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.

Table 2. Evidence for Pharmacological Treatment of Depression in Patients with Comorbid Medical Illness

Comorbidity	Treatment	Evidence	Effect of Antidepressant Treatment: On Depression	Effect of Antidepressant Treatment: On Comorbidity	Comments
Cardiac	SSRI[abc] Bupropion[d]	1 DB, RCT w/PBO[a] 1 DB, RCT w/active-C[c] 1 open, RCT w/active-C[b] 1 open w/no control[d]	Improvement on HAM-D,[ac] CGI-I[a]	Clinically benign effect on conduction, blood pressure, heart rate[abcd]	SSRIs may be cardioprotective[ae] ● Normalization of platelet activation[efghij] ● Additional antiplatelet effects in patients taking antithrombotic medication[h]
Cerebrovascular	TCA[klmn] SSRI[lmno] Trazadone[p]	5 DB, RCT w/PBO[kmop] 1 DB, RCT w/PBO and active-C[l] 1 retrospective analysis[q]	Improvement on HAM-D,[klm] ZUNG,[kp] MADRS,[o] DST[p]	Improvement on ADL,[lnpq] MMSE[nr]	Successful antidepressant treatment has been associated with long-term improvement in cognitive function[s] and lower mortality rates[t]
Alzheimer's Disease	TCA[uv] SSRI[wxyzaa] Moclobemide[bb]	8 DB, RCT w/PBO[uvwxzbb] 1 DB, RCT w/PBO and open phase[y]	Improvement on HAM-D,[uwzbb] MADRS,[z] CSDD[w]	Improvement on MMSE,[ubb] GBS ratings,[yz] SCAG[b]	4 trials demonstrate antidepressant effect[uwzbb] vs. 4 trials showing no effect[vxyaa] 2 trials demonstrate cognitive benefit[uz] vs. 2 trials showing no clear change in cognitive function[vw]
Parkinson's Disease	TCA[ccddee]	3 DB, RCT w/PBO[ccddee]	Improvement in depression[ccddee] and fatigue[dd]	Inconclusive evidence	SSRI open-label studies demonstrate improvement of depression with no observed change in motor function,[eeffgghhii] but there are data that suggest increased parkinsonism with SSRI treatment[ij]
Epilepsy	TCA[kk] Nomifensine[kk]	1 DB, RCT, w/PBO and active-C[kk]	Improvement on depression	Might lower seizure threshold, especially bupropion, maprotiline, and amoxetine[ll]	With only 1 PBO-controlled, DB study published to date ($n = 39$),[kk] evidence for treatment is largely empirically based[ll]
Diabetes	TCA[mm] SSRI[nn]	2 DB, RCT w/PBO controlled[mmnn]	Improvement on BDI[mmnn]	Nonsignificant reduction in HbA_{1c}[mmnn]	
Cancer	TCA[ooppqq] SSRI[oopprr] Mianserin[sstt] Mirtazapine[uu]	7 DB, RCT w/PBO[pprrssttuu] 1 DB, RCT w/active-C[oo] 1 open, pilot study[qq] 1 open, RCT[uu]	Improvement on HAM-D,[ooqqsstt] MADRS,[pp] CGI-I,[pptt] CGI-S,[oott] ZUNG[ttuu]	Improvement on FLIC,[oopp] SF-36 health survey,[oo] PAIS,[qq] FACT-G[uu]	All but 1[rr] of the listed studies demonstrated improvement in depression scores
HIV/AIDS	TCA[vvww] SSRI[vvxxyyzzABCDE] Nefazadone[F] Mirtazapine[G]	4 DB, RCT w/PBO-C[vvyyzz] 1 DB, RCT w/PBO and active-C[vv] 4 open[ABEFG] 1 open w/active-C[C]	Improvement on HAM-D,[vvwwzzG] CGI-I,[wwF] BDI,[zzBCE] BHS[AB]	Improves QoL and adherence to retroviral Rx regimens[xx] Promotes weight gain, decreases nausea[xx]	No evidence of adverse effect on immune status[wwyyABD] Potential drug interactions may limit treatment[xx] (e.g., interaction between nefazodone and protease inhibitors)

active-C, active comparator; ADL, activities of daily living; AIDS, acquired immune deficiency syndrome; BDI, Beck Depression Inventory; BHS, Beck Hopelessness Scale; CGI-I, Clinical Global Impression Improvement Item; CGI-S, Clinical Global Impression Severity Item; CSDD, Cornell Scale for Depression in Demention; DB, double blind; DST, dexamethasone suppression test; FACT-G, Functional Assessment of Cancer Therapy-General; FLIC, Functional Living Index-Cancer; GBS, Gottfries-Bråne-Steen geriatric rating scale; HAM-D, Hamilton Depression Rating Scale; HbA_{1c}, glycosylated hemoglobin; HIV, human immunodeficiency virus; MADRS, Montgomery-Åsberg Depression Rating Scale; MMSE, Mini Mental State Examination; PAIS , Psychosocial Adjustment to Illness Scale; PBO, placebo; QoL, quality of life; RCT, randomized, clinical trial; Rx, prescription; SCAG, Sandoz Clinical Assessment Geriatric Scale; SF-36, 36-Item Short Form Health Survey; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; ZUNG, Zung Self-Rating Depression Scale.

