

The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and select comorbid medical conditions

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BACKGROUND: Medical comorbidity in patients with mood disorders has become an increasingly important clinical and global public health issue. Several specific medical conditions are associated with an increased risk of mood disorders, and conversely, mood disorders are associated with increased morbidity and mortality in patients with specific medical disorders.

METHODS: To help understand the bidirectional relationship and to provide an evidence-based framework to guide the treatment of mood disorders that are comorbid with medical illness, we have reviewed relevant articles and reviews published in English-language databases (to April 2011) on the links between mood disorders and several common medical conditions, evaluating the efficacy and safety of pharmacologic and psychosocial treatments. The medical disorders most commonly encountered in adult populations (ie, cardiovascular disease, cerebrovascular disease, cancer, human immunodeficiency virus, hepatitis C virus, migraine, multiple sclerosis, epilepsy, and osteoporosis) were chosen as the focus of this review.

RESULTS: Emerging evidence suggests that depression comorbid with several medical disorders is treatable and failure to treat depression in medically ill patients may have a negative effect on medical outcomes.

CONCLUSIONS: This review summarizes the available evidence and provides treatment recommendations for the management of comorbid depression in medically ill patients.

KEYWORDS: bipolar disorder, cancer, cerebrovascular disease, comorbidity, coronary heart disease, epilepsy, HCV, HIV, major depressive disorder, migraine, multiple sclerosis, osteoporosis

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INTRODUCTION

Mood disorders are a multisystem group of disorders that can adversely affect a variety of end organ systems. Conversely, diseases of several organ systems increase the risk of mood disorders. This article reviews the available evidence on the bidirectional comorbid relationships between mood disorders and several common medical conditions, evaluates the evidence of efficacy and safety of pharmacologic and psychosocial treatments, and provides recommendations regarding the management of patients with these comorbid conditions. The medical conditions chosen as the focus of this review are among the more commonly encountered medical disorders in clinical practice and include cardiovascular disease (CVD), cerebrovascular disease, cancer, human immunodeficiency virus (HIV), hepatitis C virus (HCV), migraine, multiple sclerosis (MS), epilepsy, and osteoporosis.

Cardiovascular disease

Mood disorders are overrepresented in patients with CVD, and up to 20% of patients with CVD also meet criteria for major depressive disorder (MDD) or bipolar disorder (BD).^{1,2} As a consequence, a significant amount of research has been focused on understanding this association. Since the late 1990s, there have been >100 narrative reviews of this literature, as well as numerous meta-analyses examining the role of mood disorders on cardiovascular morbidity and mortality.^{3,4} Despite differences in samples, duration of follow-up, and assessment of depression and depressive symptoms, these studies have demonstrated relatively consistent results. Less research has focused on BD and CVD, but the results of studies examining mortality and hospitalization indicate that patients with BD have higher mortality from cardiac disorders than the general population.⁵ As a result of these findings, several clinical guidelines recommend that screening for mood disorders be considered in patients with CVD, and conversely, that screening for CVD occur in patients experiencing mood changes, highlighting the bidirectional nature of this association.⁶⁻⁹

These recommendations are not without controversy, however, in part because of equivocal outcomes in interventional studies. In the past decade, 3 large studies have not shown a positive effect of MDD treatment on medical endpoints.¹⁰⁻¹² Despite these negative findings, meta-analyses have concluded that psychosocial interventions are associated with significant reductions

in mortality and cardiac morbidity,^{13,14} although mortality benefits may differ by sex.⁵ A systematic review published in the *Journal of the American Medical Association* examining the effects of MDD treatment in CVD patients identified 4 efficacy studies of antidepressant medications that met search inclusion criteria; these included studies using fluoxetine,¹⁶ sertraline,¹⁷ citalopram,¹⁸ and mirtazapine.¹⁹ In the fluoxetine study,¹⁶ Strik et al compared the efficacy and safety of fluoxetine administered to patients after their first myocardial infarction (MI) and found a trend toward antidepressant efficacy. The Sertraline Antidepressant Heart Attack Randomized Trial (N = 369)¹⁷ tested the efficacy and safety of sertraline in patients with MDD. Here the investigators conducted a randomized study of MDD in patients with unstable ischemic heart disease and found no difference in cardiovascular adverse events between the drug and placebo groups after 16 weeks of therapy. The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy Trial (N = 284)¹⁸ compared citalopram to placebo and compared short-term interpersonal psychotherapy plus clinical management to clinical management alone in patients with coronary artery disease; the results showed antidepressant efficacy and no evidence of harm. However, in the Myocardial Infarction and Depression-Intervention Trial,¹⁹ which used mirtazapine, the drug showed superiority to placebo on some but not all depression scales. Further complicating the picture is the outcome of a systematic review that did not find evidence for or against the recommendations that MDD be evaluated or that screening for MDD be considered part of standard care in patients with CVD.²⁰

A number of factors support an association between mood disorders and CVD. From a behavioral perspective, patients with MDD or BD are more likely to engage in unhealthy behaviors, such as smoking or having a sedentary lifestyle, that increase the risk of CVD.²¹ When diagnosed with heart disease, having a mood disorder is associated with lack of medical adherence to pharmacologic treatments or interventions such as exercise.^{22,23} Patients with a mood disorder also have a lower frequency of hospitalization for heart disease and lesser exposure to cardiac treatment.²⁴ Although not always consistent, several studies in depressed patients with coronary artery disease also have reported reduced heart rate variability (suggesting increased sympathetic activity and/or reduced vagal activity)²⁵ and hypothalamic-pituitary-adrenal (HPA)

axis dysfunction,²⁶ increased plasma platelet factor 4 and β -thromboglobulin (suggesting enhanced platelet activation),^{27,28} impaired vascular function,²⁹ and increased C-reactive protein, interleukin (IL) 6, intercellular adhesion molecule-1, and fibrinogen levels (suggesting an increased innate inflammatory response).^{30,31}

