Depression and Chronic Diseases: It Is Time for a Synergistic Mental Health and Primary Care Approach

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ABSTRACT

Objective: To identify the growing significance of depression as a global leading cause of years lost to disability and its role as a major independent risk factor in many chronic illnesses. The distinct effects of depression on morbidity and mortality in cancer, diabetes, heart disease, and stroke are investigated, including behavioral factors and plausible biological mechanisms (psychoneuroimmunology of depression).

Data Sources: PubMed articles in English were searched from 1992 to 2012 (20-year span) using the following search criteria: *psychoneuroimmunology of depression*, *immune-mediated inflammation*, *depression treatment recommendations*, *depression screening*, *years lost to disability*, *underserved populations and depression*, *chronic illnesses and depression*, and *selective serotonin reuptake inhibitors and immune system*.

Data Synthesis: Evidence of the robust bidirectional relationship between depression and individual chronic diseases is presented and discussed. A brief overview of currently recommended psychotherapeutic and psychopharmacologic treatment approaches in regard to depression in chronic diseases is provided.

Results: Discordance between mental health and primary care within the US public health system is a systematic problem that must be addressed. This situation leads to a potentially high hidden prevalence of underdiagnosed and undertreated depression, especially in the underserved populations.

Conclusion: Measures must be implemented across the communities of mental health and primary care practitioners in order to achieve a synergistic approach to depression.

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The World Health Organization predicts that by the year 2030, depression will result in more years of life lost to disability than any other illness.[1] Today, depression is already the second cause of disability adjusted life years in the age category 15 to 44 years for both sexes combined. Depression occurs in persons of all genders, ages, and backgrounds. Studies of the epidemiology of major depressive disorder have shown that the mean life span in depressed patients is 25 to 30 years shorter than that of the general population, which is a lot of life lost to a condition that can be reliably diagnosed in the primary care setting. Antidepressant medications and brief, structured forms of psychotherapy used together are effective for up to 80% of those affected by depression and can be delivered in primary care. Unfortunately, worldwide, fewer than 25% of those affected (in some countries fewer than 10% of those affected) receive such treatments.[1] In the United States, depression was reported in 9.1% of the adult population for the past 12 months, and up to 17% of the adult population will experience depressive symptoms at least once during their lifetime.[2] In the United States, however, fewer than 50% of those affected have access to effective treatments.[2]

This review summarizes the vast set of literature that probes into the effect of depression on morbidity and mortality in 4 of the most prevalent chronic illnesses in the United States—cancer, diabetes, heart disease, and stroke—including behavioral factors and plausible biological mechanisms. We provide a brief overview of currently recommended psychotherapeutic and psychopharmacologic treatment approaches in regard to depression in chronic diseases and identify and discuss the issue of discordance between the mental health and primary care fields within the US public health system. This issue of discordance may lead to potentially higher rates of underdiagnosed and undertreated depression than reported. Also, measures are outlined that must be implemented across the communities of mental health and primary care practitioners in order to achieve a synergistic approach to depression treatment.

METHOD

PubMed articles in English were searched from 1992 to 2012 (20-year span) using the following search criteria: *psychoneuroimmunology of depression*, *immune-mediated inflammation*, *depression treatment recommendations*, *depression screening*, *years lost to disability*, *underserved populations and depression*, *chronic illnesses and depression*, and *selective serotonin reuptake inhibitors and immune system*.

Evidence of the robust bidirectional relationship between depression and individual chronic diseases is presented and discussed. A brief overview of currently recommended psychotherapeutic and psychopharmacologic treatment approaches with regard to depression in chronic diseases is provided.

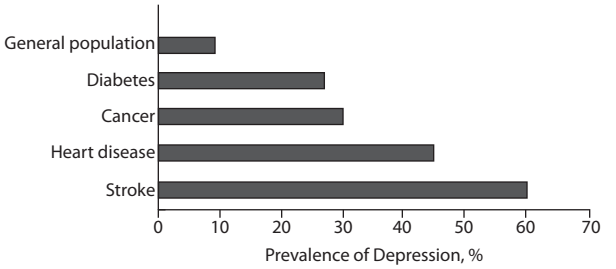
ROLE OF DEPRESSION IN CHRONIC ILLNESSES

There is an increasing understanding throughout the psychiatric community of the role of depression as a major independent risk factor and a negative prognostic indicator for many important chronic illnesses including heart disease, stroke, cancer, and diabetes. The prevalence of depression associated with the above-mentioned chronic illnesses is thought to be significantly higher in affected patients than in the general population. Mykletun et al[3] reported that

Clinical Points

- The mean life span in depressed patients is 25 to 30 years shorter than that in the general population, and the impact of depression on public health is on par with that of smoking and obesity.
- Depression can be reliably diagnosed and treated in the primary care setting.
- There are evidence-based, simple, and cost-effective screening tools to identify depression.

Figure 1. Prevalence of Depression in Major Chronic Illnesses



depression as an independent risk factor for mortality was comparable in strength to smoking. Since depression can disrupt many aspects of life, such as maintaining employment and productivity in the workplace, its negative impact on job performance has been estimated to be even greater than that of chronic conditions such as arthritis, hypertension, back problems, and diabetes.[4] Figure 1 shows the prevalence of depression in major chronic illnesses.

