

Mood Disorders and Medical Illness: A Major Public Health Problem

Despite efficacious and widely available antidepressants and psychotherapeutic interventions, the psychosocial and medical burden of depression is increasing. In fact, the World Health Organization projects that depression will continue to be prevalent, and by the year 2020, will remain a leading cause of disability, second only to cardiovascular disease (Michaud et al 2001). Although we do not know with certainty why rates and disability associated with depression are increasing, it is likely that this mood disorder continues to be remarkably under-recognized and under-treated. Depression frequently occurs in the context of chronic medical illness, and it is only relatively recently that the research community has turned its attention to the relationship between depression and chronic medical conditions. However, there is much work yet to be done. The recently released Institute of Medicine report (2003) acknowledged depression as one of a number of chronic conditions that requires priority action, but did not address the importance of comorbid depression and medical illness.

The relationship between depression and medical illnesses is complex. A chronically ill patient who also is clinically depressed may experience enhanced morbidity, a poorer prognosis, and even increased mortality from the medical diagnosis. Simply put, depression makes everything worse. But the association with depression goes beyond the effects of comorbidity on the course and outcome of a medical illness. A burgeoning body of evidence has now demonstrated that the relationship between depression and certain medical illnesses may indeed be bidirectional in nature. Depression may be both a cause and a consequence of some medical illnesses, such as cardiovascular disease, stroke, HIV/AIDS, cancer, and epilepsy.

In recognition of the need to increase awareness about this topic and improve the quality of life for persons with depression, the Depression and Bipolar Support Alliance, the world's largest patient advocacy organization, convened a two-day, multidisciplinary consensus conference on November 12, 2002 in Washington, DC. Nearly 50 experts in the fields of psychiatry, cardiology, immunology, oncology, neurology, endocrinology, internal medicine, family medicine, federal health care agency policy and research, and patient advocacy participated in this process. Formal presentations centered around the perspectives and goals of the National Institutes of Health and the Food and Drug Administration, the personal and

societal burden of depression and medical illness, and the epidemiology, mechanisms, diagnosis, treatment, and prognosis of depression in the context of cardiovascular disease, cancer, HIV/AIDS, stroke, neurologic diseases, diabetes, osteoporosis, obesity, and chronic pain. Workgroups met to discuss specific issues related to these topics and on the second day, workgroup leaders presented their findings and facilitated open discussions from the group.

Burden of Mood Disorders and Medical Illness

The functional impairment associated with depression contributes significantly to the economic burden of chronic medical illness. Depression also is becoming recognized as a cause of increased morbidity and mortality in chronic medical illness. As reviewed by Katon (2003), medical costs for patients with major depression are approximately 50% higher than the costs of chronic medical illness alone. In addition, Katon (2003) underscores the equally important, but often less appreciated, effects of depression on adverse health behaviors, such as smoking, unhealthy diet, sedentary lifestyle, and poor adherence to medical regimens (e.g., cardiac rehabilitation). The findings from a number of studies have established that major depression is associated with significant functional impairment, lost work productivity, occupational disability, and increased health care resource utilization, and that effective treatment restores functioning. Simon (2003) reviews these data in the context of evidence from recent cross-sectional, longitudinal, and treatment studies of depressed patients with and without arthritis, chronic obstructive pulmonary disease, diabetes, or heart disease. This emerging body of evidence demonstrates that depression significantly increases the burden of functional impairment in medical illness, and that treatment reduces disability and health service costs. The effect of other mood disorders, such as dysthymia or bipolar disorder, on the burden of chronic medical illness is remarkably understudied.

Cardiovascular Disease

It is now recognized that major depression and bipolar disorder are associated with increased rates of death from

coronary heart disease (CHD), and that major depression or depressive symptoms increase the risk of incident CHD (Musselman et al 1998). As reviewed by Rudisch and Nemeroff (2003), as many as 27% of patients with CHD have major depression, but a substantially larger number of cardiac patients have subsyndromal depressive symptoms. Depression is a particularly lethal development for patients with acute myocardial infarction (MI). In the United States, there are approximately 150,000 deaths in the first year after an initial MI, and Carney and Freedland (2003) estimate that at least 90,000 of these deaths may be related to post-MI depression. The cumulative body of evidence in support of an association between depression and cardiovascular disease is large and impressive; Carney and Freedland (2003) evaluate this literature and outline future directions for research, including studies that will better elucidate the role of depression in the development and progression of atherosclerosis, ischemia, and arrhythmias.