Treatment recommendations. The nature of the association between mood disorders and CVD has not been fully elucidated, and research is needed to determine the effectiveness and efficacy of various treatment outcomes. The evidence we do have, however, supports adoption of the following recommendations:

1. Routine screening for depression in patients with CVD in various settings, including hospitals, physicians' offices, and cardiac rehabilitation centers (level 2).

2. Selective serotonin reuptake inhibitors (SSRIs) and noradrenergic and specific serotonergic antidepressants have been shown to be beneficial in treating depression after a cardiac event with no worsening of cardiac events (level 2).

3. There is first-line evidence that patients with CVD who are receiving treatment for MDD should be carefully monitored for adherence to their medical care, drug efficacy, and safety with respect to both their cardiovascular and mental health (level 1).

4. The use of psychotherapeutic techniques such as cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), or problem-solving therapy is beneficial alone or in combination with medication for mild to moderate depression (level 2).

5. There are no systematic studies evaluating electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS). ECT can be performed safely in most patients with underlying cardiac conditions, with the caveat that appropriate cardiac treatments are administered at the time of neuromodulation treatment (level 3).

Cerebrovascular disease

Stroke represents a major public health problem worldwide. It is the third leading cause of mortality in patients age ≥ 50 and the sixth leading cause of burden of disease worldwide.^{32,33} An association between depression and stroke has long been recognized, but only in the last 20 to 25 years have studies examined the comorbid relationship between the two. Depression following stroke is often termed *post-stroke depression* (PSD), although the validity of this entity as a specific type of secondary depression remains controversial.³⁴

Epidemiology of comorbidity. There is robust evidence that stroke increases the risk of depression³⁵ and that depression increases the risk of vascular disease.^{22,36} Mania is relatively rare following stroke, and although 2 cases of secondary mania post-stroke were reported in a cohort of 309 stroke patients,³⁷ other large-scale studies did not find a single case of mania.^{34,38}

PSD negatively influences stroke recovery by impairing physical and cognitive functions,^{39,40} and it increases both the risk of medical mortality⁴¹ and death by suicide.⁴² Since 1990, 9 prospective studies have shown evidence for an association between antecedent depression and stroke, supporting the bidirectional relationship between these 2 disorders.⁴³ Larson et al reported a relative risk of 2.67 for stroke in patients who had depressive disorder, which was higher than the relative risk reported in other studies using broadly defined depressive symptoms, suggesting a dose-response relationship between depression and stroke.⁴⁴

Etiologic mechanisms of comorbidity. Several lines of evidence suggest that PSD may be influenced by physical factors such as cerebral ischemia and stroke lesions, psychosocial factors such as stress related to physical and cognitive impairment associated with stroke,⁴⁵ and genetic factors linked to serotonin transporter polymorphisms.^{46,47} Cerebral ischemia also leads to alterations in proinflammatory cytokines and stroke lesions that may cause depletion in monoamines, increased HPA activity, and disruption in emotional neural circuits.^{48,49} There is also evidence that personal and family history of depression increases the risk of PSD.^{50,51} Conversely, depression might contribute to illness onset and progression of vascular diseases with stroke outcome by increasing platelet activation and adhesions, HPA activity, heart rate variability, sympathetic activity, proinflammatory cytokines, and insulin resistance.⁴³

Efficacy of interventions in the treatment and prevention of depression in stroke. Several randomized control trials (RCTs) have examined the safety and efficacy of pharmacologic and psychotherapeutic interventions in PSD. A recent Cochrane systematic review of 13 RCTs of pharmacotherapy interventions found a small but significant effect of pharmacotherapy on achieving remission and reducing depression or depressive symptoms after stroke.⁵² The results of that review also found evidence of increased adverse events associated with antidepressant treatment. Based on these results, the authors did not recommend routine use of antidepressants.

sants in PSD. Another meta-analytic review of 16 RCTs involving a total of 1,320 patients disputed this finding, concluding that antidepressant treatment was effective in patients with PSD.⁵³ Based on the data available from RCTs of SSRIs, citalopram was found to be safe and effective,⁵⁴ the effect of fluoxetine and sertraline on PSD was either inconclusive or negative,⁵⁵⁻⁵⁸ and among the tricyclic antidepressants (TCAs), nortriptyline was found to be effective.^{56,59} Methylphenidate treatment also showed small improvements in activities of daily living (ADLs) over the course of treatment.⁶⁰ Regarding psychotherapeutic interventions, no benefit was noted in 4 trials of psychotherapy involving counseling or specific psychotherapy compared with standard care in the treatment of depression associated with stroke.⁵² However, a Cochrane review did note that problem-solving therapy and motivational interviewing seem to have benefit in preventing depression in stroke patients.⁶¹ Regarding antidepressant treatment in the prophylaxis of depression, a Cochrane review showed negative results, whereas 2 other meta-analytic reviews and one recent RCT showed evidence for efficacy in preventing depression.⁶²⁻⁶⁴

Treatment recommendations. The available evidence supports adoption of the following recommendations:

1. Only nortriptyline treatment has level 1 evidence^{56,59} in terms of efficacy for the treatment of PSD. Given the risk of delirium⁶⁵ and safety concerns in patients with concomitant cardiac disease, it is recommended as a second-line treatment.

