Review

Mood Disorders in the Medically Ill: Scientific Review and Recommendations

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Objective: *The purpose of this review is to assess the relationship between mood disorders and development, course, and associated morbidity and mortality of selected medical illnesses, review evidence for treatment, and determine needs in clinical practice and research.*

Data Sources: *Data were culled from the 2002 Depression and Bipolar Support Alliance Conference proceedings and a literature review addressing prevalence, risk factors, diagnosis, and treatment. This review also considered the experience of primary and specialty care providers, policy analysts, and patient advocates. The review and recommendations reflect the expert opinion of the authors.*

Study Selection/Data Extraction: *Reviews of epidemiology and mechanistic studies were included, as were open-label and randomized, controlled trials on treatment of depression in patients with medical comorbidities. Data on study design, population, and results were extracted for review of evidence that includes tables of prevalence and pharmacological treatment. The effect of depression and bipolar disorder on selected medical comorbidities was assessed, and recommendations for practice, research, and policy were developed.*

Conclusions: *A growing body of evidence suggests that biological mechanisms underlie a bidirectional link between mood disorders and many medical illnesses. In addition, there is evidence to suggest that mood disorders affect the course of medical illnesses. Further prospective studies are warranted.*

Key Words: Mood disorders, medical comorbidity, depression, antidepressant therapy

The burden of depression is chronic and disabling. Depression is the leading global cause of life-years lived with disability and ranks fourth for disability-adjusted life-years worldwide, a measure that considers premature mortality (Insel and Charney 2003). The independent morbidity and mortality might indicate the anticipated burden of depression in the context of medical illness. A strong body of evidence demonstrates the coexistence of depression in many chronic medical illnesses. Onset of a disabling medical illness is, understandably, a risk factor for a depressive episode in vulnerable persons; however, a burgeoning field of research is discovering that depression itself might be a causal factor in different illnesses, such as ischemic heart disease (IHD), stroke, cancer, and epilepsy. A number of well-controlled studies demonstrate the efficacy of antidepressants and psychotherapy in treatment of depression in medically ill patients.

Unfortunately, this evidence has not resulted in improved patient care. Medically ill patients often remain depressed and suffer needlessly. Many barriers prevent patients from receiving appropriate treatment. Clinicians, patients, and families might trivialize or fail to appreciate the implications of mood disorders in the belief that depression is an expected and unavoidable consequence of serious illness or that the medical condition supersedes concerns for mental illness. Depression and bipolar disorder might be particularly difficult to diagnose in patients with multiple somatic and cognitive symptoms. Despite the gains that have been achieved through a multitude of educational campaigns and patient advocacy efforts, mental illness stigma remains problematic. Finally, belief that quality-of-life issues are somehow less important in chronically or terminally ill patients also might preclude efforts at intervention.

The Depression and Bipolar Support Alliance (DBSA), formerly the National Depressive and Manic Depressive Association, is the nation's leading patient-directed, illness-specific or-

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ganization. In November 2002, DBSA convened an expert consensus conference to address issue of medical comorbidity in patients with mood disorders. The group consisted of nearly 50 experts in psychiatry, primary care, cardiology, endocrinology, oncology, neurology, mental health research, healthcare policy, adolescent health, and patient advocacy who assembled to review the bi-directional impact of mood disorders on risk for development, progression, treatment, and outcomes of medical illness.

Methods

For this review, the conference cochairs led a development panel in examining the existing literature, assessing weight of evidence, and outlining areas of unmet need that is related to research, clinical practice, and healthcare policy (Evans and Charney 2003). Given the paucity of prospective, randomized, controlled trials, evidence that was provided in expert presentations during the conference also was considered. When evidence was inconclusive or unavailable, the panel relied on conscientious interpretation of the published literature or clinical experience to make recommendations. Members of the development panel provided their assessments of the evidence and recommendations during draft manuscript review. Thus, this review represents the expert opinion of the authors.

Results

Cardiac Disease

Depression has been shown to increase risk for onset of coronary disease by 1.64-fold (95% confidence interval [CI], 1.41–1.90; Wuslin and Singal 2003) and incident IHD by 1.5- to 2-fold (Abramson et al 2001 Anda et al 1993; Ariyo et al 2000; Ferketich et al 2000; Ford et al 1998), and it predicts morbidity and death in patients with existing cardiac disease (Barefoot and Schroll 1996; Burg et al 2003; Carney et al 1987; Connerney et al 2001; Hermann et al 2000). There is particularly strong evidence for poor post-myocardial infarction (MI) prognosis in patients with depression or depressive symptoms (Ahern et al 1990; Bush et al 2001; Forrester et al 1992; Frasure-Smith et al 1993, 1995). Risk of cardiac death in the 6 months after an acute MI is approximately four times greater in patients with depression compared with nondepressed control subjects (Frasure-Smith et al 1993). Five years after an acute MI, depression or significant depressive symptomatology increased risk of cardiac death by >3.5-fold (Lespérance et al 2002).

