dimer levels.[107,108] Observational studies have also reported lower stroke risk in patients with cardiovascular disease treated with selective serotonin reuptake inhibitors (SSRIs, which are known inhibitors of platelet activity).[109]

Recent research has emphasized the importance of endothelial dysfunction in patients with CHD which is present even in preclinical stages of atherosclerosis.[24] The endothelium through the process of nitric oxide production inhibits smooth muscle cell growth, platelet aggregation, and leukocyte adhesion and maintains vascular tone.[24] Depression has been linked in several studies to endothelial dysfunction.[110,111] Sherwood and colleagues showed that brachial flow-mediated dilation in 143 patients with CHD was impaired in patients reporting at least mild symptoms of depression.[110] Depression has also been linked to higher levels of endothelin-1 in patients with CHD.[111] Endothelin-1 has been found to be associated with plaque rupture and post-acute coronary syndrome survival.[111]

Depression has been shown to be associated with elevated 24-hour, urine-free cortisol levels, adrenal gland enlargement and, in patients with severe depression, failure to suppress cortisol response to the dexamethasone suppression test.[112] Researchers have recently posited that in subjects with depression there is reduced responsiveness of the HPA axis to experimental and physiologic challenges due to chronic hyperactivity of this endocrine system.[102] Thus, blunted cortisol response to acute mental stressors has been shown in depressed compared with nondepressed patients with multiple cardiovascular risk factors.[113] Some,[114,115] but not all,[116] studies have shown flatter diurnal cortisol profiles in individuals with depression. Several studies have also shown an association of depression with impaired awakening cortisol levels.[117,118]

A potential consequence of long-term activation of cortisol is the development of central adiposity. Higher cortisol levels may lead to redistribution of fat from subcutaneous to visceral fat depots.[119] Several studies have shown that community respondents with depression had an increased risk of higher amounts of visceral adipose tissue (VAT).[120,121] VAT promotes insulin resistance more than subcutaneous fat, and is associated with a higher risk of cardiovascular disease.

Depression is also associated with abnormalities in sympathetic nervous system functioning, including decreased heart rate variability (HRV), higher resting heart rates, and higher heart rate responses to physical stressors.[24,101,102] Increases in catecholamines and cytokines associated with sympathetic hyperactivity may also lead to insulin resistance and increases in blood pressure.[121,122] Low HRV has been linked to mortality in patients with CHD and is a marker for excessive sympathetic and/or decreased parasympathetic nervous system activity.[122,123] Most,[124,125] but not all,[126] studies have found depression to be linked with decreased HRV in patients with coronary disease. Other predictors of increased mortality and autonomic nervous system dysfunction that have been found in patients with comorbid depression and CHD include increased heart rate response to orthostatic challenge,[127] increased QT interval variability reflecting abnormal ventricular repolarization,[128] elevated resting and 24-hour heart rates,[124,127] and abnormal heart rate response to premature ventricular contractions.[129] Delayed heart rate recovery after the treadmill test is a risk factor for cardiac mortality, and depression has been linked to slower heart rate recovery.[130] This finding was mediated by a reduced exercise capacity, which may reflect the role of depression in leading to a more sedentary lifestyle. Depression in early adulthood has also been linked in large population-based studies to increased risk of development of hypertension.[11,131] Both the increase in insulin resistance and hypertension typical of the metabolic syndrome may raise the risk of both type 2 diabetes and CVD.[101,102] Moreover, hypertension may lead to a higher risk of cerebrovascular disease which can provoke vascular depression.[132]

Insulin resistance is a risk factor for development of both type 2 diabetes and cardiovascular disease.[101,102] Several large-scale, population-based studies have shown that depression is associated with insulin resistance.[133] For instance, a Finnish 1966 birth cohort study that followed young adult males over time found that males

with severe depressive symptoms had an over 3-fold higher risk of insulin resistance. The Finnish findings have been replicated in Chinese[134] and Dutch[135] samples of similar age groups. On the other hand, a study of Welsh males in midlife that were followed three times over 14 years did not find a significant association between insulin resistance and depression.[136] Thus, the research in this area is promising but further large prospective population-based studies are needed.

Several longitudinal studies have examined whether the effect of depression on mortality in patients with CHD was mediated by psychophysiologic changes or health risk behaviors associated with depression. Kop et al showed that the increased mortality associated with depression in 907 patients in the Cardiovascular Health Study was partially mediated by autonomic dysfunction (heart rate variability) and inflammatory factors (white cell count, fibrinogen levels).[137] However, a large portion of the predictive value of depression remained unexplained by these biological factors. A recent study of 1107 outpatients with stable coronary heart disease found that depression was associated with a 31% increased rate of cardiovascular events after controlling for sociodemographic factors, comorbid conditions, and cardiac disease severity.[138] Controlling for inflammatory factors explained a small part of this increased risk;, however, no significant relationship was found after adjusting for physical activity and other health risk behaviors.[138]

Treatment of depression in patients with diabetes and CHD

Large observational studies have found that the severity of medical illness was a predictor of chronicity of depressive symptoms in aging populations with medical illness.[4] Therefore, a key research question is whether evidence-based psychotherapeutic and pharmacologic treatment that are efficacious in depressed patients without chronic medical illness are as effective in patients with depression and comorbid illnesses such as diabetes and CHD.