Up to the mid-1980s, the universal thinking across the community of mental health practitioners was that the effect of depression in chronic diseases is solely based on behavioral factors (ie, reduced adherence to medications, impaired sleep and nutrition, lack of physical exercise, unhealthy behaviors such as smoking and alcohol and substance abuse). Effects of these factors on increased death and disability in comorbid chronic diseases are well established in the literature and are reviewed in Table 1.

Biological Mechanisms Linking Depression and Chronic Illnesses

The research literature spanning the past 2 decades indicates that depression has a distinct and direct effect on the innate, adaptive, and cellular immune systems employing multiple pathways. The newly emerged field of psychoneuroimmunology has matured enough to provide compelling evidence of the relationship between depression and disruption of the immune system. It became evident that depression and chronic illnesses have a bidirectional relationship in which sustained low-grade chronic inflammation, impaired cellular immunity, disruption of neurotransmitter systems relevant to depression, and depressive behavior all feed off of each other in a decompensatory feedback loop.[5] Several mechanisms have been identified that may potentially link depression to negative health outcomes as follows.

Immune-mediated inflammation. Characterized by overexpression of proinflammatory cytokines, immune-mediated inflammation is considered to contribute to the destabilization of atherosclerotic plaques and induce rupture and thrombosis in the later stages of atherosclerosis.[6] Levels of other inflammatory markers, such as IL-6, C-reactive protein, and TNF-α, are found to be significantly higher in patients with comorbid depression than in those with a chronic illness alone. Such elevations impose an increased risk of major adverse cardiovascular events and mortality[7] via direct effects on myocardial contractility and apoptosis[8] and via hippocampal neuronal loss. The hypothalamic-pituitary-adrenal (HPA) axis plays a central role in the human stress response, and its end product cortisol is heavily involved in the regulation of normal physiology.

HPA axis dysregulation. This activity is reportedly seen in depression and is associated with a variety of important risk factors, such as abdominal obesity, hypercholesterolemia, hypertriglyceridemia, hypertension, and glucose intolerance.[9]

Increased thrombogenesis. Platelets are involved in thrombus formation, a key pathophysiologic mechanism in atherosclerosis, stroke, and myocardial infarction. In depression, plasma serotonin and norepinephrine levels are increased.[10] Since serotonin and norepinephrine are platelet agonists, higher levels of these neurotransmitters will result in increased platelet activation via positive feedback loops.[11]

Effects of serotonin. Serotonin has diverse cardiovascular effects including arrhythmia and vasoconstriction. Long-term exposure to serotonin results in proliferative diseases of the endothelium and thickening of the cardiac valves.[12]

Immune-Mediated Inflammation Links Depression to Chronic Illnesses

Emerging literature on the role of depression as an inducer of chronic immune-mediated inflammation correlates with growing recognition that chronic inflammation itself lays at the basis of pathogenesis in such disorders as heart disease,[13] stroke,[14] Alzheimer's disease,[15] many cancers,[16] autoimmune diseases such as multiple sclerosis and rheumatoid arthritis,[17–20] obesity, and diabetes.[21] Depression in these conditions is reported to increase serum proinflammatory cytokines (IL-1, IL-6, TNF-α) and other multiple inflammatory biomarkers, thus feeding in and sustaining the chronic maladaptive inflammation. Further research in clinical translation of these findings has followed and, interestingly enough, several clinical trials of using antiinflammatory drugs like celecoxib (cyclooxygenase inhibitor) or etanercept (TNF-α inhibitor) as adjunctive therapy to traditional antidepressants for the treatment of mood disorders confirmed their effectiveness.[22] Additional research is needed to further delineate a potential for novel treatments of resistant depression with anti-inflammatory drugs.

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Table 1. Behavioral Mechanisms Linking Depression and Chronic Illnesses

Mechanism	Comment	Effect on Comorbid Chronic Illness
Sleep disturbance	Common in depression; may be exacerbated by chronic illness symptoms	Leads to autonomic hyperactivity, which is linked to obesity, diabetes, hypertension, and the metabolic syndrome
Lack of physical activity	Common in depression	Increases morbidity and mortality in obesity, diabetes, hypertension, and the metabolic syndrome
Cigarette smoking, alcohol and/or substance abuse	Individuals with depression are more likely to smoke and abuse alcohol and/or illicit drugs; depressed smokers and substance abusers are less likely to quit	Increases morbidity and mortality in obesity, diabetes, hypertension, and the metabolic syndrome; increases the likelihood of schizophrenia exacerbation
Adherence to treatment	Patients with depression are less likely to adhere to medical therapy and risk-reducing behaviors	Poor adherence to medical therapy is associated with increased morbidity and mortality in obesity, diabetes, hypertension, and the metabolic syndrome