[a]Glassman et al 2002; [b]Roose et al 1998a; [c]Roose et al 1998b; [d]Roose et al 1991; [e]Sauer et al 2001; [f]Musselman et al 2000; [g]Pollock et al 2000; [h]Serebrauny et al 2003; [i]Serebrauny et al 2001a; [j]Serebrauny et al 2001b; [k]Lipsey et al 1984; [l]Robinson et al 2000; [m]Andersen et al 1994; [n]Gonzalez-Torrecillas et al 1995; [o]Wiart et al 2000; [p]Reding et al 1986; [q]Gainotti et al 2001; [r]Kimura et al 2000; [s]Narushima et al 2003; [t]Jorge et al 2003; [u]Petracca et al 1996; [v]Reifler et al 1989; [w]Lyketsos et al 2003; [x]Magai et al 2000; [y]Nyth and Gottfries 1990; [z]Nyth et al 1992; [aa]Petracca et al 2001; [bb]Roth et al 1996; [cc]Andersen et al 1980; [dd]Laitinen 1969; [ee]Strang 1965; [ff]Ceravolo et al 2000; [gg]Hauser and Zesiewicz 1997; [hh]Montastruc et al 1995; [ii]Rampello et al 2002; [jj]McDonald et al 2003; [kk]Robertson and Trimble 1985; [ll]Kanner 2003; [mm]Lustman et al 1997; [nn]Lustman et al 2000b; [oo]Holland et al 1998; [pp]Pezzella et al 2001; [qq]Evans et al 1988; [rr]Razavi et al 1996; [ss]van Heeringen and Zivkov 1996; [tt]Costa et al 1985; [uu]Theobald et al 2002; [vv]Elliott et al 1998; [ww]Rabkin et al 1994a; [xx]Cruess et al 2003; [yy]Rabkin et al 1999; [zz]Zisook et al 1998; [A]Rabkin et al 1994b; [B]Rabkin et al 1994c; [C]Ferrando et al 1997; [D]Grassi et al 1997; [E]Ferrando et al 1999; [F]Elliott et al 1999; [G]Elliott and Roy-Byrne 2000.

reinfarction rates. Post hoc analysis suggested that treatment with SSRIs was associated with decreased risk of dying and nonfatal MI (Writing Committee for the ENRICHD Investigators 2003)—findings that must be interpreted cautiously, because the trial did not randomize patients to antidepressant therapy.

Although effective for treatment of depression, use of tricyclic antidepressants (TCAs) in this population is relatively contraindicated because TCAs are type 1A antiarrhythmics, which might increase mortality in patients with IHD (Echt et al 1991; Glassman et al 1993).

Limited data suggest that SSRIs might be cardioprotective (Table 2), although these data require confirmation by larger, prospective trials. In a study of patients hospitalized for acute MI or unstable angina, SSRI treatment was associated with a trend toward lower composite relative risk for serious cardiac events compared with placebo (Glassman et al 2002); however, this study was powered to address safety and tolerability, not cardiac morbidity or mortality. Additional studies are needed to evaluate the effects of SSRIs on platelet aggregation as a potential cardiac risk factor for medically or surgically compromised patients (Movig et al 2003; van Walraven et al 2001). Few data exist on the effects of treatment for bipolar disorder on cardiac mortality (Angst et al 2002).

Cerebrovascular Disease

Comorbid depression complicates recovery from stroke or other cerebrovascular diseases by hindering return to activities of daily living and impairing cognitive function (Bolla-Wilson et al 1989; House et al 1990; Kauhanen et al 1999; Robinson et al 1985, 1986). Mortality rates in poststroke patients with depression or depressive symptoms are increased compared with nondepressed patients (House et al 2001; Wade et al 1987) by 3.4-fold (Morris et al 1993). Emerging evidence suggests that depression might increase risk of incident cerebrovascular disease.

Prevalence. Prevalence of poststroke depression exceeds rates in the general population (Table 1). Variability in reports of prevalence rates likely reflects differences in stroke severity and use of nonstandardized diagnostic criteria (Robinson 2003). Prevalence rates among minority populations are not known. Mania might occur in poststroke patients, but large-scale studies are lacking.