A recent meta-analysis of randomized trials of depression interventions in patients with diabetes and depression found five studies that tested the efficacy of psychotherapy and seven that tested the efficacy of antidepressant medications.[139] Four of the five psychotherapy studies were quite small with 60 or fewer patients, and all of the antidepressant trials had less than

90 patients. The meta-analysis showed both evidence based depression psychotherapies and antidepressants were efficacious in treating depression among patients with diabetes with moderate to large effect sizes compared with control treatments.[139]

The meta-analysis also examined the results of three large collaborative depression trials that provided a choice of starting with antidepressants versus problem-solving therapy (PST) and used stepped care principles to increase intensity of depression treatment based on lack of response to initial treatment.[63,98,140] In each trial, a care manager supervised by a psychiatrist worked with the primary care physician to enhance exposure to evidence-based depression treatments. Thus, if the patient chose PST and showed a lack of response an antidepressant medication could be added, and if they chose medication and depressive symptoms did not improve, either PST could be added, another medication could be started, or a second antidepressant could be added as an augmenting agent. These collaborative care trials enrolled 329 to 417 patients each with few exclusion criteria and in all three trials, collaborative care was more effective in reducing depressive symptoms compared with usual primary care.[63,98,140] Thus, collaborative care is an effective health service model to improve exposure to evidence-based depression care and depression outcomes in large primary care populations with comorbid depression and diabetes.

In patients with comorbid depression and either CHD or CHF there have been four large antidepressant trials.[141-143] The SADHEART trial randomized 369 patients with major depression after acute MI to sertraline versus placebo.[141] Patients treated with sertraline had significantly greater improvement on the Clinical Global Impression (CGI) scale (67% vs 53% (*P*=.01) responders) but not on the Hamilton depression rating scale (HAM-D) (*P*=.14). In the subsample of patients with a history of recurrent major depression, both CGI and HAM-D measures were significantly improved in those assigned to sertraline versus placebo.[141] A Dutch trial randomized 91 patients post-MI with comorbid major or minor depression to mirtazapine versus placebo.[142] Using the last observation carried forward, mirtazapine did not show significance compared with placebo on the HAM-D, but did on the Beck Depression Index, the SCL-20 depression scale, and CGI at 8 weeks.[142] Lesperance et al randomized 224 patients with depression and CHD to either citalopram versus placebo or interpersonal psy-

chotherapy plus clinical management to clinical management alone.[99] Citalopram was superior to placebo in reducing HAM-D scores and Beck depression scores. However, interpersonal therapy and clinical management was not significantly better than clinical management alone.[99] The SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure Trial) randomized 469 patients with comorbid major depression and CHF to sertraline versus placebo. Sertraline was not associated with greater efficacy compared with placebo in improvement in depressive symptoms.[143] The effect sizes in the three trials that showed efficacy of antidepressant medications compared with placebo were relatively small, perhaps reflecting that chronic disease problems limit the efficacy of antidepressant medications. Also, a subset of patients who develop depressive symptoms post-myocardial infarction may actually have an adjustment reaction which may improve with or without antidepressant treatment. The finding in the SADHEART trial of a larger effect size of sertraline versus placebo in those with recurrent depression compared with those with a first depressive episode occurring post-MI supports the premise that many episodes of incident depression after MI may be adjustment reactions.[141]

The ENRICHD trial randomized 2481 post-MI patients with minor or major depression to cognitive behavioral therapy (CBT) versus usual medical care, with antidepressants also recommended for patients scoring higher than 24 on the HAM-D or having less than a 50% reduction on the Beck Depression Inventory after 5 weeks.[144] A significant effect was found on the HAM-D in the intervention group that largely provided CBT without medication compared with usual care. Freedland and colleagues randomized 123 patients meeting DSM-IV criteria for major or minor depression within 1 year after coronary artery bypass surgery to CBT, supportive stress management, or to usual care. Remission of depression occurred in a higher proportion of patients treated with CBT (71%) and supportive stress management (57%) by 3 months compared with the usual care group (33%) (P<0.002).[145] The CBT and supportive stress management groups also had significantly lower Hamilton depression scores than the usual care group at 3 months.