Prevalence. Table 1 lists prevalence rates of depression in patients with coronary artery disease (CAD), unstable angina, acute MI, congestive heart failure (CHF), or coronary artery bypass graft surgery (Rudisch and Nemeroff 2003). Large numbers of persons with cardiac disease also have clinically significant, but subsyndromal, symptoms of depression, which suggests that rates of comorbidity might be higher. Depression carries equal associated risk for cardiac events in men and women (Carney et al 1991; Frasure-Smith et al 1999).

Although less well studied, cardiac disease also is common in patients with bipolar disorder (Tsuang et al 1980; Weeke et al 1987). In a study of men with bipolar disorder who were hospitalized for a cardiac event, relative risk of a fatal cardiac event ranged from 1.5 (95% CI, 1.30–1.78) to 1.9 (95% CI, 1.37–2.50) (Weeke et al 1987).

Comorbidity Mechanisms. Comorbidity mechanisms consist of physiologic and behavioral factors (Musselman et al 1998). Depression is associated with vascular pathology (Krishnan et al 1997; Steffens et al 2002), which strongly correlates with the presence of IHD. Psychologic stress might increase risk of myocardial ischemia (Jiang et al 1996; Sheps et al 2002). Autonomic function changes associated with depression, such as ventricular tachycardia (Carney et al 1993), increased QT variability (Carney et al 2003; Yeragani et al 2000), and decreased heart rate variability (Carney et al 2001; Watkins and Grossman 1999; Yeragani 2000), are plausible mechanisms by which depression might increase cardiac mortality risk (Frasure-Smith et al 1993, 1995). Elevated levels of proinflammatory cytokines, which are causal factors in development and progression of atherosclerosis, occur in patients with depression (Kop et al 2002; Musselman et al 2001b; Thomas et al 2000). Depression is linked to increased platelet activation and hypercoagulability (Kop et al 2002; Kuijpers et al 2002; Laghrissi-Thode et al 1997; Lederbogen et al 2001; Musselman et al 1996, 2002; von Känel et al 2001). Evidence suggests depression-related alterations in neurohormonal mechanisms, such as hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and increases in plasma cortisol (Ehlert et al 2001; Maas et al 1994; Plotsky et al 1998), might correlate with increased CHF risk (Francis et al 1993; Pepper and Lee 1999).

Behavioral factors also increase risk for cardiac disease for patients with depression who might not adhere to smoking cessation goals, dietary changes, daily aspirin therapy, antihypertensive regimens, or cardiac rehabilitation (Anda et al 1990; Blumenthal et al 1982; Carney et al 1995; Glazer et al 2002; Wang et al 2002). These processes might collectively or independently contribute to an increased risk for CAD (Rozanski et al 1999).

Treatment. The efficacy and safety of selective serotonin reuptake inhibitors (SSRIs) in cardiac patients with depression was evaluated in several studies, including one placebo-controlled and two comparative studies (Table 2). The landmark Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial, which randomized 2481 post-MI patients with depression or low perceived social support to a 6-month course of either cognitive-behavioral therapy (CBT) or usual care (both of which included antidepressants, if warranted), evaluated effect of treatment on mortality and reinfarction. Although the modest improvements in depression and social support scores in the intervention group were significantly greater than in the usual care group, there were no differences in mortality or

Table 1. Depression in Patients With Comorbid Medical Illness

Comorbid Medical Illness	Prevalence Rate (%)
Cardiac Disease	17–27 (Rudisch and Nemeroff 2003)
Cerebrovascular Disease	14–19 (Robinson 2003)
Alzheimer's Disease	30–50 (Lee and Lyketsos 2003)
Parkinson's Disease	4–75 (McDonald et al 2003)
Epilepsy	
Recurrent	20–55 (Kanner 2003)
Controlled	3–9 (Kanner 20033)
Diabetes	
Self-reported	26 (Anderson et al 2001)
Diagnostic interview	9 (Anderson et al 2001)
Cancer	22–29 (Raison and Miller 2003)
HIV/AIDS	5–20 (Cruess et al 2003)
Pain	30–54 (Campbell et al 2003)
Obesity	20–30 (Stunkard et al 2003)
General Population	10.3 (Kessler et al 1994)

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.