Depression and Suppression of Cellular Immunity

Another vast body of evidence has linked depression to suppression of the cellular immune system via decreased proliferation of lymphocytes and reduction in NK cell activity.[23,24] This effect underpins a negative prognosis in patients chronically infected with human immune deficiency, hepatitis C, Epstein-Barr, and herpes zoster viruses who also suffer with comorbid depression. One of the pathways established as the basis of pathogenesis of immune suppression works through disrupting the serotonin signaling on the membranes of the lymphocytes. It was demonstrated that dendritic cells, monocytes, and CD-4 and CD-8 cells all have serotonin-1 receptors and intracellular apparatus specific for serotonin signaling. It became evident that serotonin modulates proliferation of immune cells, and disruption of serotonergic systems in depression leads to impaired cellular immunity.[23,24]

DEPRESSION AND CORONARY ARTERY DISEASE

Epidemiology

Major depressive disorder occurs in 23% of patients post–myocardial infarction, and a range of 30%–45% of other depressive symptoms is reported in the inpatient population with coronary artery disease.[25] Morbidity and mortality in patients with cardiovascular disease and depression are significantly higher than in patients with cardiovascular disease who are not depressed. For example, patients with major depressive disorder are 4 times more likely to die in the first 6 months after an acute myocardial infarction than are those without depression. This is a mortality risk factor that is on par with other serious risk factors, such as prior myocardial infarction or left ventricular dysfunction.[25]

Independent Risk Factor

The negative effect of depression is independent of severity of coronary artery disease, myocardial infarction, left ventricular dysfunction, or other indices of cardiac diseases.[25] Depression is therefore recognized as an independent risk factor for coronary artery disease (in this instance, independent risk factor means that even if patients do everything recommended to protect their heart, if they are depressed, they would still be at greater risk for serious coronary artery blockage). Depression also increases disability in patients with coronary artery disease and their utilization of medical care, leading to significant burden on the public health system, both financial and medical.

Symptom Domains of Depression and Cardiac Mortality

Of particular interest are the results of the recent study by de Jonge et al [26] that looked at the timing of the onset of depression in patients with coronary artery disease and at the same time controlled for various sets of symptoms of depression to investigate which particular symptom sets are more "cardiotoxic" than others. Large data sets from more than 2,000 patients were analyzed comparing 3 dimensions of depressive symptoms (derived from the Beck Depression Inventory) in relation to cardiovascular risk factors, mortality, and readmissions over a mean of 2.5 years after acute coronary syndrome. There is strong evidence that somatic/affective symptoms (pessimism, fatigue, sadness) and appetitive symptoms (loss of appetite, weight loss) are associated with increased risk of cardiac mortality independent of coronary artery disease severity at baseline. The cognitive/affective symptoms (social withdrawal, work difficulty, loss of concentration) were not found to be predictive of any increase in cardiac mortality.[26]

Antidepressants in the Post–Myocardial Infarction Period

Selective serotonin reuptake inhibitors (SSRIs) are safe in the immediate post–myocardial infarction period and are effective antidepressants. There is strong suggestion that antidepressants in general, and SSRIs in particular, reduce morbidity and mortality in post–myocardial infarction patients who are depressed.[27]

DEPRESSION AND STROKE

Epidemiology

Depression is a very common condition in poststroke patients, and its prevalence in this population ranges from 20% to 60% in various studies. This wide range can be explained by vague symptoms of depression, overlapping signs and symptoms of stroke and depression, lack of properly trained health care personnel, and insufficient assessment tools for proper diagnosis.[28] However, all researchers involved in the relevant studies seem to be in agreement that the rate of the poststroke depression may be markedly underestimated

due to such factors as impairment of memory and cognitive functioning in poststroke patients, making it difficult to effectively gauge their mood. In a 10-year follow-up study, the mortality rate in patients with an acute poststroke depression was reported to be 70% compared to a 10-year mortality rate of 40% in poststroke patients with no depression.[29] The highest rate of poststroke mortality in depressed patients was reported during the first 12 months and was estimated as a 3-fold risk of the fatal outcome compared to that of nondepressed poststroke patients.[30]

Relationship of Depression and Stroke

There is emerging evidence of a bidirectional relationship of depression and cerebrovascular disease, whereas premorbid depression can cause transient ischemic attack or stroke. The largest-to-date meta-analysis reviewed 28 prospective cohort studies (comprising 317,540 participants) that reported 8,478 stroke cases during a follow-up period ranging from 2 to 29 years.[31] The researchers concluded that depression is associated with a significantly increased risk of stroke morbidity and mortality.[31] Depression was found to be associated with poor health behaviors (ie, smoking, lack of physical inactivity, poor diet, lack of adherence to medication),[31] all of which increase the risk of stroke.[32] The magnitude of the depression-stroke association observed in the study by Pan et al[31] is similar to the associations that have been found between smoking and stroke[33] and between obesity and stroke.[34]

Depression may also contribute to pathogenesis of cerebrovascular disease through several biological mechanisms including (1) HPA axis dysregulation, which leads to hypertension, obesity, and hypercholesterolemia; (2) overactivation of platelet aggregation and subsequent thrombus formation; and (3) chronic inflammation associated with elevated serum C-reactive protein, IL-1, IL-6, and TNF-α. These inflammatory factors were positively associated with an increased risk of stroke.[35]

Antidepressants in Treatment of Depression Comorbid With Cerebrovascular Disease

Classically, main goals of treatment are to reduce depressive symptoms, improve mood and quality of life, and reduce the risk of medical complications including relapse. Antidepressants are generally not indicated in milder forms of depression because the balance of benefit and risk is not satisfactory in elderly stroke patients. SSRIs are the first choice for poststroke depression treatment in elderly patients due to their lower potential for drug interaction and side effects, which are more common with tricyclic antidepressants.