Two recent trials have tested whether collaborative depression care is an effective health services model compared with usual care to improve exposure to evidence-based depression treatment in patients with cardiac disease and comorbid depression.[100,146] Rollman et al tested a telephone-delivered depression collaborative care model provided by nurses working with patients' primary care physicians and supervised by a psychiatrist and primary care physician to enhance antidepressant medication treatment and patient psychoeducation and behavioral activation.[100] A total of 302 post-coronary artery bypass graft patients with depression were randomized to this intervention versus usual care. Intervention versus usual care patients had significantly greater improvement on mental health functioning (P=0.02) and were more likely to report a >50% decline on HAM-D scores (50% vs. 29.6%), P<0.001) at 8-month follow-up compared with usual care patients.[100] Davidson and colleagues tested a depression collaborative care model that gave patients a choice of starting with pharmacotherapy or problem-solving therapy (PST) to treat depression.[146] Stepped care was provided based on physician supervision of case managers so that medications could be added to PST if patients had limited response to psychotherapy or medications could be changed, or PST added for patients not responding to the initial antidepressant medication trial. A total of 157 patients with depression persistently present 3 months after an acute coronary event were randomized and intervention patients had significant improvements compared with usual care patients on the Beck Depression Inventory (P>0.005).[146]

These two collaborative depression care trials, like the three trials completed in patients with depression and diabetes, demonstrate that this health services model is an effective way to expose cardiac patients with depression to evidence-based depression treatments and to improve depressive outcomes in large primary care populations.

An important question raised by the epidemiologic data is whether enhanced treatment of depression could lead to decreased complications, and mortality in patients with CHD or diabetes. With the exception of the ENRICHD trial, all other trials are underpowered to answer this important question. The small treatment effect size in ENRICHD also limited the ability of researchers to answer this question. Future trials with as many as 5000 to 10 000 patients are likely needed with enhanced quality control over the depression intervention. However, regardless of the effect on complications and mortality, effective treatment of depression

has been shown to improve symptom burden, functionality, quality of life, and overall adaptation to chronic medical illness.

Conclusion

Depression is a risk factor for development of chronic illnesses such as diabetes and CHD and adversely affects the course, complications and management of chronic medical illness. Both maladaptive health risk behaviors and psychobiological factors associated with depression may explain depression's negative effect on outcomes of chronic illness. Most treatment studies have found that both evidence-based depression therapies and antidepressant medications are efficacious treatments in patients with depression and comorbid medical illness, and that collaborative care is an effective health services model to deliver these treatments to large primary care populations. ❑

REFERENCES

1. Chang CK HR, Broadbent M, Fernandes AC, Lee W, Hotopf M, Stewart R. All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. *BMC Psychiatry*. 2010;10:77.
2. Roshanaei-Moghaddam B, Katon W. Premature mortality from general medical illness among persons with bipolar disorder: a review. *Psychiatr Serv*. 2009;60:147-156.
3. Katon W, Russo J, Lin EH, et al. Depression and diabetes: factors associated with major depression at five-year follow-up. *Psychosomatics*. 2009;50:570-579.
4. Kennedy GJ, Kelman HR, Thomas C. Persistence and remission of depressive symptoms in late life. *Am J Psychiatry*. 1991;148:174-178.
5. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of comorbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabet Med*. 2006;23:1165-1173.
6. Schleifer SJ M-HM, Coyle DA, Slater WR, Kahn M, Gorlin R, Zucker HD. The nature and course of depression following myocardial infarction. *Arch Intern Med*. 1989;149:1785-1789.
7. Spijkerman T dJP, van den Brink RH, Jansen JH, May JF, Crijns HJ, Ormel J. Depression following myocardial infarction: first-ever versus ongoing and recurrent episodes. *Gen Hosp Psychiatry*. 2005;27:411-417.
8. Katon W, Schulberg H. Epidemiology of depression in primary care. *Gen Hosp Psychiatry*. 1992;14:237-247.
9. Patten S. Long-term medical conditions and major depression in a Canadian population study at waves 1 and 2. *J Affect Disord*. 2001;63:35-41.
10. Wells KB, Golding JM, Burnam MA. Psychiatric disorder in a sample of the general population with and without chronic medical conditions. *Am J Psychiatry*. 1988;145:976-981.
11. Von Korff M, Scott KM, Gureje O, eds. *Global Perspectives on Mental-Physical Comorbidity in the WHO World Mental Health Surveys*. Cambridge, UK: Cambridge University Press; 2009.
12. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care*. 2008;31:2383-2390.
13. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and metaanalysis. *Int J Geriatr Psychiatry*. 2007;22:613-626.
14. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry*. 2003;54:216-226.
15. Kendler K, Gardner C, Prescott C. Toward a comprehensive developmental model for major depression in women. *Am J Psychiatry*. 2002;159:1133-1145.
16. Caspi A SK, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301:386-389.