Comorbidity Mechanisms. Poststroke depression or mania might be caused by cerebral ischemia, and the type of mood disorder might be related to location of the lesion. Although some findings are equivocal (Carson et al 2000; Gainotti et al 2001), depression might be more common with left-sided lesions (Narushima et al 2003; Robinson 2003). Preliminary data suggest that right-sided, subcortical lesions might be associated with poststroke mania (Robinson 2003).

Depression might be a risk factor for stroke, perhaps by increasing platelet hyperreactivity (Musselman et al 1996, 2000), risk for CAD (Ferketich et al 2000), and adrenocortical hyperactivity (Ehlert et al 2001), which leads to atherosclerosis and stroke (Rosmond and Bjorntorp 2000). Two large-scale, prospective studies demonstrate an adjusted relative risk of approximately 2.6 for development of stroke in persons with a history of depression (Larson et al 2001) or significant psychological distress (May et al 2002).

Diagnosis and Treatment. Diagnosis of poststroke depression is challenging, because of the vegetative and psychologic symptoms common to both conditions. Cognitive impairment might hinder interview-based diagnostic approaches, and standardized diagnostic criteria are lacking. At present, diagnosis of poststroke depression should be based on a mental state examination and the DSM-IV criteria for depression due to stroke (Robinson 2003).

Data from randomized, controlled studies support the utility of antidepressants in poststroke depression (Table 2). Efficacy also is suggested for electroconvulsive therapy (Murray et al 1986), psychostimulants (Grade et al 1998), and CBT (Hibbard et al 1990).

Antidepressant treatment enhances poststroke functional status and survival (Table 2). Although improved cognition has not been established conclusively (Gonzalez-Torrecillas et al 1995; Lipsey et al 1984; Robinson et al 2000), data suggest improved mini-mental state examination scores and long-term survival (Table 2). Few data exist on the effects of bipolar treatment and cerebrovascular mortality (Angst et al 2002).

Prevention of poststroke depression was assessed in three controlled studies. Treatment with an SSRI was associated with significantly lower rates of depression at 3 months (Narushima et al 2002) and 1 year (Rasmussen et al 2003) compared with placebo, but mianserin (a heterocyclic serotonin receptor antagonist) was ineffective (Palomäki et al 1999).

Alzheimer's Disease, Parkinson's Disease, Epilepsy

Depression has a profoundly adverse effect on patients with Alzheimer's disease (AD) and Parkinson's disease (PD) by impairing quality of life (Kuopio et al 2000; Phillips 1999), hindering activities of daily living (Kuhn et al 1996; Lyketsos et al 1997b), accelerating the need for institutionalization (Steele et al 1990), and compromising cognitive function (Bassuk et al 1998; Kuzis et al 1997; Mayeux et al 1981; Troster et al 1995). In AD, depression is associated with increased mortality (Hoch et al 1993). Epilepsy is associated with high rates of depression and a 10-fold increase in suicide rates (Robertson 1997).

Prevalence. Table 1 lists prevalence of depression in AD, PD, and epilepsy from epidemiologic studies, but few studies were prospective, and different definitions of depression, heterogeneous patient populations, varying clinical settings, and nonstandardized sampling methods preclude definitive prevalence estimates. Little is known about prevalence of comorbid depression with neurological disorders in minority populations or prevalence of bipolar disorder in patients with epilepsy; however, a temporal association might exist between onset of manic symptoms and seizure occurrence (Kanner 2003).

Comorbidity Mechanisms. Relationships between depression and neurological diseases are complex and bidirectional. Development of depression in neurological disorders might be secondary to associated psychological stress and disability. Depression, however, might be a consequence of underlying neurodegenerative process (Zubenko et al 2003), particularly in PD (Mössner et al 2001), and genetically predisposed persons with AD might be at increased risk for major depression (Lee and Lyketsos 2003). A history of depression might be a risk factor for development of AD (adjusted odds ratio, 2.13; 95% CI, 1.71–2.67; Green et al 2003) and might increase the risk for epilepsy by 4- to 6-fold (Forsgren and Nystrom 1990; Hesdorffer et al 2000), suggesting common pathogenic mechanisms.

Diagnosis and Treatment. Under the best of circumstances, diagnosis of depression in patients with neurological diseases is challenging. Depressive symptoms might change with progression of neurological disease or be caused by medications used to treat the disorder. Thus, lack of standardized approaches for diagnosing depression in patients with neurological disorders represents a tremendous unmet need (Kanner 2003; Lee and

Lyketsos 2003; McDonald et al 2003). The National Institute of Mental Health (NIMH) is working to develop standardized diagnostic criteria for depression in AD (Olin et al 2002), and the National Institute of Neurological Disorders and Stroke (NINDS) is working to define depression in PD (Edwards et al 2002). The atypical nature of depressive symptoms, mania, hypomania, and brief, recurrent episodes of peri-ictal dysphoria in patients with epilepsy is recognized, but evidence-based data that can guide diagnosis are lacking (Kanner 2003).