DEPRESSION AND DIABETES

Epidemiology

Depression is a very common condition in patients with diabetes. As many as 1 in 4 patients are confronted with depression during a 2.5-year period, and, once present, depression often becomes a chronic/recurrent condition in this group.[36] Mortality in patients with diabetes with comorbid major depression is almost 3 times higher compared to that in patients with diabetes only.[37] Of note, several groups at increased risk of diabetes were identified in the United States including African Americans, Pacific Americans, Native Americans, and Hispanics.[38] Mortality from comorbid depression in these populations quite reasonably should be expected to be higher. However, the majority of studies on correlation of depression and diabetes were done in Europe and contemplated predominantly white populations. Very few studies investigated effects of comorbid depression in the above-mentioned minority groups in the United States and those that did reported significant differences in health outcomes compared to the white population. For example, a prospective study of 2,830 Mexican Americans with type 2 diabetes over age 65 years, followed up over 7 years, demonstrated that depressed individuals were almost 5 times more likely to die and were significantly more likely to develop early-onset diabetes complications than nondepressed individuals.[39]

Relationship Between Depression and Diabetes

There is a strong and robust association of depression and incidence of type 2 diabetes. In the meta-analysis of lifetime effects of depression in diabetes, depression was associated with a 60% increase in the risk of developing type 2 diabetes. Depression, therefore, is a risk factor that rivals other known risk factors for diabetes such as smoking.[40]

Behavioral Factors

Depression is associated with reduced physical activity and sleep disturbances, which increases the risk for obesity and consequently increases the risk for type 2 diabetes. Depression is associated with poor diabetes self-care including poor adherence to medication, dietary modifications, exercising, and monitoring of blood glucose.[41]

Biological Factors

As mentioned above, the HPA axis and simpatico-adrenal nervous systems are both overactivated by stress. Sympathetic overactivation results in the increased catecholamine and proinflammatory cytokine levels (IL-1, IL-6, TNF-α, CRP) associated with increased insulin resistance. The overactivated HPA axis results in persistently increased cortisol levels, which in turn, leads to increased central adiposity and increased insulin resistance.

DEPRESSION AND CANCER

Challenging Epidemiology

Effects of depression in cancer patients have been investigated for more than 30 years starting with the groundbreaking research of David Spiegel and his group at Stanford University in the late 1970s. Spiegel[42] found that those advanced breast cancer patients who attended a weekly support group lived twice as long as those who did not. Numerous studies that followed collected and analyzed tremendous volumes of evidence; however, the results are very conflicting. The prevalence of depression in cancer

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patients has been reported in a range of 1%–69%, which are not very practical data for the health care administrators in charge of allocating overstretched resources. Diagnosing depression in cancer patients may be challenging partially for the following reasons:

- *DSM-IV* diagnostic criteria include several symptoms overlapping with symptoms of cancer or side effects of treatments (ie, appetite loss, weight loss, sleep disturbances, fatigue, loss of energy, difficulty concentrating, and psychomotor retardation).
- Prevalence rates are often assessed at varying time points in the trajectory of the disease, although emotional distress is known to change as patients transition through stages of diagnosis, acute treatment, and posttreatment.[43] Prevalence rates for depression also greatly depend on whether or not patients have responded to treatment or not.[44]
- The majority of the relevant published literature relied on depression symptom screening methods, rather than gold standard diagnostic instruments.[45]

Recent meta-analytic studies[46,47] narrowed their pool of literature to only those works that diagnosed depression spectrum symptoms in cancer patients using the *DSM* or *ICD* criteria, resulting in the overall prevalence rate of depression in cancer patients of 29%.

The study by Lloyd-Williams et al[48] reported a significantly decreased rate of survival among cancer patients with depression compared to nondepressed cancer patients. This study used the Edinburgh Depression Scale, an instrument that excludes the somatic symptoms of depression that may overlap with those of cancer. Depression was reported as an independent risk factor for a poor survival prognosis in cancer patients.[48] In another population-based study with over 10,000 participants, cancer patients with depression had a significantly greater risk of death at 8-year follow-up than those who were not depressed.[49] Cancer types highly associated with depression include brain (41%–93%), pancreas (up to 50%), head and neck (up to 42%), breast (up to 37%), gynecologic (23%), and lung (11%).[50]

Behavioral Factors

Noncompliance with the prescribed medication regimen has been recognized as depression's main mediator to poor survival in cancer patients.[51] The ways by which depression affects adherence to anticancer treatments are as follows:

- Inability to integrate cancer diagnosis and treatment information;
- Reduced motivation toward self-care, difficulty planning;
- Negative health beliefs and pessimism about treatment;
- Avoidance of health-promoting behaviors;
- Social isolation and withdrawal;
- Reduced use of community resources;
- Greater difficulty tolerating treatment side effects.