2. Although citalopram has level 2 evidence,⁵⁴ it is recommended as first-line treatment because of its safety in cardiac and elderly patients, whereas other treatments with level 2 evidence, such as amitriptyline and trazodone, should be considered third-line treatments due to side effects and efficacy only in subgroups.⁶⁶⁻⁶⁸

3. Paroxetine and fluoxetine should be avoided, as they are potent inhibitors of cytochrome P450 and interact with several cardiac medications.⁶⁹ Typical or atypical antipsychotics may increase the risk of stroke in elderly individuals, and caution should be exercised in using antipsychotics as add-on treatment for resistant depression or BD⁷⁰ (level 2).

4. There is inadequate evidence at present to support the use of psychotherapy as monotherapy in the treatment of PSD. However, structured psychological therapies such as problem-solving therapy and motivational interviewing in combination with antidepressants

may have a role in the treatment of MDD resistant to first-line antidepressants and in relapse prevention. However, controlled studies for these combination treatments are needed.

5. Because of a lack of adequate evidence, the routine use of antidepressants in stroke patients to prevent depression and improve stroke recovery is not recommended at the present time. More research is needed to examine the benefits of pharmacologic preventive intervention for the entire stroke population.

6. ECT, repetitive TMS, and treatment with psychostimulants^{60,71,72} have only level 3 evidence and are recommended as third-line treatment for patients with treatment-resistant PSD.

Cancer

Cancer is associated with distress at all points in the disease trajectory. Psychological concerns contributing to such distress include uncertainty about the future, loss of autonomy and sense of control with increasing disability, perceived alterations in the life trajectory, existential concerns, and fear of dying.⁷³ Adding to the burden of disease are the functional limitations in occupational and recreational activities, family role functioning, and ADLs that may be associated with cancer. In a substantial minority of individuals with cancer, mood disorders such as MDD, dysthymia, minor depression, and adjustment disorder with depressed mood may develop.

Epidemiology and comorbidity. The reported prevalence of clinically significant depression in cancer patients has varied widely depending on the cancer type, demographics of the population studied, stage of cancer, diagnostic criteria and strategy applied, timing and method of assessment, measurement tools used, and diagnostic thresholds.^{74,75} Overall, it is estimated that 10% to 25% of cancer patients have clinically significant depressive symptoms,^{76,77} with a higher prevalence toward the end of life⁷⁸ and in cancers with poorer prognoses, such as pancreatic and oropharyngeal cancer.^{79,80} These overall rates of depression in cancer are approximately 2 to 4 times that found in the general population.⁸¹ Depression in patients with cancer has been associated with reduced quality of life,⁸² an elevated rate of suicide and a desire for hastened death,^{76,83} poorer treatment compliance,⁸⁴ greater physical distress,⁸⁵ and more prolonged hospital stays.⁸⁶ It has also been shown to be an independent risk factor for mortality⁸⁷⁻⁸⁹ and has been reported by some to be associated with increased resis-

TABLE 1

Evidence for efficacy of pharmacologic interventions in preventing or relieving depression in cancer patients

Medication	Positive trials	Negative trials	Level of evidence
Antidepressants			
Paroxetine	Morrow et al, 2003 ¹⁰⁴ Musselman et al, 2001 ¹⁰⁵ Roscoe et al, 2005 ¹⁰⁶	Pezzella et al, 2001 ¹⁰⁷ Musselman et al, 2006 ¹⁰⁸	1
Fluoxetine	Navari et al, 2007 ¹⁰⁹	Razavi et al, 1996 ¹¹⁰ Holland et al, 1998 ¹¹¹ Fisch et al, 2003 ¹¹²	2
Citalopram	Lydiatt et al, 2008 ¹¹³		2
Mianserin	Costa et al, 1985 ¹¹⁴ van Heeringen et al, 1996 ¹¹⁵	Tarrier et al, 1984 ¹¹⁶	1
Desipramine		Holland et al, 1998 ¹¹¹ Musselman et al, 2006 ¹⁰⁸	Negative evidence
Amitriptyline		Pezzella et al, 2001 ¹⁰⁷	Negative evidence
Mirtazapine	Ersoy et al, 2008 ¹¹⁷ Kim et al, 2008 ¹¹⁸		3
Bupropion	Moss et al, 2006 ¹¹⁹		3
Anxiolytics			
Alprazolam	Holland et al, 1991 ¹²⁰	Wald et al, 1993 ¹²¹	2
Steroids			
Prednisone	Bruera et al, 1985 ¹²²		2
Stimulants			
Methylphenidate	Fernandez et al, 1987 ¹²³ Homsí et al, 2001 ¹²⁴ Macleod, 1998 ¹²⁵ Olin et al, 1996 ¹²⁶ Natenshon, 1956 ¹²⁷		3
Mazindol		Bruera et al, 1986 ¹²⁸	Negative evidence

tance and slower response rates to antidepressant medication and higher rates of depressive relapse.