Although SSRIs and TCAs are widely used for treatment of depression in patients with PD (Richard et al 1999), evidence-based data to guide treatment of depression in patients with PD, AD, or epilepsy are scant (Table 2). Lack of consistent study design prevents extrapolation of findings to clinical practice. Concerns about increased seizure risk from antidepressants might contribute to undertreatment of depression in patients with epilepsy, although the actual risk might be small and should not preclude pharmacologic treatment of depression when otherwise appropriate. Selective serotonin reuptake inhibitors should be considered first-line treatment for depression in patients with epilepsy (Kanner 2003); however, data are needed to evaluate safety of newer antidepressants and efficacy of antidepressants in various atypical presentations of mood disorders (Kanner 2003). There is a need for studies on treatment of bipolar disorder in patients with epilepsy, particularly in view of the merging utility of some anticonvulsants in primary bipolar disorder, AD, and PD.

Diabetes

Depression has been shown to be an independent risk factor for type 2 diabetes mellitus (Eaton et al 1996; Kawakami et al 1999) and is associated with nonadherence to oral hypoglycemics (Ciechanowski et al 2000), poor glycemic control (de Groot et al 2001), increased healthcare costs (Ciechanowski et al 2000), and progression and earlier onset of microvascular and macrovascular complications, disability, and death (Black et al 2003; de Groot et al 2001). Depression is associated with biological abnormalities, such as increased serum glucocorticoids, catecholamines, and growth hormone (which counter the effects of insulin), insulin resistance, and secretion of inflammatory cytokines, which could ultimately facilitate development of diabetes (Musselman et al 2003). Diabetes also is a risk factor for depression, and this increased risk is associated with socioeconomic adversity (Fisher et al 2001), female gender (Peyrot and Rubin 1997), poor glycemic control (Lustman et al 2000a), and diabetic complications (de Groot et al 2001).

Prevalence. Although many epidemiologic studies have evaluated depression rates in diabetic patients, methodological inconsistencies preclude definitive prevalence estimates. Prevalence rates are lower in studies where depression is determined via diagnostic interviews compared with reported rates when using patient self-report symptom scales (Anderson et al 2001; Gavard et al 1993) (Table 1). Although diabetes is common in African Americans, Latin Americans, and Native Americans, few prevalence data evaluate comorbid depression in these populations (Fisher et al 2001; Gary et al 2000; Warnock and Mutzig 1998). Rates of comorbidity in children and adolescents with diabetes (Grey et al 2002) and in patients with bipolar disorder and dysthymia (Regenold et al 2002) are not precisely known.

Diagnosis and Treatment. Diagnosing depression in diabetic patients is not straightforward. Shared symptoms such as fatigue and weight loss can impede recognition of depression in patients with diabetes. To aid in diagnosis, the Beck Depression Inventory is a sensitive and specific self-reporting tool that distinguishes depressive symptoms in this population. Depression has been associated with amplification of diabetic symptoms in diabetic patients with depression compared with those who are not depressed (Ciechanowski et al 2003).

There are only three relatively small, placebo-controlled treatment studies of depression in patients with diabetes. Both antidepressant studies (Table 2) showed efficacy for treatment of depression, although these studies lacked power to demonstrate significant improvements in glycemic control. Ten weeks of CBT significantly improved depressive symptoms with some suggestion of lower glycosylated hemoglobin (HbA_{1c}) levels at 6-month follow-up (Lustman et al 1998). Clinicians should screen for diabetes in patients who experience weight gain while being treated for depression, especially in individuals whose antidepressant treatment is augmented with antipsychotics (Koro et al 2002) or anticonvulsants (Isojarvi et al 1998).

Cancer

Depression frequently is comorbid with cancer and is associated with poor prognosis and increased morbidity. Simply receiving a diagnosis of cancer and enduring the declining physical status, pain, and invasive oncological therapies increase use of mental health services (Hewitt and Rowland 2002). Depression also might be a direct consequence of antineoplastic therapy (Brown et al 2003; Raison and Nemeroff 2000). Patients with cancer might develop "sickness behavior" related to activation of proinflammatory cytokines secondary to heavy tumor-cell burden, tissue destruction, radiation treatments, and chemotherapy (Newport and Nemeroff 1998; Raison and Miller 2003). Patients with depression might be poorly adherent to cancer treatment regimens or might engage in adverse health behaviors (e.g., smoking). Although emotional distress has been associated with shortened survival times in cancer patients (Brown et al 2003; Faller et al 1999), psychological coping styles are not associated with increased cancer survival (Petticrew et al 2002).