Biological Factors

In the oncology setting, the significance of neuroendocrine dysregulation caused by depression is particularly important. Activation of the HPA axis is a normal adaptive reaction to stress, but in response to long-term cumulative stressors, the HPA axis shifts into a state of being constantly "on." That, in turn, leads to hypercortisolism among other adverse outcomes. Persistently increased levels of cortisol have been reported to (1) promote tumor growth,[52] (2) lead to a functional immunosuppression, and (3) down-regulate expression of tumor suppressor genes (BRCA1) and therefore decelerate apoptosis of malignant cells.[53]

There is growing evidence that the simpatico-adrenal system, also overactivated in depression, may accelerate tumor progression via triggering release of vascular endothelial growth factors, which in turn, stimulates proliferation of blood vessels inside the tumor. Several studies that investigated effects of norepinephrine blockade in tumor progression reported significantly improved survival rates in cancer patients treated with β-blockers.[54,55]

Psychotherapy in Cancer Patients

Current evidence does not support relative superiority of one pharmacologic treatment over another or the superiority of pharmacologic treatment over psychosocial interventions. Therefore, mild-to-moderate forms of depression in cancer patients are recommended to be managed with psychotherapy (eg, cognitive-behavioral and supportive-expressive group therapy being the most beneficial).[56,57]

Antidepressant Therapy

Antidepressant therapy is generally reserved for cancer patients diagnosed with major depressive syndrome or when depression co-occurs with other mental disturbance (depression and anxiety, depression and substance abuse, depression and bipolar disorder). As mentioned above, current evidence does not support one pharmacologic regimen over another, and antidepressants are being chosen on the basis of their side effect profile as applicable to the actual cancer patient.[57]

DISCUSSION

The strong and robust bidirectional relationship between depression and chronic illnesses exists beyond a reasonable doubt as demonstrated above, and there is enough compelling evidence that depression negatively contributes to the development of chronic illnesses, just as as chronic illnesses contribute to the development and negative prognosis of depression. Furthermore, there is growing recognition of the role of immune-mediated inflammation as the universal pathophysiologic process that underlies many chronic diseases and mental disorders. This model views mental disruptions and chronic diseases as clinical manifestations of the same underlying pathophysiologic process. This

emerging understanding potentially paves the way to novel clinical approaches; however, it needs more research.

As demonstrated in detail elsewhere in this article, the chronic immune-mediated inflammation leads to systematic neuroendocrine and immune dysregulation, which in turn contributes to development of chronic medical illnesses.[58] Unfortunately, there is a lack of clinical translation of these findings into finer-tuned recommendations for psychosomatic treatment approaches, so more randomized placebo-controlled studies are needed.

Integration of Mental Health and Primary Care

In the US public health system, the main burden for providing mental health care falls on primary care physicians. According to the American Academy of Family Physicians,[59] 54% of individuals with a mental health condition are served in primary care settings, and 42% of patients with clinical depression were first diagnosed by a primary care physician. Of note, research published by Mental Health America in 2011[60] reported that most individuals prefer to receive their mental health care within the primary care setting since it is perceived as less stigmatizing than the traditional mental health system.

Primary care plays an even more important role in identification and treatment of mental health conditions in underserved populations including older adults and low-income minorities. Mental conditions in these populations are likely to go undiagnosed and undertreated due to a lack of access to mental health care and other barriers to care including socioeconomic and cultural factors.

If the already existing screening and diagnostic methodology, as well as pharmacologic and treatment guidelines, were effectively applied, the life span and overall quality of life of patients suffering with major depressive disorder would be greatly improved. Given the significant rate of depression associated with chronic medical illnesses and its impact on the outcome of treatment regimens, screening for depression should be as routine as taking vital signs at an office visit.[61] Therefore, raising depression awareness and clinical knowledge among primary care practitioners is in our view among the most important challenges that currently face the US public health system. Knowing the treatment options for depression should be no different for primary care providers than knowing the options for any other chronic illness.

Interdisciplinary Prevention Approach: Screening for Depression

The American Heart Association Prevention Committee recommends routine screening of all cardiac patients for depression using 2 short instruments—the 2-item Patient Health Questionnaire, which asks 2 simple questions and tests feelings, mood, and anhedonia ("Over the past 2 weeks have you felt down, depressed, or hopeless?" and "Over the past 2 weeks have you felt little interest or pleasure in doing things?").[27] Patients may easily answer these questions while they are waiting for their appointment. If patients answer positively on either question, their primary care physician is encouraged to proceed with the 9-item Patient Health Questionnaire, a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression.[62] Psychiatric referrals would follow for those patients who qualified. This approach was endorsed by the American Psychiatric Association in 2008 and was reviewed by Sowden et al in 2010,[63] who found it to be feasible, well-accepted, and not resource intensive. There are several evidence-based screening instruments available in the public domain and currently recommended for age groups other than adults to identify patients with depression in the primary care setting.

Center for Epidemiologic Studies Depression Scale for Children. This 20-item questionnaire[64] focuses on how an individual may have felt or acted over the past week. Scores range from 0 to 60, with a score ≥15 being clinically significant of depressive symptoms in children and adolescents.