17. Bifulco A, Moran PM, Ball C, Bernazzani O. Adult attachment style. I: Its relationship to clinical depression. *Soc Psychiatry Psychiatr Epidemiol*. 2002;37:50-59.
18. Bifulco A MP, Ball C, Lillie A. Adult attachment style. II: Its relationship to psychosocial depressive-vulnerability. *Soc Psychiatry Psychiatr Epidemiol*. 2002;37:60-67.
19. Katon W RL, Russo J, McCarty CA, Rockhill C, McCauley E, Richards J, Grossman DC. Depressive symptoms in adolescence: the association with multiple health risk behaviors. *Gen Hosp Psychiatry*. 2010;32:233-239.
20. Goodman E, Whitaker RC. A prospective study of the role of depression in the development and persistence of adolescent obesity. *Pediatrics*. 2002;110:497-504.
21. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry*. 2007;29:147-155.
22. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *JAMA*. 1989;262:914-919.
23. Lin EH, Katon W, Von Korff M, et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care*. 2004;27:2154-2160.
24. Carney RM, Freedland KE. Depression in patients with coronary heart disease. *Am J Med*. 2008;121(11 suppl 2):S20-27.
25. Hahn SR KK, Spitzer RL, Brody D, Williams JB, Linzer M, deGruy FV 3rd. The difficult patient: prevalence, psychopathology, and functional impairment. *J Gen Intern Med*. 1996;11:1-8.
26. Ciechanowski P, Russo J, Katon W, et al. Where is the patient? The association of psychosocial factors and missed primary care appointments in patients with diabetes. *Gen Hosp Psychiatry*. 2006;28:9-17.
27. Callahan EJ BK, Azari R, Robbins J, Helms LJ, Miller J. The influence of depression on physician-patient interaction in primary care. *Fam Med*. 1996;28:346-351.
28. Katon W, Von Korff M, Lin E, et al. Collaborative management to achieve treatment guidelines. Impact on depression in primary care. *JAMA*. 1995;273:1026-1031.
29. Ciechanowski PS, Katon WJ, Russo JE. The association of depression and perceptions of interpersonal relationships in patients with diabetes. *J Psychosom Res*. 2005;58:139-144.
30. Ciechanowski P, Russo J, Katon W, et al. Influence of patient attachment style on self-care and outcomes in diabetes. *Psychosom Med*. 2004;66:720-728.
31. Ciechanowski PS, Walker EA, Katon WJ, Russo JE. Attachment theory: a model for health care utilization and somatization. *Psychosom Med*. 2002;64:660-667.
32. Swenson SL, Rose M, Vittinghoff E, Stewart A, Schillinger D. The influence of depressive symptoms on clinician-patient communication among patients with type 2 diabetes. *Med Care*. 2008;46:257-265.
33. Schenker Y, Stewart A, Na B, Whooley MA. Depressive symptoms and perceived doctor-patient communication in the Heart and Soul study. *J Gen Intern Med*. 2009;24:550-556.

State of the art

Epidemiología y tratamiento de la depresión en pacientes con una enfermedad médica crónica

Hay una relación bidireccional entre la depresión y los trastornos médicos crónicos. Las conductas de riesgo adversas para la salud y los cambios psico-biológicos asociados con la depresión aumentan el riesgo de trastornos médicos crónicos, y los cambios biológicos y las complicaciones asociadas con los trastornos médicos crónicos pueden precipitar episodios depresivos. La depresión comórbida está asociada con un aumento de las repercusiones de los síntomas médicos, del deterioro funcional, de los costos médicos, de una pobre adherencia a los regímenes de auto-cuidado, y un mayor riesgo de morbilidad y mortalidad en los pacientes con trastornos médicos crónicos. La depresión puede empeorar la evolución de los trastornos médicos debido a su efecto sobre los factores proinflamatorios, en el eje hipotálamo-hipofisiario, en el sistema nervioso autónomo y sobre los factores metabólicos, además de estar asociada con un mayor riesgo de obesidad, de un estilo de vida sedentario, de tabaquismo y de una pobre adherencia a los tratamientos médicos. Tanto las psicoterapias basadas en la evidencia como los fármacos antidepresivos son tratamientos eficaces para la depresión. Los modelos de atención en salud de tipo colaborativo aplicados a la depresión han demostrado ser una forma efectiva para entregar estos tratamientos a grandes poblaciones de pacientes en atención primaria con depresión y enfermedades médicas crónicas.

Épidémiologie et traitement de la dépression chez les patients ayant une pathologie chronique

La dépression et les pathologies chroniques sont liées à double titre. Les comportements à risque délétères pour la santé et les modifications psycho-biologiques associés à la dépression augmentent le risque de pathologies chroniques, tandis que les complications et modifications biologiques associées aux pathologies chroniques peuvent précipiter des épisodes dépressifs. La dépression, chez les patients présentant des pathologies chroniques, est associée à une augmentation de la charge symptomatique, à une détérioration fonctionnelle, à des coûts médicaux, à une mauvaise observance de l'autosurveillance et à une augmentation du risque de morbidité et de mortalité.. Elle peut aggraver le cours des maladies à cause de ses effets sur les facteurs pro-inflammatoires, sur l'axe hypothalamo-hypophysaire, sur le système nerveux autonome et sur les facteurs métaboliques, avec en plus un risque majoré d'obésité, de vie sédentaire, de tabagisme et de mauvaise observance des traitements médicaux. Les psychothérapies validées et les antidépresseurs sont deux approches utiles pour traiter la dépression. La prise en charge de la dépression de manière collaborative est efficace pour soigner un grand nombre de patients traités en soins primaires atteints de dépression comorbide de pathologies chroniques.

34. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000;160:2101-2107.
35. Katon W, Russo J, Lin EH, et al. Diabetes and poor disease control: is comorbid depression associated with poor medication adherence or lack of treatment intensification? *Psychosom Med*. 2009;71:965-972.
36. Ziegelstein RC, Fauerbach JA, Stevens SS, Romanelli J, Richter DP, Bush DE. Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Arch Intern Med*. 2000;160:1818-1823.
37. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. *Arch Intern Med*. 2005;165:2508-2513.
38. Carney RM, Freedland KE, Eisen SA, Rich MW, Jaffe AS. Major depression and medication adherence in elderly patients with coronary artery disease. *Health Psychol*. 1995;14:88-90.

39. Rieckmann N, Gerin W, Kronish IM, et al. Course of depressive symptoms and medication adherence after acute coronary syndromes: an electronic medication monitoring study. *J Am Coll Cardiol*. 2006;48:2218-2222.
40. Blumenthal JA, Williams RS, Wallace AG, Williams RB, Jr., Needles TL. Physiological and psychological variables predict compliance to prescribed exercise therapy in patients recovering from myocardial infarction. *Psychosom Med*. 1982;44:519-527.
41. Simon GE. Psychiatric disorder and functional somatic symptoms as predictors of health care use. *Psychiatr Med*. 1992;10:49-59.
42. Katon W, Von Korff M, Lin E, et al. Distressed high utilizers of medical care. DSM-III-R diagnoses and treatment needs. *Gen Hosp Psychiatry*. 1990;12:355-362.
43. Katon WJ, Lin E, Russo J, Unutzer J. Increased medical costs of a population-based sample of depressed elderly patients. *Arch Gen Psychiatry*. 2003;60:897-903.
44. Unutzer J, Patrick DL, Simon G, et al. Depressive symptoms and the cost of health services in HMO patients aged 65 years and older. A 4-year prospective study. *JAMA*. 1997;277:1618-1623.

45. Simon G, Katon W, Lin E, et al. Diabetes complications and depression as predictors of health care costs. *Gen Hosp Psychiatry*. 2005;27:344-351.

46. Sullivan M, Simon G, Spertus J, Russo J. Depression-related costs in heart failure care. *Arch Intern Med*. 2002;162:1860-1866.

47. Simon GE, VonKorff M, Barlow W. Health care costs of primary care patients with recognized depression. *Arch Gen Psychiatry*. 1995;52:850-856.

48. Katon W, Unutzer J, Fan MY, et al. Cost-effectiveness and net benefit of enhanced treatment of depression for older adults with diabetes and depression. *Diabetes Care*. 2006;29:265-270.

49. Simon GE, Katon WJ, Lin EH, et al. Cost-effectiveness of systematic depression treatment among people with diabetes mellitus. *Arch Gen Psychiatry*. 2007;64:65-72.

50. Katon WJ, Russo JE, Von Korff M, Lin EH, Ludman E, Ciechanowski PS. Long-term effects on medical costs of improving depression outcomes in patients with depression and diabetes. *Diabetes Care*. 2008;31:1155-1159.

51. Katon W, Sullivan M, Walker E. Medical symptoms without identified pathology: relationship to psychiatric disorders, childhood and adult trauma, and personality traits. *Ann Intern Med*. 2001;134(9 Pt 2):917-925.

52. Kroenke K, Spitzer RL, Williams JB, et al. Physical symptoms in primary care. Predictors of psychiatric disorders and functional impairment. *Arch Fam Med*. 1994;3:774-779.

53. Gureje O, Simon GE, Von Korff M. A cross-national study of the course of persistent pain in primary care. *Pain*. 2001;92:195-200.

54. Sullivan MD, Edlund MJ, Zhang L, Unutzer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Arch Intern Med*. 2006;166:2087-2093.

55. Sullivan MD. Who gets high-dose opioid therapy for chronic non-cancer pain? *Pain*. 2010;151:567-568.

56. Fields HL. Pain modulation: expectation, opioid analgesia and virtual pain. *Prog Brain Res*. 2000;122:245-253.

57. Okada K, Murase K, Kawakita K. Effects of electrical stimulation of thalamic nucleus submedius and periaqueductal gray on the visceral nociceptive responses of spinal dorsal horn neurons in the rat. *Brain Res*. 1999;834:112-121.

58. Hirakawa N, Tershner SA, Fields HL. Highly delta selective antagonists in the RVM attenuate the antinociceptive effect of PAG DAMGO. *Neuroreport*. 1999;10:3125-3129.

59. Stahl SM. Does depression hurt? *J Clin Psychiatry*. 2002;63:273-274.

60. Ludman EJ, Katon W, Russo J, et al. Depression and diabetes symptom burden. *Gen Hosp Psychiatry*. 2004;26:430-436.

61. Borson S, McDonald GJ, Gayle T, Deffebach M, Lakshminarayan S, VanTuinen C. Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients with chronic obstructive pulmonary disease. *Psychosomatics*. 1992;33:190-201.

62. Lin EH, Katon W, Von Korff M, et al. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA*. 2003;290:2428-2429.

63. 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;33:706-713.

64. van Melle JP, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med*. 2004;66:814-822.

65. Blumenthal JA, Lett HS, Babyak MA, et al. Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet*. 2003;362:604-609.

66. Burg M. Depression prior to CABG predicts 6-month and 2-year morbidity and mortality [abstract]. *Psychosom Med*. 2001;63:103.