Although studies have yielded mixed results (Croyle 1998), two large, prospective studies suggesting that chronic depression or stressful life events might increase cancer risk are intriguing, but by no means definite. Among nearly 5000 elderly persons, those with chronic depression had an adjusted hazard ratio for cancer of 1.88 (95% CI, 1.13–3.14) at 6-year follow-up (Penninx et al 1998). In another study of nearly 11,000 women during a 20-year period, severe life stressors (e.g., death of spouse) yielded a multivariable adjusted hazard ratio for breast cancer of 1.35 (95% CI, 1.09–1.67; Lillberg et al 2003). Patients with a history of depression have a 2.6-fold greater risk of dying from cancer than those with no prior depression (Stommel et al 2002). Depression has been associated with immunosuppression (Evans et al 1992; Herbert and Cohen 1993; Newport and Nemeroff 1998; Spiegel and Giese-Davis 2003), which might increase risk of cancer in susceptible individuals. The reported association between depression and cancer is interesting, but further studies are needed to validate a possible causal role for depression in etiology of cancer.

Prevalence. Depression is common in patients with cancer, but available studies have evaluated heterogeneous populations with different malignancies, variable or absent clinical staging, nonstandardized definitions of depression, and small sample sizes, which preclude exact prevalence estimates. Nonetheless, depression appears more common in patients with cancer than in the general population (Evans et al 1986; Raison and Miller 2003) (Table 1) and might be up to four times greater than

population estimates (Carr et al 2002). Reported rates of depression are highest for pancreatic, oropharyngeal, and breast cancers, ranging from 20% to 50% (McDaniel et al 1995; Newport and Nemeroff 1998). Prevalence rates of depression in the context of cancer are not known for children, elderly, or minority populations.

Diagnosis and Treatment. No standardized approach exists for diagnosis of depression in patients with cancer. Symptoms associated with cancer and its treatment, such as sleep disturbance, anorexia, weight loss, psychomotor retardation, and cognitive impairment, often overlap with depressive symptoms. It is difficult to differentiate depression from bereavement or grief reactions. There is controversy regarding the merits of an exclusive diagnostic approach (i.e., overlapping symptoms are not counted toward diagnosis of depression) versus an inclusive approach (i.e., all symptoms are considered when making diagnosis) in research (Newport and Nemeroff 1998; Raison and Miller 2003), but the inclusive approach is generally recommended in clinical settings.

Although studies have assessed the effect of psychosocial interventions on different clinical domains associated with cancer, none was designed to evaluate effectiveness of depression treatment. Five of 10 randomized trials provide evidence that psychosocial intervention, which in some studies reduced depressive symptoms, resulted in longer survival (Fawzy et al 2003; Kuchler et al 1999; McCorkle et al 2000; Richardson et al 1990; Spiegel et al 1989). Among the five other trials that showed no survival benefit (Cunningham et al 1998; Edelman et al 1999; Goodwin et al 2001; Ilnyckyj et al 1994; Linn et al 1982), only two demonstrated alleviation of psychological distress (Goodwin et al 2001; Linn et al 1982). Although all of the trials showing an effect on survival might have influenced adherence or use of medical care, the two studies that examined this as an outcome found survival effects independent of changes in subsequent medical care (Koenig et al 1992; Richardson et al 1990). Some of the interventions reduced distress, but not depressive symptoms specifically (Spiegel et al 1989); therefore, the mediating role of improvement in depression has not been definitively shown. Further studies are needed to address the effectiveness of psychotherapeutic intervention for the treatment of depression in patients with cancer.

There are a growing number of antidepressant treatment trials in patients with cancer. Available evidence strongly suggests that depression in the patient with cancer responds to TCAs, SSRIs, mirtazapine, and mianserin (Table 2).

A novel approach involves using antidepressants to prevent development of depression in patients receiving medications known to cause severe depressive symptoms. In a landmark, placebo-controlled study, paroxetine administered to patients with malignant melanoma before treatment with high-dose interferon-α, an agent known to cause depression, decreased rates of major depression, anxiety symptoms, and neurotoxicity. Importantly, antidepressant pretreatment enabled more patients to continue interferon-α (35% compared with 5% of placebo-treated patients, who discontinued because of neurotoxicity and depressive symptoms; Musselman et al 2001a). Researchers caution, however, against routine prophylactic antidepressant use in cancer patients, many of whom will not experience serious depressive episodes and are often reluctant to take more medications.

Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome

Depression compounds physical and emotional stressors of living with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS). Depression, depressive symptoms, and psychological stress are associated with poor adherence to antiretroviral treatment, deterioration in psychosocial functioning, more rapid progression of HIV/AIDS, and higher mortality rates (Burack et al 1993; Evans et al 1995, 2002a; Ickovics et al 2001; Leserman et al 2002; Lyketsos et al 1993, 1996; Mayne et al 1996; Page-Shafer et al 1996; Patterson et al 1996). Bereavement also accelerates disease progression (Goodkin et al 1996; Kemeny and Dean 1995).

Depression and mania might be risk factors for HIV infection by promoting high-risk behaviors (Perretta et al 1998). Immune-system changes associated with depression might even affect HIV entry and replication, thereby increasing the risk of HIV infection (Clerici et al 1997; Corley 1996; Gorman et al 1991; Leserman 2003).

Prevalence. Up to one third of persons with HIV/AIDS might have mood disorders or clinically significant depressive symptoms (Atkinson et al 1988; Bing et al 2001; Lipsitz et al 1994; Perkins et al 1994; Stern et al 1992). Persons with HIV have a 2-fold greater risk of major depression than HIV-negative control subjects (Ciesla and Roberts 2001). Table 1 lists prevalence rates for depression in patients with HIV/AIDS. Women infected with HIV are more likely to have depression than HIV-infected men (Ciesla and Roberts 2001; Maj 1996; Morrison et al 2002; Rabkin et al 1997). Bipolar disorder is common in people with HIV/AIDS (Ellen et al 1999; Kieburtz et al 1991; Lyketsos et al 1993).

Comorbidity Mechanisms. Depression is linked to biological changes in HIV/AIDS that might contribute to disease progression and mortality (Cruess et al 2003; Leserman 2003). Abnormalities in HPA axis and hypercortisolemia associated with depression might alter immune response (Clerici et al 1997; Corley 1996; Goodkin et al 1996; Gorman et al 1991; Leserman 2003; Petitto et al 2000) and contribute to HIV progression (Clerici et al 1997; Corley 1996; Leserman et al 2002; Maggi et al 1994; Nair and Schwartz 1995; Nair et al 2000; Vago et al 1994). Increased sympathetic activity via norepinephrine has been shown to affect HIV replication (Cole et al 1998). Alterations in functioning of killer lymphocytes (natural killer and cytotoxic T-lymphocytes) associated with depression might diminish host defense against HIV infection (inhibiting viral replication and lysing HIV-infected cells) (Evans et al 2002b; Leserman et al 1997), protection against symptoms in people with low CD4 counts (Ironson et al 2001), and might be a mechanism whereby depression might influence HIV disease progression. Chronic depression, poor social support, and stressful life events are risk factors for more rapid decline in CD4 lymphocyte counts (Burack et al 1993; Kemeny and Dean 1995; Kemeny et al 1995) and progression to AIDS (Ickovics et al 2001; Leserman 2003; Leserman et al 1999, 2002).

Diagnosis and Treatment. Depression in HIV/AIDS might exist as a primary disorder or occasionally might be secondary to neurological effects of viral infection (Evans et al 2002a; Treisman et al 1998). Hallmark features of depression, including fatigue, weight loss, poor appetite, and cognitive impairment, mirror HIV-associated symptoms. In addition, complications associated with substance abuse might mask symptoms of depression (Perkins et al 1995; Regier and Farmer 1990).

Relatively more is understood about bipolar disorder in HIV/AIDS, which is unlike most other medical illnesses. The differential diagnosis of mania in a patient with HIV/AIDS must consider a past history of mania and severity and course of manic symptoms. Mania might occur secondary to HIV infection or primarily in a patient with a history of mania (Lyketsos et al

1997a; Treisman et al 1998). Mania secondary to HIV infection is differentiated from other forms of mania by marked cognitive slowing and dementia, greater severity of presentation and course, and more pronounced irritable mood (Cruess et al 2003).

Antidepressant efficacy has been demonstrated in randomized studies of depression in HIV-positive patients (Table 2). The SSRIs are the most widely studied antidepressants to date, although venlafaxine (Ereshefsky and Dugan 2000), psychostimulants (Fernandez et al 1995; Wagner and Rabkin 2000; Wagner et al 1997), testosterone (Rabkin et al 2000b), and dehydroepiandrosterone (DHEA) (Rabkin et al 2000a) might offer benefit. Lithium (el-Mallakh 1991; Parenti et al 1988) and anticonvulsants (Halman et al 1993; Maggi and Halman 2001) for mania and antipsychotics for patients with psychotic symptoms (Lera and Zirulnick 1999; Singh et al 1997) might be beneficial in patients with HIV infection.