Etiology. Psychosocial factors that increase the risk of depression in cancer patients include younger age, personal or family history of depression, less social support, greater attachment anxiety, poor communication with medical caregivers, greater illness intrusiveness, and maladaptive coping strategies.⁹¹ There is little evidence that psychosocial factors or depression increase the incidence of cancer or the risk of disease progression,^{80,92} although recent work is beginning to explore plausible biological mechanisms by which this could occur.⁹³

Immune-activated systemic inflammation is a proposed shared biologic mechanism mediating the bidirectional relationship between depression and cancer. This

has been supported by mounting evidence that tumor cell burden and treatment-induced tissue destruction results in the release of proinflammatory cytokines that alter neurotransmitter and neuroendocrine function, leading to behavioral changes termed *sickness behavior*.⁹⁴

Effectiveness of treatment for depression in cancer. There have been 4 systematic reviews of pharmacologic treatment for depression in cancer, which have provided mixed evidence for effectiveness.⁹⁵⁻⁹⁸ Jacobsen et al identified 9 RCTs, in which 13 of 26 depression outcomes (total observer and self-report measures combined across all follow-up assessments) revealed significant treatment effects.⁹⁵ Six RCTs were identified by Williams and Dale, of which only 2 demonstrated reductions in caseness for MDD, although 5 found reductions in depressive symp-

toms.⁹⁶ In a systematic review limited to studies reported to June 2005, in which clinically significant depression was an inclusion criterion, Rodin et al identified only 3 of 7 RCTs in which a significant reduction of depressive symptoms was reported.⁹⁷ Ng et al⁹⁸ extended this review to February 2010, identifying only 3 of 8 RCTs with positive findings for effectiveness. This review also reported on 5 open-label studies that demonstrated the efficacy of methylphenidate in treating depression in cancer patients, although there were no controlled trials of this intervention for depression⁹⁸ (TABLE 1).¹⁰⁴⁻¹²⁸

Evidence for the effectiveness of psychosocial interventions for depression in cancer is considerably larger but similarly mixed, in part because of significant variation in demographic, disease, and treatment characteristics in the populations studied and methodological differences in inclusion criteria, outcome assessments, and duration of follow-up. Jacobsen et al comprehensively reviewed 9 systematic reviews and 4 meta-analyses⁹⁹ of the effects of interventions such as psychoeducation, problem-solving therapy, CBT, IPT, supportive-expressive psychotherapy, and relaxation therapies for depression in cancer. Based on 9 of 13 publications, they reached positive conclusions about the efficacy of psychosocial interventions. Only 3 RCTs of psychosocial interventions to treat depression in cancer patients demonstrated reductions in caseness for depression.⁹⁶ Only 50% of psychosocial intervention studies limited to clinically significant depression demonstrated reductions in depressive symptoms,⁹⁷ and a meta-analysis yielded a negligible effect size (Cohen's $d = .19$).¹⁰⁰ Although controversy persists regarding the overall efficacy of psychosocial interventions in cancer,^{101,102} Jacobsen⁹⁹ has proposed deriving specific clinically relevant recommendations based on the number of RCTs that demonstrate efficacy in managing depression per intervention type and patient disease or treatment status (TABLE 2).¹²⁹⁻¹⁵³

Treatment recommendations. The available evidence supports adoption of the following recommendations:

1. It is difficult to derive clinically relevant first-line treatment recommendations based on the current RCT literature for pharmacologic treatment of depression in cancer. Level 1 evidence is available only for paroxetine in depression prevention trials, but caution should be used based on its strong inhibition of cytochrome P450 2D6¹⁰³ and its relatively pronounced anticholinergic side effects. At present, there is no evidence that any particu-

lar antidepressant is more efficacious than others in the management of depression in cancer.

2. First-line treatment recommendations for specific psychosocial interventions in depressed cancer patients are similarly difficult to derive, because the evidence does not support the superiority of 1 treatment modality over another. The use of a psychotherapeutic intervention has been shown to be helpful, with choice guided by patient characteristics.

Human immunodeficiency virus and hepatitis C virus

Human immunodeficiency virus. Approximately 33 million people are infected with HIV globally, and the prevalence rate is 0.6% in North America.¹⁵⁴ Furthermore, nearly 50% of HIV-infected patients have a comorbid psychiatric disorder such as a depressive or anxiety disorder, which is often unrecognized in this patient population.^{155,156}

The high degree of comorbidity between depression and HIV has a significant impact on treatment outcomes. Depression and other factors, such as substance use and poor social support, have deleterious effects on adherence to highly active antiretroviral therapy (HAART) in HIV-infected patients and can potentially influence HIV illness outcomes.^{157,158} In a study of 765 HIV-seropositive women, depression severity and chronicity was associated with decreased CD4+ cell counts and survival.¹⁵⁹ Although a retrospective study of 1,713 HIV-infected patients showed an improvement in HAART adherence with antidepressant treatment, the relationship between depression treatment and HIV adherence is less clear.¹⁶⁰

The presentation of depression in HIV is further complicated by common somatic symptoms related to HIV infection itself, resulting in sleep disturbance, fatigue, impaired concentration, and loss of appetite. Although there is considerable overlap between somatic symptoms of depression and HIV, studies have shown improvement in both affective and somatic symptoms with antidepressant treatment.^{161,162}

ETIOLOGY OF DEPRESSION IN HIV. Depression in the context of HIV infection can be conceptualized as primary or secondary in nature and can complicate the diagnosis of depression in this patient population. As stated above, depression in HIV often is associated with somatic symptoms related to HIV illness itself, and symptomatic HIV disease is associated with an increased risk of depression compared with controls.¹⁶³ Harbingers for depression sec-

ondary to HIV include the absence of a family history of depression and central nervous system involvement of HIV.