67. Connerney I. In-hospital depression after CABG surgery predicts 12-month outcome [abstract]. *Psychosom Med*. 2000;62:106.

68. Pelle AJ, Gidron YY, Szabo BM, Denollet J. Psychological predictors of prognosis in chronic heart failure. *J Card Fail*. 2008;14:341-350.

69. Lin EH, Heckbert SR, Rutter CM, et al. Depression and increased mortality in diabetes: unexpected causes of death. *Ann Fam Med*. 2009;7:414-421.

70. Zhang X, Norris SL, Gregg EW, Cheng YJ, Beckles G, Kahn HS. Depressive symptoms and mortality among persons with and without diabetes. *Am J Epidemiol*. 2005;161:652-660.

71. Katon WJ, Rutter C, Simon G, et al. The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care*. 2005;28:2668-2672.

72. Black SA, Markides KS, Ray LA. Depression predicts increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes. *Diabetes Care*. 2003;26:2822-2828.

73. Egede LE, Nietert PJ, Zheng D. Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. *Diabetes Care*. 2005;28:1339-1345.

74. Katon W, Fan MY, Unutzer J, Taylor J, Pincus H, Schoenbaum M. Depression and diabetes: a potentially lethal combination. *J Gen Intern Med*. 2008;23:1571-1575.

75. Williams LH, Rutter CM, Katon WJ, et al. Depression and incident diabetic foot ulcers: a prospective cohort study. *Am J Med*. 2010;123:748-754 e743.

76. Williams LH, Miller DR, Fincke G, et al. Depression and incident lower limb amputations in veterans with diabetes. *J Diabetes Complications*. In press.

77. Ritchie K, Carriere I, Ritchie CW, Berr C, Artero S, Ancelin ML. Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. *BMJ*. 2010;341:c3885.

78. Katon W, Lin E, Williams L, et al. Comorbid depression is associated with an increased risk of dementia diagnosis in patients with diabetes: a prospective cohort study. *J Gen Intern Med*. In press.

79. Lavoie KL, Fleet RP, Lesperance F, et al. Are exercise stress tests appropriate for assessing myocardial ischemia in patients with major depressive disorder? *Am Heart J*. 2004;148:621-627.

80. Sullivan M, Levy WC, Russo JE, Spertus JA. Depression and health status in patients with advanced heart failure: a prospective study in tertiary care. *J Card Fail*. 2004;10:390-396.

81. Von Korff M, Katon W, Lin EH, et al. Potentially modifiable factors associated with disability among people with diabetes. *Psychosom Med*. 2005;67:233-240.

82. Von Korff M, Katon W, Lin EH, et al. Work disability among individuals with diabetes. *Diabetes Care*. 2005;28:1326-1332.

83. Sarkar U, Ali S, Whooley MA. Self-efficacy and health status in patients with coronary heart disease: findings from the heart and soul study. *Psychosom Med*. 2007;69:306-312.

84. Morgan AL, Masoudi FA, Havranek EP, et al. Difficulty taking medications, depression, and health status in heart failure patients. *J Card Fail*. 2006;12:54-60.

85. Bruce ML, Hoff RA. Social and physical health risk factors for first-onset major depressive disorder in a community sample. *Soc Psychiatry Psychiatr Epidemiol*. 1994;29:165-171.

86. Bruce ML, Seeman TE, Merrill SS, Blazer DG. The impact of depressive symptomatology on physical disability: MacArthur Studies of Successful Aging. *Am J Public Health*. 1994;84:1796-1799.

87. Katz I. On the inseparability of mental and physical health in aged persons: lessons from depression and medical comorbidity. *Am J Geriatr Psychiatry*. 1996;4:1-16.

88. Prince MJ, Harwood RH, Thomas A, Mann AH. A prospective population-based cohort study of the effects of disablement and social milieu on the onset and maintenance of late-life depression. The Gospel Oak Project VII. *Psychol Med*. 1998;28:337-350.

89. Ormel J, Rijsdijk FV, Sullivan M, van Sonderen E, Kempen GI. Temporal and reciprocal relationship between IADL/ADL disability and depressive symptoms in late life. *J Gerontol B Psychol Sci Soc Sci*. 2002;57:P338-347.

90. Von Korff M, Ormel J, Katon W, Lin EH. Disability and depression among high utilizers of health care. A longitudinal analysis. *Arch Gen Psychiatry*. 1992;49:91-100.

91. Ormel J, Von Korff M, Van den Brink W, Katon W, Brilman E, Oldehinkel T. Depression, anxiety, and social disability show synchrony of change in primary care patients. *Am J Public Health*. 1993;83:385-390.

92. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol*. 2000;35:1245-1255.

93. Sullivan MD, Newton K, Hecht J, Russo JE, Spertus JA. Depression and health status in elderly patients with heart failure: a 6-month prospective study in primary care. *Am J Geriatr Cardiol*. 2004;13:252-260.

State of the art

94. Rumsfeld JS, Havranek E, Masoudi FA, et al. Depressive symptoms are the strongest predictors of short-term declines in health status in patients with heart failure. *J Am Coll Cardiol*. 2003;42:1811-1817.