One particularly diverse and robust field of research is dedicated to better understanding the mechanisms that underlie the relationship between depression and cardiovascular disease. In their paper, Joynt and colleagues (2003) overview seven probable mechanisms associated with depression that may be related to cardiovascular disease: noncompliance with cardiac rehabilitation and medical regimens; risk factor clustering (e.g., smoking, hypertension, diabetes, hypercholesterolemia, obesity); hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and cortisol elevation; decreased heart rate variability; elevated plasma levels of pro-inflammatory cytokines leading to atherosclerosis; platelet activation and hypercoagulability; and psychological stress.

The demonstrated adverse effect of depression on the risk of new and progression of established CHD has spurred the next emergent area of clinical study in this field: the consequences of depression treatment on cardiovascular morbidity and survival. As noted in the paper by Roose (2003), findings from the few open-label or randomized, controlled clinical trials suggest that the selective serotonin reuptake inhibitors (SSRIs), bupropion, and certain psychotherapeutic interventions are safe and effective treatment of depression in patients with CHD. The tricyclic antidepressants (TCAs) increase heart rate, cause orthostatic hypotension and conduction delays, have been shown to increase the risk of cardiac mortality, and should be avoided in this patient population. There is one published placebo-controlled trial, which suggests that SSRI treatment of depressed post-MI patients may improve outcome and increase survival, but this study was not adequately powered to find significant changes in these cardiac disease outcomes. Thus, it is still not known

whether treatment of depression enhances the outcome of the cardiac disease. Further study is clearly needed.

Cancer

As with cardiovascular disease, there is a large and growing body of evidence in support of a relationship between depression and cancer. Research efforts have focused on depression as a risk factor for cancer, depression as a consequence of cancer, and the dynamics of comorbid depression and cancer. Large population studies suggest that depressed mood or stressful life events may increase the risk of cancer. Although it is acknowledged that these observations of increased risk may be due in part to earlier, undetected malignancies or factors other than depression (Lillberg et al 2003; Penninx et al 1998), these findings are compelling and further study is warranted.

Depression also is a common occurrence in patients with a wide range of different malignancies and often prevents patients from complying with treatment regimens and other health-promoting behaviors, thus worsening the prognosis. A diagnosis of cancer represents a significant life stressor, which in vulnerable persons can precipitate an episode of depression. In addition, patients with cancer may develop "sickness behavior" or depressive syndromes due to proinflammatory cytokine activation that is the result of tumor cell burden, tissue destruction, radiation treatments, and chemotherapy. The papers by Raison and Miller (2003) and Spiegel and Giese-Davis (2003) review the relationships between depression and cancer and offer insight into disease progression and treatment. Of immediate clinical utility are the findings of studies showing that pretreatment with serotonergic antidepressants can prevent neurotoxicity and clinical depression in patients treated with interferon-alpha.

HIV/AIDS

Mood disorders, including depression and mania, are prevalent in persons with human immunodeficiency virus (HIV) disease and may be associated with impaired quality of life, neurocognitive and functional impairment, and poor adherence to antiretroviral therapy. In addition, emerging data suggest that depression is associated with declining CD4 cell counts, accelerated disease progression, and increased mortality. In their paper, Cruess and colleagues (2003) discuss the negative impact of mood disorders on HIV/AIDS and review evidence for safety and efficacy of antidepressants, mood stabilizers, and novel pharmacotherapies in this population (Evans et al 2002a). Leserman (2003) also reviews this topic, but with a focus on the biological mechanisms underlying the relationship between mood disorders and HIV disease

and the immune effects that result from this comorbidity (Leserman et al 1997; Evans et al 2002b). Patients with HIV/AIDS and comorbid depression are a significantly underserved and understudied population. Further epidemiologic, biological, and therapeutic studies are urgently needed to better understand the nature of this comorbidity, increase case-finding, and develop effective treatment strategies.