Depression can influence immune activity in HIV and the course of infection. A decline in natural killer cell functioning and numbers has been associated with depression in HIV patients.¹⁶⁴ In a study of HIV-infected women, depression resulted in increased activated CD8 lymphocytes and viral load.¹⁶⁵ Psychosocial factors such as stigma associated with HIV and interpersonal losses may also contribute to the development of depression in HIV-infected patients.

Treatment with specific HAART, such as efavirenz, a nonnucleoside reverse transcriptase inhibitor, can also induce depressive symptoms—specifically, sadness and suicidal ideation—in up to 19.3% and 9.2% of patients, respectively.¹⁶⁶ These changes have been linked to increased proinflammatory cytokines (interleukin-1 and tumor necrosis factor α) in rat studies with efavirenz, which are attenuated by paroxetine treatment.¹⁶⁷ Given the high prevalence of depression in HIV and potential responsiveness to treatment, assessment and subsequent treatment of depression in HIV is important to HIV illness outcomes.

TREATMENT OF DEPRESSION IN HIV. Pharmacologic management of depression in patients with HIV has been an emerging focus over the last 20 years. A recent meta-analysis of all published RCTs for antidepressant medications among HIV-positive individuals demonstrated a moderate effect size (0.57) in this patient population.¹⁶⁸ Heterogeneity across studies in this meta-analysis was associated with high placebo response (>33%).

The available evidence supports adoption of the following recommendations:

1. Despite initial studies demonstrating the efficacy of TCAs for depression in this population, the side effects of TCAs, such as dry mouth, constipation, heart palpitations, headache, and insomnia, have led to higher drop-out rates compared with other agents.¹⁶⁹ These adverse effects often are compounded by the side effects from HAART regimens and somatic symptoms that are prevalent in HIV-infected patients; therefore, TCAs should be used only after SSRIs have failed to demonstrate efficacy or tolerability (level 2).

2. Stimulant agents such as dextroamphetamine and methylphenidate have been shown in 2 RCTs to be effective in treating depression in HIV-positive patients.^{170,171} In a recent trial, modafinil failed to show a significant change in depressive symptoms in patients with HIV,

TABLE 2
Evidence for efficacy of psychosocial interventions to prevent or relieve depression in cancer patients

Patient or treatment status	RCT evidence	Level of evidence
Relaxation techniques		
Newly diagnosed patients	Arakawa et al, 1997 ¹²⁹ Bindemann et al, 1991 ¹³⁰ Edgar et al, 2001 ¹³¹	1
Undergoing surgery	Fawzy et al, 1990 ¹³² Petersen et al, 2002 ¹³³	1
Undergoing chemotherapy	Ando et al, 2009 ¹³⁴ Burish et al, 1987 ¹³⁵ Burish et al, 1981 ¹³⁶ Jacobsen et al, 2002 ¹³⁷ Mantovani et al, 1996 ¹³⁸	1
Undergoing radiotherapy	Decker et al, 1992 ¹³⁹ Evans et al, 1995 ¹⁴⁰ Pruitt et al, 1993 ¹⁴¹	1
Completion of active treatment	Simpson et al, 2001 ¹⁴²	2
Terminal phase of illness	Lioffi et al, 2001 ¹⁴³	2
Psychoeducation		
Newly diagnosed patients	McQuellon et al, 1998 ¹⁴⁴	2
Undergoing surgery	McArdle et al, 1996 ¹⁴⁵	2
Undergoing chemotherapy	Rawl et al, 2002 ¹⁴⁶	2
Supportive-expressive therapies		
Undergoing surgery	Watson et al, 1988 ¹⁴⁷	2
Undergoing chemotherapy	Mantovani et al, 1996 ¹³⁸	2
Undergoing radiotherapy	Evans et al, 1995 ¹⁴⁰	2
Patients with metastatic disease	Kissane et al, 2007 ¹⁴⁸ Edelman et al, 1999 ¹⁴⁹ Goodwin et al, 2001 ¹⁵⁰	1
Cognitive-behavioral therapies		
Undergoing chemotherapy	Pitceathly et al, 2009 ¹⁵¹ Marchioro et al, 1996 ¹⁵²	1
Patients with metastatic disease	Savard et al, 2006 ¹⁵³ Edelman et al, 1999 ¹⁴⁹	1

although it was effective in reducing fatigue¹⁷² (level 2).

3. Because of the improved tolerability of SSRIs, more recent RCTs have predominantly focused on these agents in the treatment of depression in HIV-positive individuals. Fluoxetine and paroxetine have shown efficacy in the treatment of depressive symptoms compared with

placebo and TCA control treatments, respectively.^{173,174} Evidence from open-label studies support the use of sertraline and citalopram in treating depression in patients with comorbid HIV.^{175,176} Escitalopram and citalopram may be preferred in this patient population due to their limited drug-drug interactions with HAART¹⁷⁷ (level 1).

4. In addition to pharmacotherapy, psychosocial interventions have been studied in the treatment of depression in HIV-positive patients. Although trials have focused predominantly on CBT, supportive psychotherapy and psychoeducational groups have demonstrated efficacy comparable to CBT group interventions.^{162,178,179} Moreover, IPT has demonstrated efficacy in treating depression in HIV patients and was superior to supportive psychotherapy and CBT in 2 studies.^{162,180} Therefore, evidence exists for the use of a range of psychosocial interventions in managing depression in the context of HIV (level 2).