95. Sullivan MD, LaCroix AZ, Baum C, Grothaus LC, Katon WJ. Functional status in coronary artery disease: a one-year prospective study of the role of anxiety and depression. *Am J Med*. 1997;103:348-356.

96. Sullivan MD, LaCroix AZ, Spertus JA, Hecht J. Five-year prospective study of the effects of anxiety and depression in patients with coronary artery disease. *Am J Cardiol*. 2000;86:1135-1138, A1136, A1139.

97. Mayou RA, Gill D, Thompson DR, et al. Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosom Med*. 2000;62:212-219.

98. Williams JW, Jr., Katon W, Lin EH, et al. The effectiveness of depression care management on diabetes-related outcomes in older patients. *Ann Intern Med*. 2004;140:1015-1024.

99. Lesperance F, Frasure-Smith N, Koszycki D, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA*. 2007;297:367-379.

100. Rollman BL, Belnap BH, LeMenager MS, et al. Telephone-delivered collaborative care for treating post-CABG depression: a randomized controlled trial. *JAMA*. 2009;302:2095-2103.

101. Ismail K. Unraveling the pathogenesis of the depression-diabetes link. In: Katon W, Maj M, Sartorius, eds. *Depression and Diabetes*. Oxford, UK: Wiley-Blackwell; 2010:29-62.

102. Champaneri S, Wand GS, Malhotra SS, Casagrande SS, Golden SH. Biological basis of depression in adults with diabetes. *Curr Diab Rep*. 2010;10:396-405.

103. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67:446-457.

104. Deverts DJ, Cohen S, DiLillo VG, et al. Depressive symptoms, race, and circulating C-reactive protein: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Psychosom Med*. 2010;72:734-741.

105. Pizzi C, Manzoli L, Mancini S, Bedetti G, Fontana F, Costa GM. Autonomic nervous system, inflammation and preclinical carotid atherosclerosis in depressed subjects with coronary risk factors. *Atherosclerosis*. 2010;212:292-298.

106. Laghrissi-Thode F, Wagner WR, Pollock BG, Johnson PC, Finkel MS. Elevated platelet factor 4 and beta-thromboglobulin plasma levels in depressed patients with ischemic heart disease. *Biol Psychiatry*. 1997;42:290-295.

107. Musselman DL, Tomer A, Manatunga AK, et al. Exaggerated platelet reactivity in major depression. *Am J Psychiatry*. 1996;153:1313-1317.

108. von Kanel R. Platelet hyperactivity in clinical depression and the beneficial effect of antidepressant drug treatment: how strong is the evidence? *Acta Psychiatr Scand*. 2004;110:163-177.

109. Serebruany VL GA, Malinin AI, Nemeroff CB, et al; Sertraline AntiDepressant Heart Attack Randomized Trial Study Group. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events: the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy. *Circulation*. 2003;108:939-944.

110. Sherwood A, Hinderliter AL, Watkins LL, Waugh RA, Blumenthal JA. Impaired endothelial function in coronary heart disease patients with depressive symptomatology. *J Am Coll Cardiol*. 2005;46:656-659.

111. Burg MM, Martens EJ, Collins D, Soufer R. Depression predicts elevated endothelin-1 in patients with coronary artery disease. *Psychosom Med*. 2011;73:2-6.

112. Golden S. A review of the evidence for a neuroendocrine link between stress, depression and diabetes mellitus. *Curr Diabetes Rev*. 2007;3:252-259.

113. Taylor CB, Conrad A, Wilhelm FH, et al. Psychophysiological and cortisol responses to psychological stress in depressed and nondepressed older men and women with elevated cardiovascular disease risk. *Psychosom Med*. 2006;68:538-546.

114. Van den Bergh BR VCB. Diurnal cortisol profiles and evening cortisol in post-pubertal adolescents scoring high on the Children's Depression Inventory. *Psychoneuroendocrinology*. 2009;34:791-794.

115. Bhattacharyya M, Molloy G, Steptoe A. Depression is associated with flatter cortisol rhythms in patients with coronary artery disease. *J Psychosom Res*. 2008;65:107-113.

116. Conrad A WF, Roth WT, Spiegel D, Taylor CB. Circadian affective, cardiopulmonary, and cortisol variability in depressed and nondepressed individuals at risk for cardiovascular disease. *J Psychiatr Res*. 2008;42:769-777.

117. Kuehner C HS, Huffziger S. Decreased cortisol response to awakening is associated with cognitive vulnerability to depression in a nonclinical sample of young adults. *Psychoneuroendocrinology*. 2007;32:199-209.

118. Huber TJ IK, Schik G, Wolf OT. The cortisol awakening response is blunted in psychotherapy inpatients suffering from depression. *Psychoneuroendocrinology*. 2006;31:900-904.

119. Gutt M DC, Spitzer SB, Llabre MM, Kumar M, Czarnecki EM, Schneiderman N, Skyler JS, Marks JB. Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. *Diabetes Res Clin Pract*. 2000;47:177-184.