Neurologic Disease

This special issue also includes papers devoted to the topics of depression and comorbid neurologic disorders, such as stroke, Parkinson's disease, Alzheimer's disease, and epilepsy. Of these neurologic disorders, the relationship between mood disorders and cerebrovascular accidents is particularly well-studied. As reviewed by Robinson (2003), depression is common in poststroke patients, with reported prevalence rates of approximately 20%; bipolar disorder is less common. There is no standardized diagnostic approach for poststroke depression, and the controversies surrounding various approaches are summarized by Robinson (2003). The findings of treatment studies showing efficacy of antidepressants, electroconvulsive therapy, psychostimulants, and cognitive behavioral therapy in patients with poststroke depression are of considerable clinical importance. Importantly, treatment of depression improves measures of function and cognition and may result in improved survival. Evidence that antidepressants may prevent poststroke depression offers hope. As with many other medical comorbidities, depression may increase the risk of stroke, and the findings of two large epidemiologic studies support the role of depression as a risk factor for stroke. These findings further underscore the importance of identifying the underlying biological mechanisms associated with depression comorbidity.

Depression occurs in roughly half of patients with Parkinson's disease and is associated with significant impairment, including reduction in fine motor skills and cognitive function. In their paper, McDonald and colleagues (2003) review the distinct presentation of depression in this population, discuss the challenges associated with diagnosis, and highlight the need for more sensitive screening and diagnostic tools.

Depression in this population may not be due simply to the disability and added life stressors associated with Parkinson's disease. Rather, emerging evidence suggests that depression in these patients may be a consequence of neurodegeneration. Treatment of depression in Parkinson's disease is complicated by variable responses, sensitivity to adverse effects, and drug interactions. Randomized, placebo-controlled trials, particularly of the SSRIs

and dopamine agents, are needed. The findings of functional neuroimaging studies are presented, which may eventually lead to the improved understanding of the neurocircuitry of depression in Parkinson's disease.

Even though depression occurs in as many as 50% of patients with Alzheimer's disease, contributing to accelerated functional and cognitive decline, impaired quality of life, care-giver depression, and earlier institutionalization, surprisingly little evidence-based data are available to inform diagnosis and treatment. The diagnosis of depression in this cohort is particularly challenging because symptoms, such as psychomotor retardation, insomnia, and emotional lability, which occur in nondepressed patients with Alzheimer's disease may be difficult to differentiate from a true depressive episode. Moreover, symptoms of dementia may mask an underlying depressive disorder. In an effort to guide research and better inform clinical care, the National Institute of Mental Health has undertaken the task of developing diagnostic criteria for depression in Alzheimer's disease. Lee and Lyketsos (2003) review these developments and describe an ongoing longitudinal study of depression and other neuropsychiatric comorbidities in new cases of Alzheimer's disease, which will provide valuable information on the epidemiology, natural course, and diagnosis of depression in this population.

Epilepsy is another neurologic disorder that often is complicated by comorbid depression. As many as 50% of epileptic patients seen in tertiary treatment centers may have depression, and suicidality among depressed epileptics have been reported to be as high as 10 times the rate than in the general population. Kanner (2003) reviews the challenges related to diagnosing depression in epilepsy: patients often present with atypical depressive symptoms (e.g., anxiety, irritability, hypomania, pain); the peri-ictal period often is associated with a recurrent and short-lived dysphoria that is clinically significant but does not conform to standard diagnostic criteria; and antiepileptic drugs and surgical intervention can be iatrogenic causes of depression. Clearly, epilepsy is a risk factor for depression; however, recent evidence suggests that depression may increase the risk for epilepsy by 4- to 6-fold. Further studies are needed to better characterize this complex relationship.

Call for Action

The contributions made by this conference and the papers published in this special issue of *Biological Psychiatry* should not simply be measured by the quality and quantity of the data, which are impressive. Rather, the strength of this publication also lies in the fact that the views of experts from widely divergent fields of clinical and scien-

tific endeavor resonate along 4 basic themes: 1) Depression is very common in chronic medical illness; 2) Comorbidity with depression inevitably hinders recovery and worsens prognosis; 3) Medical illness is a risk factor for depression because of psychosocial stressors, functional impairment, and other biological mechanisms (e.g., Parkinson's disease); and 4) Depression may figure prominently as an etiologic factor in the onset and course of medical illness, particularly cardiovascular disease, stroke, HIV/AIDS, cancer, and epilepsy. The latter observation is truly remarkable. Much more research is needed to better understand this bidirectional relationship and identify possible common pathogenic, mechanistic pathways that link depression and serious medical illness.