Hepatitis C virus. Approximately 140 million people worldwide are infected with HCV, which is primarily transmitted through intravenous drug use.¹⁸¹ Following acute HCV infection, up to 85% of individuals will develop chronic HCV infection, which will eventually lead to liver cirrhosis in 20% of patients over 20 years.^{182,183}

HCV is associated with high rates of lifetime psychiatric comorbidity, with substance use disorders, mood disorders, and anxiety disorders occurring at high rates in these patients.¹⁸⁴

ETIOLOGY OF DEPRESSION IN HEPATITIS C. A paucity of research has examined potential mechanisms of depression in untreated patients with HCV. However, studies have explored the etiology of interferon (IFN)- α -induced depression (IFN-MDD) on treatment in HCV patients. Research studies purport abnormal serotonin metabolism as a potential mechanism for IFN-MDD. IFN- α activates indoleamine 2,3-dioxygenase, a catabolizing enzyme for tryptophan (TRP), resulting in decreased TRP and serotonin (5-HT) levels and increased neurotoxic metabolites, specifically kynurenine and quinolinic acid.¹⁸⁵ Treatment with paroxetine did not alter levels of kynurenine or quinolinic acid or attenuate behavioral symptoms secondary to IFN- α -mediated TRP depletion.¹⁸⁶ In addition, proinflammatory cytokines, specifically IL-1, IL-2, IL-6, and IL-10, are increased with IFN- α treatment and have been linked to increased depressive symptoms.^{185,187}

EVIDENCE FOR TREATMENT OF DEPRESSION IN HCV. The available evidence regarding treatment of depression in HCV is as follows:

1. Open trials of citalopram and escitalopram have shown a significant reduction in depressive symptoms in patients with HCV, and both agents were well tolerated^{188,189} (level 3).

2. Two randomized placebo-controlled trials involving paroxetine pretreatment in HCV-infected patients failed to reduce the incidence of IFN-MDD compared with the placebo group^{190,191} (level 2).

3. Trials involving amantadine have failed to demonstrate a significant effect on IFN-MDD and are limited by poor tolerability^{192,193} (level 2).

4. Treatment of IFN-MDD with fluoxetine, sertraline, venlafaxine, bupropion, mirtazapine, nortriptyline, and imipramine is supported by anecdotal and case series evidence¹⁹⁴⁻¹⁹⁹ (level 3).

5. Limited research exists for psychosocial interventions either alone or in combination with pharmacotherapy in treating depression in HCV-infected patients. These interventions may be of benefit but further research is needed (level 3).

TREATMENT RECOMMENDATIONS FOR DEPRESSION IN HCV.

Because of lack of evidence, there are no first-line or second-line treatment recommendations for the management of depression in HCV and IFN-MDD.

Migraine

Migraine is a primary headache disorder characterized by recurrent episodes of headache associated with gastrointestinal, neurologic, and autonomic symptoms.²⁰⁰ Migraine and MDD have long been noted to co-occur, and most studies suggest the frequency of this phenomenon is greater than can be explained by chance.²⁰¹ Several clinical and epidemiologic studies have consistently reported a positive correlation between depression and migraine.²⁰²⁻²¹¹ Such studies demonstrated a higher risk for depression among individuals with migraine and a higher risk for migraine among depressed patients. A bidirectional relationship also was observed,²⁰² with migraine predicting first onset of depression and depression predicting first onset of migraine; these observations were further confirmed by several subsequent studies.^{204,205,212} A review of studies carried out since the introduction of the explicit and widely accepted diagnostic criteria for primary headache disorders, including migraine, by the International Classification Committee of Headache Disorders (first edition in 1988, followed by a revised edition in 2004) suggested that the specificity of the migraine-depression

association remains unclear, and the authors concluded no difference was demonstrated between patients with migraine and those with tension headache in terms of prevalence of psychopathology.²¹³ A more recent study that investigated migraine prevalence in cases of recurrent depression in comparison to psychiatrically healthy controls reported a significant association between depression and headache in general; however, among individuals with headache, migraine with aura had the strongest association with depression (odds ratio [OR] 5.63; 95% confidence interval [CI], 3.94 to 9.0).²¹¹

Etiologic mechanisms. Several studies have attempted to explore the mechanisms behind the association between migraine and depression; however, such mechanisms remain unclear. Causal and non-causal interpretations have been proposed. Studies on biological markers such as dexamethasone suppression,²¹⁴ tyramine conjugation,²¹⁵ and [3H]-imipramine platelet binding²¹⁶ suggest shared mechanisms between migraine and depression. The observations of TCA and monoamine oxidase inhibitor (MAOI) antidepressant efficacy in both disorders, along with evidence suggesting a dysfunction in the serotonergic and noradrenergic neurotransmitter systems, might further provide an understanding of the common mechanisms underpinning this comorbidity.²¹⁷⁻²¹⁹ More recently, with the expansion of genetic studies, migraine and depression were reported to be independently associated with a functional genetic variant.^{220,221}

Evidence and treatment recommendations. The available evidence supports adoption of the following recommendations:

1. Individuals with depression should be screened for migraine using standardized and validated questionnaires that range from a simple 3-item questionnaire (the ID Migraine)²²² or a more detailed questionnaire that can distinguish different subtypes of migraine, such as the Structured Migraine Interview questionnaire.²²³

2. Somatic treatments such as TMS or vagus nerve stimulation (VNS) have shown promise in the treatment of depression and migraine (level 3).