Frequent modification of medication regimens, which is customary in HIV treatment, complicates comorbid depression management. Treatment considerations for mood disorders in persons with HIV/AIDS include awareness of increased susceptibility to adverse effects, drug-drug interactions, and multiple factors associated with advanced-stage AIDS (e.g., protein binding, changes in appetite, energy, and pain) that might necessitate treatment modification (Penzak et al 2000). St John's wort significantly increased clearance of protease inhibitors by inducing the CYP3A4 isoenzyme, thereby attenuating the therapeutic potential of protease inhibitors (Piscitelli et al 2000). Tricyclic antidepressants are effective, but adverse effects limit their utility (Rabkin et al 1994a). In contrast, SSRIs are comparably effective and better tolerated, yielding increased overall effectiveness (Elliott et al 1998; Zisook et al 1998).

Other Medical Comorbidities

Chronic Pain. Depression is common in patients with chronic pain (Table 1). Severity and duration of chronic pain are directly proportional to severity of depression. Rates of suicidal behavior among persons with chronic pain are high (Fishbain et al 1997). Extensive literature supports the efficacy of serotonergic/noradrenergic antidepressants (Fishbain 2000; Lynch 2001) and cognitive-behavioral psychotherapy (Keefe 2000) for managing certain chronic pain syndromes and depression. Pain and depression might occur concurrently because of their respective neurochemical associations with serotonin and norepinephrine, and altered levels of these neurotransmitters might affect changes that precipitate occurrence of pain and depression (Campbell et al 2003).

Obesity. Childhood and adolescent depression are predictors of obesity in adulthood (Pine et al 2001), and rates of major depression are 20% for obese boys and 30% for girls (Stunkard et al 2003). In a nationally representative sample of adolescents from the National Comorbidity Survey, lifetime prevalence of major depression was 15% (Kessler and Walters 1998). Activation of HPA axis influences depression and obesity as indicated by elevated levels of cortisol (Stunkard et al 2003). Although weight loss in obese persons is associated with improvement in mood, amelioration of depression or bipolar disorder is not clearly associated with improvement in weight, perhaps because of weight gain associated with pharmacologic treatment (Stunkard et al 2003).

Osteoporosis. Neuroendocrine effects of depression might increase risk of osteoporosis. Valproate and carbamazepine, which are commonly used for bipolar disorder, might reduce bone mineral density, potentially increasing risk of osteoporosis (Cizza et al 2001; Gold et al 2002; Halbreich and Palter 1996).

Conclusions

Mood disorders are prevalent in patients with chronic medical illnesses and are more than simply a consequence of medical comorbidity. Presence of depression considerably worsens medical prognosis, because it hinders adherence to treatment regimens, impairs physical and cognitive function, diminishes quality of life, increases morbidity, and in some cases, decreases survival. Depression might be an etiologic factor for incident disease (e.g., cardiac disease, stroke, cancer, epilepsy), which has important implications for prevention and early intervention for both depression and the medical illness itself. Depression also might affect the course of medical diseases (e.g., cardiac, cerebrovascular, neurological disorders, diabetes, cancer, and HIV/AIDS). Depression in medically ill patients is treatable. Preliminary data on treatment of depression in patients with comorbid medical conditions are encouraging, but additional studies are needed to confirm that treating depression improves overall medical outcomes.

Bipolar disorder also might precipitate medical conditions and have a negative effect on medical prognoses; however, the underlying mechanisms, risk factors, and effects of treatment of bipolar disorder in medically ill patients are less well understood.

The following recommendations reflect of the expert opinion of the authors on the basis of the available evidence and clinical experience of the development panel:

Research

- **Include depression assessments in all future large-scale epidemiologic studies.** Questions about mood disorders should be routinely included in studies such as the National Health and Nutrition Examination Studies (NHANES), Cache County Study, and other collaborative studies.
- **Establish a standardized database.** A national effort, led by the NIMH in collaboration with other institutes (e.g., NINDS, National Institute on Aging [NIA]), is critical to standardize diagnosis and treatment of depression in medical illness. Such an effort could be modeled on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), which has developed standardized diagnostic instruments.
- **Conduct prospective, rigorously designed studies.** Inconsistent design and insufficient power of many available studies limit comparison and analysis. Additional well-designed studies are imperative to provide reliable and standardized data on prevalence, underlying biological mechanisms, risk, diagnosis, pharmacological and psychotherapy treatment, and prevention of depression and bipolar disorder in the context of medical illness. Longitudinal studies of the course of depression and bipolar disorder in patients with chronic medical illness are needed. Clinical trial designs should consider inclusion of population pharmacokinetics to detect variable drug exposure secondary to partial or nonadherence to treatment, unexpected drug interactions, and potential concentration differences in those with comorbid medical conditions. Appropriate symptom-specific quality-of-life assessments should be included in all treatment studies.
- **Focus on special populations.** Epidemiology, risk, diagnosis, treatment, and prevention of depression and bipolar disorder are remarkably understudied in medically ill minor-

ities, women, children, adolescents, and the elderly. Increased funding must be designated for studies in these populations to document rates of diagnosis and treatment of mood disorders in medically ill patients.