These are powerful messages that must not be ignored. The weight of evidence is so persuasive that there should never again be a valid reason for not aggressively seeking out and treating depression in medically ill patients. Increasing awareness, reducing stigma, and maintaining a high level of vigilance for depression in medically ill patients must become a priority for clinicians. In addition, the efforts of the research communities must continue to better elucidate the prevalence, risk profile, diagnostic criteria, treatment, and biological underpinnings of the comorbid relationship between depression and medical illness. Only by furthering research efforts and aggressively diagnosing and treating depression, will we be able to achieve substantive gains in health care and in our patients' quality of life.

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References

- Carney RM, Freedland KE (2003): Depression, mortality, and medical morbidity in patients with coronary heart disease. *Biol Psychiatry* 54:241-247.
- Cruess DG, Evans DL, Repetto MJ, Gettes D, Douglas SD, Petitto JM (2003): Prevalence, diagnosis, and pharmacological treatment of mood disorders in HIV disease. *Biol Psychiatry* 54:307-316.
- Evans DL, Mason K, Bauer R, Leserman J, Petitto J (2002a): Neuropsychiatry manifestations of HIV-1 Infection and AIDS. In: Charney D, Coyle J, Davis K, Nemeroff C, editors. *Neuropsychopharmacology: The Fifth Generation of Progress*. New York, NY: Raven Press, 1281-1300.
- Evans DL, Ten Have TR, Douglas SD, Gettes DR, Morrison M, Chiappini MS, et al (2002b): Association of depression with viral load, CD8 T lymphocytes, and natural killer cells in women with HIV infection. *Am J Psychiatry* 159:1752-1759.
- Institute of Medicine (2003): *Priority Areas for National Action: Transforming Health Care Quality*. In: Adams K, Corrigan JM, editors. Washington, DC: The National Academies Press.
- Joynt KE, Whellan DJ, O'Connor CM (2003): Depression and cardiovascular disease: Mechanisms of interaction. *Biol Psychiatry* 54:248-261.
- Kanner AM (2003): Depression in epilepsy: Prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biol Psychiatry* 54:388-398.
- Lee HB, Lyketsos CG (2003): Depression in Alzheimer's disease: Heterogeneity and related issues. *Biol Psychiatry* 54:353-362.
- Leserman J (2003): HIV disease progression: Depression, stress, and possible mechanisms. *Biol Psychiatry* 54:295-306.
- Leserman J, Petitto JM, Perkins DO, Folds JD, Golden RN, Evans DL (1997): Severe stress, depressive symptoms, and changes in lymphocyte subsets in human immunodeficiency virus-infected men: A 2-year follow-up study. *Arch Gen Psychiatry* 54:279-285.
- Lillberg K, Verkasalo PK, Kaprio J, Teppo L, Helenius H, Koskenvuo M (2003): Stressful life events and risk of breast cancer in 10,808 women: A cohort study. *Am J Epidemiol* 157:415-423.
- Katon WJ (2003): Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry* 54:216-226.
- Michaud CM, Murray CJ, Bloom BR (2001): Burden of disease: Implications for future research. *JAMA* 285:535-539.
- McDonald WM, Richard IH, DeLong MR (2003): The prevalence, etiology, and treatment of depression in Parkinson's disease. *Biol Psychiatry* 54:363-375.
- Musselman DL, Evans DL, Nemeroff CB (1998): The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* 55:580-592.
- Penninx BW, Guralnik JM, Pahor M, Ferrucci L, Cerhan JR, Wallace RB, et al (1998): Chronically depressed mood and cancer risk in older persons. *J Natl Cancer Inst* 90:1888-1893.
- Raison CL, Miller AH (2003): Depression in cancer: New developments regarding diagnosis and treatment. *Biol Psychiatry* 54:283-294.
- Robinson RG (2003): Poststroke depression: Prevalence, diagnosis, treatment, and disease progression. *Biol Psychiatry* 54:376-387.
- Roose SP (2003): Treatment of depression in patients with heart disease. *Biol Psychiatry* 54:262-268.
- Rudisch B, Nemeroff CB (2003): The epidemiology of comorbid coronary artery disease and depression. *Biol Psychiatry* 54:227-240.
- Simon GE (2003): Social and economic burden of mood disorders. *Biol Psychiatry* 54:208-215.
- Spiegel D, Giese-Davis J (2003): Depression and cancer: Mechanisms and disease progression. *Biol Psychiatry* 54:269-282.