3. Psychotherapeutic approaches, including patient education, CBT, and biofeedback, have a role in both conditions. Evidence-based literature is seldom available to support such effectiveness for comorbid depression and migraine (level 3).

4. There are no RCTs available to establish efficacy

TABLE 3
Evidence for migraine prophylactic treatment

Drug group	Level of Evidence	Comments
Antidepressants	—	—
Amitriptyline	1	Most commonly used
Citalopram	2	Tested in subjects with migraine and depression
Escitalopram	2	Tested in migraine without depression
Fluoxetine	2	May worsen headache
Sertraline	3	May worsen headache
Paroxetine	3	May worsen headache
Bupropion	3	—
Mirtazapine	4	Individual case reports
Venlafaxine	1	—
Duloxetine	3	—
Antiepileptics	—	—
Gabapentin	2	—
Lamotrigine	3	—
Topiramate	1	May worsen depression
Valproate	1	First-line migraine prophylaxis
Beta blockers	—	—
Propranolol	1	—
Calcium channel blockers	—	—
Verapamil	2	—

of antidepressant treatment in individuals with both migraine and depression. Amitriptyline and, to a lesser extent, SSRIs and serotonin-norepinephrine reuptake inhibitor (SNRIs), have all shown a significant effect on migraine treatment in case control and observational studies (levels 2 and 3).²²⁴

5. **TABLE 3** shows the most commonly used medications for the prophylactic treatment of migraine that overlaps greatly with the treatment of depression.

6. Although SSRIs are the first-line treatment for depression,²²⁵ in the presence of migraine, SSRIs may exacerbate migraine headaches (level 2).

7. Combination therapy is recommended to control the symptoms of migraine in depressed individuals. Such combination therapy may include anticonvulsants such as valproate, beta blockers, or calcium channel blockers (level 1).

Multiple sclerosis

MS has been historically regarded as a demyelinating disease, but axonal damage has been increasingly implicated, especially in the progression of disability.²²⁶ According to an atlas produced by the World Health Organization, the prevalence of MS in Canada is 132.5 per 100,000,²²⁷ one of the highest in the world. MDD is an important issue for individuals with MS.²²⁸

Epidemiology of comorbidity. Epidemiologic studies indicate that the annual prevalence of MDD is 16%²²⁹ and the lifetime prevalence may be as high as 50%.²³⁰⁻²³² These prevalence estimates are approximately 3 times higher than corresponding general population frequencies and may contribute to the high suicide rates reported in MS.²³³⁻²³⁶ Approximately 1% of men and 0.5% of women with MS die by suicide during the first 10 years after diagnosis.²³⁴ Female sex, being under the age of 35, experiencing high stress, and having a family history of MDD may all be associated with high MDD prevalence in this population.

Etiologic mechanisms of comorbidity. The etiology of MDD in MS is complex and poorly understood. Presumably it is at least partially related to the neurologic impact of MS, because lesion location and regional cerebrospinal fluid volume are correlated with major depression.²³⁷ However, bidirectional effects (an effect of major depression on MS course or outcome) also may be important. For example, treatment of depression may improve medication adherence²³⁸ and may even be associated with favorable immunologic changes.²³⁹

Treatment guidelines. Diagnosing depression can be complicated in the context of MS. Pseudobulbar affective changes, which are common in MS,²⁴⁰ can superficially resemble depressive episodes. Also, irritability is believed to be a common manifestation of major depression in individuals with MS, often overshadowing symptoms of sadness and anhedonia, whereas symptoms such as fatigue and cognitive dysfunction are found in both illnesses. These symptoms often occur with increased intensity or with a change in quality contributing to the diagnosis of MDD in people with MS.²⁴¹

Current evidence supports adoption of the following recommendations:

1. The literature of treatment studies is small but has generally reported positive outcomes.²²⁸ In addition to a few uncontrolled studies,²⁴²⁻²⁴⁴ 3 controlled trials of antidepressant medication for the treatment of depressive

disorders have been published.²⁴⁵⁻²⁴⁷ These studies evaluated desipramine, sertraline, and paroxetine, respectively. A meta-analysis has confirmed the positive impact of antidepressant treatment in MS when data from all 3 studies are combined.²⁴⁸ Use of antidepressants in this population should strongly be considered (level 2).

2. A meta-analysis found that psychotherapies emphasizing coping strategies are more effective than those focusing on insight²⁴⁹ (level 2).

3. Due to issues with fatigue, orthostatic hypotension, balance, cognitive issues, and bladder problems, antidepressants with significant sedating or anticholinergic side effects should be avoided (level 3).

4. The prevalence of BD is markedly elevated in MS,^{232,250} suggesting that people with MS should be monitored for hypomanic and manic symptoms while they are being treated with antidepressant medications (level 4).