- **Expand research agenda for bipolar disorder.** Bipolar disorder occurs in patients with HIV/AIDS, PD, AD, and other medical illnesses, but little is known about the directional nature of risk, diagnosis, clinical course, and treatment response of these patients. Research is needed for this much-overlooked population.

Clinical

- **Screen for depression in all medically ill patients.** Routine screening is recommended throughout the medical community and must not be limited to primary or mental health care, but should also be implemented by medical specialties. Clinicians and healthcare benefit providers should include mood disorder screening as part of routine assessment for other indicators of overall health (e.g., screening for elevated blood pressure, serum lipids, breast and colon cancers), and additional resources needed to support these screening measures should be accessible. There is, however, a paucity of evidence-based data supporting the effectiveness of screening. Screening for depression improves patient outcomes only when accompanied by effective treatment and follow-up. Implementation of widespread depression screening in medically ill patients would be a costly process that will not benefit patients if sufficient resources are not made available to ensure parity, accessibility, appropriate delivery, and correct monitoring of treatment.
- **Maintain a low threshold for depression treatment.** No patient or family should have to accept diminished mental health as an expected and unavoidable consequence of medical illness, particularly when effective and safe treatments are available. If untreated, symptoms of depression might occur with escalating frequency and severity, and risk for suicide might increase. Not all patients will need treatment. A watchful waiting approach might be reasonable for patients with a new medical diagnosis or a negative change in prognosis in order to rule out a temporary adjustment reaction. Treatment should be strongly considered, however, for patients with depressive symptoms that result in undue distress or impairment. Appropriately educated patients and their families will be empowered to seek help for their mental health and associated symptoms. Additional resources must be accessible to facilitate treatment, support patient monitoring, and ensure optimal treatment. Failing to provide appropriate and available treatment to a patient with depression is as unacceptable as denying relief to a patient with pain.

Public Policy

- **Assess healthcare delivery systems and identify barriers to care.** Barriers to delivering effective treatment of mood disorders in medically ill patients should be documented, and optimal means of providing mental health care during critical times (e.g., onset, end of acute care, relapse, end of life) should be determined. Those who are documenting must be fully educated on how medical comorbidity affects course and outcome. Professional organizations, such as the American Psychiatric Association, American Psychological Association, American College of Cardiology, American Academy of Neurology, and American Diabetes Association, must educate and promote access to care. Furthermore, Congress must sponsor and approve legislation that delivers parity to patients with mood disorders and medical comorbidities.
- **Confront and reduce the stigma surrounding depression and bipolar disorder.** It is imperative that government agencies (e.g., The Substance Abuse and Mental Health Services Administration [SAMSHA]) make effective public education campaigns that reach a wide demographic, including minority populations, in order to reduce stigma and facilitate self-identification. Within the medical community, physicians must first increase awareness of their own biases and understanding of the patient perspective of living with a mood disorder. Physicians should maximize their effectiveness as patient educators to attenuate patient stigma for depression and bipolar disorder. Medical schools and residency training programs must promote awareness and provide training of healthcare professionals on mood disorders in the medically ill. In addition, because these are illnesses of isolation, patients should be referred to peer support groups.

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Development Panel

CoChairs: Dwight L. Evans, MD; Dennis S. Charney, MD
Speakers: Robert M. Carney, PhD; Sanford A. Garfield, PhD;

Philip W. Gold, MD; Thomas Insel, MD; Andres M. Kanner, MD; Wayne J. Katon, MD; Peter G. Kaufmann, PhD; Francis J. Keefe, PhD; Thomas P. Laughren, MD; Jane Leserman, PhD; Constantine G. Lyketsos, MD, MHS; William M. McDonald, MD; Bruce S. McEwen, PhD; Andrew H. Miller, MD; Dominique Musselman, MD, MS; Charles B. Nemeroff, MD, PhD; Christopher O'Connor, MD; John M. Petitto, MD; Robert G. Robinson, MD; Steven P. Roose, MD; Julia Rowland, PhD; Yvette Sheline, MD; Gregory Simon, MD, MPH; David Spiegel, MD; Albert Stunkard, MD

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Workgroup 1 - Cardiovascular:

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Workgroup 2 – Cancer and HIV:

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Workgroup 3 – Stroke, Parkinson's Disease, Alzheimer's Disease, and Epilepsy:

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