120. Beydoun MA, Kuczmarski MT, Mason MA, Ling SM, Evans MK, Zonderman AB. Role of depressive symptoms in explaining socioeconomic status disparities in dietary quality and central adiposity among US adults: a structural equation modeling approach. *Am J Clin Nutr*. 2009;90:1084-1095.

121. Everson-Rose SA, Lewis TT, Karavolos K, Dugan SA, Wesley D, Powell LH. Depressive symptoms and increased visceral fat in middle-aged women. *Psychosom Med*. 2009;71:410-416.

122. Bigger JT, Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation*. 1992;85:164-171.

123. Kleiger RE, Miller JP, Bigger JT, Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol*. 1987;59:256-262.

124. Carney RM, Rich MW, teVelde A, Saini J, Clark K, Freedland KE. The relationship between heart rate, heart rate variability and depression in patients with coronary artery disease. *J Psychosom Res*. 1988;32:159-164.

125. Krittayaphong R CW, Light KC, Sheffield D, et al. Heart rate variability in patients with coronary artery disease: differences in patients with higher and lower depression scores. *Psychosom Med*. 1997;59:231-235.

126. Gehi A MD, Pipkin S, Browner WS, Whooley MA. Depression and heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. *Arch Gen Psychiatry*. 2005;62:661-666.

127. Carney RM, Freedland KE, Veith RC, et al. Major depression, heart rate, and plasma norepinephrine in patients with coronary heart disease. *Biol Psychiatry*. 1999;45:458-463.

128. Carney RM, Freedland KE, Stein PK, et al. Effects of depression on QT interval variability after myocardial infarction. *Psychosom Med*. 2003;65:177-180.

129. Carney RM, Howells WB, Blumenthal JA, et al. Heart rate turbulence, depression, and survival after acute myocardial infarction. *Psychosom Med*. 2007;69:4-9.

130. Hughes JW CE, Luyster F, Doe VH, Waechter D, Rosneck J, Josephson R. Depression symptoms predict heart rate recovery after treadmill stress testing. *Am Heart J*. 2006;151:e1121-e1126.

131. Patten SB WJ, Lavorato DH, Campbell NR, Eliasziw M, Campbell TS. Major depression as a risk factor for high blood pressure: epidemiologic evidence from a national longitudinal study. *Psychosom Med*. 2009;71:273-279.

132. Krishnan. K. Biological risk factors in late life depression. *Biol Psychiatry*. 2002;52:185-192.

133. Timonen M RU, Jokelainen J, Keinänen-Kiukaanniemi S, Meyer-Rochow VB, Räsänen P. Depressive symptoms and insulin resistance in young adult males: results from the Northern Finland 1966 birth cohort. *Mol Psychiatry*. 2006;11:929-933.

134. Pan A YX, Franco OH, Li H, Yu Z, Zou S, Zhang Z, Jiao S, Lin X. Insulin resistance and depressive symptoms in middle-aged and elderly Chinese: findings from the Nutrition and Health of Aging Population in China Study. *J Affect Disord*. 2008;109:75-82.

135. Adriaanse MC DJ, Nijpels G, Heine RJ, Snoek FJ, Pouwer F. Associations between depressive symptoms and insulin resistance: the Hoorn Study. *Diabetologia*. 2006;49:2874-2877.

136. Lawlor DA B-SY, Ebrahim S, Davey Smith G, Stansfeld SA, Yarnell JW, Gallacher JE. Insulin resistance and depressive symptoms in middle aged men: findings from the Caerphilly prospective cohort study. *BMJ*. 2005;330:705-706.
137. Kop WJ SP, Tracy RP, Barzilay JI, Schulz R, Gottdiener JS. Autonomic nervous system dysfunction and inflammation contribute to the increased cardiovascular mortality risk associated with depression. *Psychosom Med*. 2010;72:626-635.
138. Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA*. 2008;300:2379-2388.
139. van der Feltz-Cornelis CM, Nuyen J, Stoop C, et al. Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis. *Gen Hosp Psychiatry*. 2010;32:380-395.
140. Katon WJ, Von Korff M, Lin EH, et al. The Pathways Study: a randomized trial of collaborative care in patients with diabetes and depression. *Arch Gen Psychiatry*. 2004;61:1042-1049.
141. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288:701-709.

142. Honig A, Kuyper AM, Schene AH, et al. Treatment of post-myocardial infarction depressive disorder: a randomized, placebo-controlled trial with mirtazapine. *Psychosom Med*. 2007;69:606-613.
143. O'Connor CM, Jiang W, Kuchibhatla M, et al. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SAD-HART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *J Am Coll Cardiol*. 2010;56:692-699.
144. Berkman LF, Blumenthal J, Burg M, et al. 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;289:3106-3116.
145. Freedland KE, Skala JA, Carney RM, et al. Treatment of depression after coronary artery bypass surgery: a randomized controlled trial. *Arch Gen Psychiatry*. 2009;66:387-396.
146. Davidson KW, Rieckmann N, Clemow L, et al. Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms: coronary psychosocial evaluation studies randomized controlled trial. *Arch Intern Med*. 2010;170:600-608.