Pediatric Symptom Checklist. This self-screen is used to identify cognitive, emotional, and behavioral problems in children and adolescents.[65]

Spence Children's Anxiety Scale. This instrument is a self-administered tool used to assess anxiety symptoms consistent with the dimensions of anxiety disorder outlined in the *DSM-IV*.[66]

Global Appraiser of Individual Needs—Short Screener. This evidence-based, brief survey identifies need for further assessment in the areas of mental health, substance abuse, and anger management for adolescents.[67]

Education of primary care physicians alone, albeit a great first step that provides evident benefits to the public health, still will not suffice. A lack of awareness and knowledge among the solo and small-group practitioners about the connection between depression and chronic medical illnesses is just the tip of the iceberg. The problem is much deeper, and resolving it takes a systematic approach. In fact, up until just a few years ago, mental health was not an integral part of the US national public health system. The situation that still persists today in the United States as a result can be described as 2 separate public health and mental health "silos" not working in enough congruence toward the challenge of curbing depression.

In addressing how to integrate mental and primary care health, the US Surgeon General's 2000 Report "Integration of Mental Health Services and Primary Health Care" provided a set of 12 core principles to facilitate the development and implementation of national and local programs.[68] These principles include an emphasis on consumers and their families, promotion of health and overcoming disparities, basic characteristics, financial incentives for team approaches, reimbursement to support evidence-based care, collaboration/collocation, chronic illness and continuity of care, standardized quality and outcome measures, building on existing models, research and demonstrations, investment in training, and information technology.[68]

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Spring-boarded from the US Surgeon General's 2000 report, the "Healthy People 2020"[69] and the Substance Abuse and Mental Health Services Administration's (SAMHSA) "10 × 10" wellness campaigns[70] emphasize a pressing need for well-funded synergistic mental and somatic health approach to depression. Such an approach advocates for the following measures:

- Building shared community-based clinical, systemic, and organizational capacity for combined mental/public health services;
- Achieving health equity by mobilizing traditional community coalitions and networks to address social determinants (barriers to care);
- Developing models for specialized training opportunities for public health stakeholders;
- Improving data collection and evaluation.

Health Care Reform and Integration of Mental Health and Primary Care

The Affordable Care Act was upheld by the Supreme Court of the United States on June 28, 2012, by 5 to 4 votes. The Affordable Care Act provides for a viable opportunity to improve the integration of primary and mental health care.[71] Section 2703 of the Affordable Care Act allows states to establish person-centered health homes through their Medicaid programs. Section 2703 establishes and awards primary and mental health care integration grants nationwide via the SAMHSA—Health Resources Service Administration Center for Integrated Health Solutions.[71] At the time of this publication, SAMHSA has awarded such grants to 64 community-based health agencies. Funded primarily by the Affordable Care Act's Prevention and Public Health Fund, these pilot programs are aimed to build partnerships and infrastructure needed to initiate or expand the integration of primary care services for people in treatment for serious mental illnesses and co-occurring substance use disorders.

In summary, the magnitude of the impact of depression on public health deserves to be identified as a systemic challenge of our time. It is time for the US public health system to not just recognize the importance of mental health and primary care integration but to continue efforts toward the functional transformation of the fragmented mental/somatic health model into fully unified systems of care.

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REFERENCES

1. World Health Organization. The Global Burden of Disease, 2004 Update. Part 4, Burden of Disease, DALYs. http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. Accessed January 10, 2013.
2. Centers for Disease Control and Prevention (CDC). Current depression among adults: United States, 2006 and 2008. *MMWR Morb Mortal Wkly Rep*. 2010;59(38):1229–1235.
3. Mykletun A, Bjerkeset O, Overland S, et al. Levels of anxiety and depression as predictors of mortality: the HUNT study. *Br J Psychiatry*. 2009;195(2):118–125.
4. Kessler RC, Soukup J, Davis RB, et al. The use of complementary and alternative therapies to treat anxiety and depression in the United States. *Am J Psychiatry*. 2001;158(2):289–294.
5. Blume J, Douglas SD, Evans DL. Immune suppression and immune activation in depression. *Brain Behav Immun*. 2011;25(2):221–229.
6. Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med*. 1999;340(2):115–126.
7. Sukhija R, Fahdi I, Garza L, et al. Inflammatory markers, angiographic severity of coronary artery disease, and patient outcome. *Am J Cardiol*. 2007;99(7):879–884.
8. Tousoulis D, Antoniades C, Koumallos N, et al. Pro-inflammatory cytokines in acute coronary syndromes: from bench to bedside. *Cytokine Growth Factor Rev*. 2006;17(4):225–233.
9. Brown ES, Varghese FP, McEwen BS. Association of depression with medical illness: does cortisol play a role? *Biol Psychiatry*. 2004;55(1):1–9.
10. von Känel R. Platelet hyperactivity in clinical depression and the beneficial effect of antidepressant drug treatment: how strong is the evidence? *Acta Psychiatr Scand*. 2004;110(3):163–177.
11. Wulsin LR, Musselman D, Otte C, et al. Depression and whole blood serotonin in patients with coronary heart disease from the Heart and Soul Study. *Psychosom Med*. 2009;71(3):260–265.
12. Watts SW. 5-HT in systemic hypertension: foe, friend or fantasy? *Clin Sci (Lond)*. 2005;108(5):399–412.
13. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352(16):1685–1695.
14. Vaughan CJ. Prevention of stroke and dementia with statins: effects beyond lipid lowering. *Am J Cardiol*. 2003;91(456A):23B–29B.
15. Wyss-Coray T. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? *Nat Med*. 2006;12(9):1005–1015.
16. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420(6917):860–867.
17. Capuron L, Bluthé RM, Dantzer R. Cytokines in clinical psychiatry. *Am J Psychiatry*. 2001;158(7):1163–1164.
18. Capuron L, Hauser P, Hinze-Selch D, et al. Treatment of cytokine-induced depression. *Brain Behav Immun*. 2002;16(5):575–580.
19. Capuron L, Ravaud A, Dantzer R. Early depressive symptoms in cancer patients receiving interleukin 2 and/or interferon alfa-2b therapy. *J Clin Oncol*. 2000;18(10):2143–2151.
20. Frasure-Smith N, Lespérance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Arch Gen Psychiatry*. 2008;65(1):62–71.
21. Sridhar GR. Psychiatric co-morbidity and diabetes. *Indian J Med Res*. 2007;125(3):311–320.
22. Johansson D, Falk A, Marcus MM, et al. Celecoxib enhances the effect of reboxetine and fluoxetine on cortical noradrenaline and serotonin output in the rat. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012 Oct 1;39(1):143–148.
23. Miller AH, Raison CL. Cytokines, p38 MAP kinase and the pathophysiology of depression. *Neuropsychopharmacology*. 2006;31(10):2089–2090.
24. Miller AH. Inflammation versus glucocorticoids as purveyors of pathology during stress: have we reached the tipping point? *Biol Psychiatry*. 2008;64(4):263–265.
25. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. *Biol Psychiatry*. 2003;54(3):227–240.
26. de Jonge P, van den Brink RH, Spijkerman TA, et al. Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. *J Am Coll Cardiol*. 2006;48(11):2204–2208.
27. Bigger JT, Glassman AH. The American Heart Association science advisory on depression and coronary heart disease: an exploration of the issues raised. *Cleve Clin J Med*. 2010;77(suppl 3):S12–S19.
28. Lökk J, Delbari A. Management of depression in elderly stroke patients. *Neuropsychiatr Dis Treat*. 2010;6:539–549.
29. Morris PL, Robinson RG, Samuels J. Depression, introversion and mortality following stroke. *Aust N Z J Psychiatry*. 1993;27(3):443–449.
30. House A, Knapp P, Bamford J, et al. Mortality at 12 and 24 months after stroke may be associated with depressive symptoms at 1 month. *Stroke*. 2001;32(3):696–701.
31. Pan A, Sun Q, Okereke OI, et al. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA*. 2011;306(11):1241–1249.
32. Fan AZ, Strine TW, Huang Y, et al. Self-rated depression and physician-diagnosed depression and anxiety in Florida adults: Behavioral Risk Factor Surveillance System, 2006. *Prev Chronic Dis*. 2009;6(1):A10.
33. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *BMJ*. 1989;298(6676):789–794.
34. Strazzullo P, D'Elia L, Cairella G, et al. Excess body weight and incidence of

stroke: meta-analysis of prospective studies with 2 million participants. *Stroke*. 2010;41(5):e418–e426.
35. Kaptoge S, Di Angelantonio E, Lowe G, et al; Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet*. 2010;375(9709):132–140.
36. Nefs G, Pouwer F, Denollet J, et al. The course of depressive symptoms in primary care patients with type 2 diabetes: results from the Diabetes, Depression, Type D Personality Zuidoost-Brabant (DiaDDZoB) study. *Diabetologia*. 2012;55(3):608–616.
37. Katon WJ, Rutter C, Simon G, et al. The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care*. 2005 Nov;28(11):2668–2672.
38. Agency for Healthcare Research and Quality. Diabetes Disparities Among Racial and Ethnic Minorities, Fact Sheet. US Department of Health and Human Services Web site. http://www.ahrq.gov/research/diabdisp.htm#HighDiabetes. Accessed February 11, 2013.
39. 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(10):2822–2828.
40. Mezuk B, Eaton WW, Albrecht S, et al. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care*. 2008;31(12):2383–2390.
41. Lloyd CE. Diabetes and mental health; the problem of co-morbidity. *Diabet Med*. 2010;27(8):853–854.
42. Spiegel D. Effects of psychotherapy on cancer survival. *Nat Rev Cancer*. 2002 May;2(5):383–389.
43. Stommel M, Kurtz ME, Kurtz JC, et al. A longitudinal analysis of the course of depressive symptomatology in geriatric patients with cancer of the breast, colon, lung, or prostate. *Health Psychol*. 2004;23(6):564–573.
44. Hopwood P, Sumo G, Mills J, et al; START Trials Management Group. The course of anxiety and depression over 5 years of follow-up and risk factors in women with early breast cancer: results from the UK Standardisation of Radiotherapy Trials (START). *Breast*. 2010;19(2):84–91.
45. Love RR, Duc NB, Baumann LC, et al. Duration of signs and survival in premenopausal women with breast cancer. *Breast Cancer Res Treat*. 2004;86(2):117–124.
46. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *Lancet Oncol*. 2011;12(2):160–174.
47. Mitchell AJ, Meader N, Davies E, et al. Meta-analysis of screening and case finding tools for depression in cancer: evidence based recommendations for clinical practice on behalf of the Depression in Cancer Care consensus group. *J Affect Disord*. 2012;140(2):149–160.
48. Lloyd-Williams M, Shiels C, Taylor F, et al. Depression: an independent predictor of early death in patients with advanced cancer. *J Affect Disord*. 2009;113(1–2):127–132.
49. Onitilo AA, Nietert PJ, Egede LE. Effect of depression on all-cause mortality in adults with cancer and differential effects by cancer site. *Gen Hosp Psychiatry*. 2006;28(5):396–402.
50. Massie MJ. Prevalence of depression in patients with cancer. *J Natl Cancer Inst Monogr*. 2004;(32):57–71.
51. Sand AM, Harris J, Rosland JH. Living with advanced cancer and short life expectancy: patients' experiences with managing medication. *J Palliat Care*. 2009;25(2):85–91.
52. Sapolsky RM, Donnelly TM. Vulnerability to stress-induced tumor growth increases with age in rats: role of glucocorticoids. *Endocrinology*. 1985;117(2):662–666.
53. Antonova L, Mueller CR. Hydrocortisone down-regulates the tumor suppressor gene BRCA1 in mammary cells: a possible molecular link between stress and breast cancer. *Genes Chromosomes Cancer*. 2008;47(4):341–352.
54. Barron TI, Connolly RM, Sharp L, et al. Beta blockers and breast cancer mortality: a population- based study. *J Clin Oncol*. 2011;29(19):2635–2644.
55. Melhem-Bertrandt A, Chavez-Macgregor M, Lei X, et al. Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. *J Clin Oncol*. 2011;29(19):2645–2652.
56. Price A, Hotopf M. The treatment of depression in patients with advanced cancer undergoing palliative care. *Curr Opin Support Palliat Care*. 2009;3(1):61–66.
57. Rodin G, Katz M, Lloyd N, et al. Treatment of depression in cancer patients. *Curr Oncol*. 2007;14(5):180–188.
58. Dantzer R, O'Connor JC, Freund GG, et al. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9(1):46–56.
59. Mental Health Care Services by Family Physicians Position Paper. American Academy of Family Physicians Web site. http://www.aafp.org/online/en/home/policy/policies/m/mentalhealthcareservices.htm. Accessed February 11, 2013.
60. Position Statement 13: Integration of Mental and General Health Care. Mental Health America Web site. http://www.mentalhealthamerica.net/go/position-statements/13. Accessed February 11, 2013.
61. Rosenthal MH. The challenge of comorbid disorders in patients with depression. *J Am Osteopath Assoc*. 2003;103(suppl 4):S10–S15.
62. Patient Health Questionnaire PHQ-9 for Depression. http://www.depression-primarycare.org/images/pdf/phq_9_eng.pdf. Accessed January 10, 2013.
63. Sowden G, Mastromauro CA, Januzzi JL, et al. Detection of depression in cardiac inpatients: feasibility and results of systematic screening. *Am Heart J*. 2010;159(5):780–787.
64. Faulstich ME, Carey MP, Ruggiero L, et al. Assessment of depression in childhood and adolescence: an evaluation of the Center for Epidemiological Studies Depression Scale for Children (CES-DC). *Am J Psychiatry*. 1986;143(8):1024–1027.
65. Pediatric Symptom Checklist. http://www.massgeneral.org/psychiatry/services/psc_home.aspx. Accessed January 10, 2013.
66. Spence Children's Anxiety Scale. http://www.scaswebsite.com/. Accessed January 10, 2013.
67. Dennis ML, Feeney T, Stevens LH, et al. GAIN-SS. Global Appraisal of Individual Needs–Short Screener: Administration and Scoring Manual. http://www.assessments.com/assessments_documentation/gain_ss/GAIN-SS%20Manual.pdf. Accessed January 10, 2013.
68. Office of the Surgeon General. Report of a Surgeon General's Working Meeting on The Integration of Mental Health Services and Primary Health Care. Held on November 30–December 1, 2000, at the Carter Center, Atlanta, Georgia. Rockville, Maryland: Office of the Surgeon General; 2001. http://www.ncbi.nlm.nih.gov/books/NBK44335/. Accessed February 26, 2013.
69. US Department of Health and Human Services Web site. http://www.healthypeople.gov/2020/default.aspx.
70. About SAMHSA's Wellness Efforts. Why Wellness Matters. http://promoteacceptance.samhsa.gov/10by10//. Substance Abuse and Mental Health Services Web site.
71. SAMHSA. Health homes and primary and behavioral health care integration. http://www.samhsa.gov/Healthreform/healthHomes/index.aspx. Updated July 16, 2012. Accessed January 10, 2013.