Epilepsy

Epilepsy is a chronic neurologic disorder that often manifests with recurrent seizures caused by excessive and disorderly electrical discharge of nerve tissue.²⁵¹ Approximately 5% of the general population will have epilepsy in their lifetime,²⁵² and depression is the most common comorbid psychiatric disorder associated with this seizure disorder. Comorbid BD has been reported, but the frequency of BD is less common than is unipolar depression.²⁵³

Epidemiology of comorbidity. The available epidemiologic data suggest that the relationship between depression and epilepsy is bidirectional in nature. The lifetime prevalence of depression in individuals with epilepsy ranges from 6% to 50%, exceeding rates found in the general population.²⁵⁴ Depression that is temporally related to seizure occurrence (preictal, ictal, and postictal depression) generally resolves with adequate control of epilepsy but can still be quite debilitating. Interictal depression, the most common seizure-related depression in epilepsy, impacts between 30% and 70% of those with epilepsy, presents with chronic symptoms with endogenous features, and is associated with severe impairment in ADLs and social functioning.²⁵⁵ In addition to the evidence supporting an increased risk of depression onset and progression with epilepsy, a few population-based studies have shown that the history of depression increases the likelihood of having seizure 3- to 6-fold, even after controlling for pharmacologic treatment for depression.^{256,257} This impacts outcome, as comorbid depression is one of several risk fac-

tors associated with increased suicide in patients with epilepsy, and has a mortality rate 10 times higher than that of the general population.²⁵⁴ Depression increases the experience of burden from seizures and affects all domains of quality of life even after controlling for seizure frequency, severity, and other psychosocial variables.²⁵⁴

Etiologic mechanisms of comorbidity. Seizure focus in temporal and frontal lobe epilepsy has been frequently associated with depression. Complex partial seizures (temporal lobe epilepsy) with auras of psychological symptoms (depersonalization, forced thinking, déjà vu, fear, depression, pleasure, illusions, hallucinations, and amnesias) are more commonly associated with MDD than are seizures without auras or with auras of motor and sensory symptoms²⁵⁸ suggesting that depression in epilepsy may result from disturbances in the limbic system. The findings of increased density of 5-HT₂ receptors in mesiotemporal and prefrontal areas and decreased binding of 5-HT_{1A} receptors in patients with epilepsy may also play a role in the development of depression in patients with epilepsy.^{259,260} In addition to biological factors, psychosocial factors such as poor adjustment to epilepsy, stigma, discrimination, loss of driving privileges, limited job opportunities because of seizure precautions, change of jobs, and lack of social and family support may also contribute to stress and depression in these vulnerable patients.²⁵⁴ Approximately 50% of epileptic patients with depression also have a family history of psychiatric disorder, indicating a shared vulnerability.²⁶¹ Antiepileptic drugs (AEDs) that have adverse effects on mood and cognition may also contribute to depression comorbidity, and phenobarbitone, primidone, topiramate, tiagabine, and vigabatrin can all exert negative effects on mood. The potential depressogenic effect of these AEDs may be related to potentiation of the gamma-aminobutyric acid (GABA) system, folate deficiency, forced normalization, and polytherapy.²⁶² Conversely, AEDs such as lamotrigine, carbamazepine, and valproate, which potentiate serotonin neurotransmission, have antidepressant properties.²⁶³

Several lines of evidence suggest that common pathogenic mechanisms are related to the comorbid association between epilepsy and depression. The diminished serotonergic and noradrenergic functions implicated in the pathogenesis of depression have also been shown to facilitate the kindling process of seizure foci,²⁶⁴ while other putative common pathogenic

mechanisms include dysregulation in HPA axis, glutamate, and GABAergic system.^{265,266} Animal studies have shown that increased interleukin-1 beta (IL-1beta) signaling in the hippocampus associated with status epilepticus may lead to dysregulation in HPA axis and raphe-hippocampal serotonergic neurotransmission, causing depression,²⁶⁷ while the use of antidepressants with proconvulsant properties (bupropion, maprotiline, and amoxapine) may exacerbate seizure problems and should be used only after careful clinical consideration.^{268,269}

The increased comorbidity of BD with epilepsy also may be related to underlying common neurobiological mechanisms between these 2 disorders.²⁷⁰ The kindling process has been implicated in both the recurrence of seizures and the episodic nature of BD, and changes in second messenger systems (G-protein, phosphatidylinositol, protein kinase C, myristoylated alanine-rich C kinase substrate, calcium activity) have been reported in both conditions. Alternatively, antkindling, calcium antagonism, and potassium outward current modulation have been suggested as the basis for antiepileptic and mood-stabilizing effects of AEDs.^{270,271}

Evidence of treatment efficacy and safety.

1. With respect to antidepressants, only 1 published randomized, placebo-controlled, double-blind study examined the efficacy and safety of antidepressants in this population. It showed that mianserin or amitriptyline can be used in patients with epilepsy²⁷² (level 2).

2. No controlled data are available to evaluate the safety and efficacy of first-line antidepressants (SSRIs, SNRIs) in depression associated with epilepsy. In 2 open, uncontrolled studies, citalopram was found to be effective in the treatment of interictal depression (level 3).^{273,274} In one of these 2 studies, citalopram was associated with reduction in seizure frequency.²⁷⁴ Some authors have recommended the use of escitalopram based on its low potential for P450 enzyme pharmacokinetic interactions with AEDs²⁷⁵ (level 4).

3. Sertraline in the dose range of 50 to 200 mg and venlafaxine in the dose range of 75 to 225 mg have also been recommended by experts based on their clinical experience²⁵⁴ (level 4).

4. In a secondary analysis of a randomized, double-blind, placebo-controlled study, lamotrigine treatment has been shown to improve depressive symptoms independent of seizure reduction in patients with generalized seizure.²⁷⁶ In an open-label, multicenter study involving

epileptic patients age ≥ 50 , lamotrigine add-on treatment for epilepsy showed efficacy in the reduction of depressive symptoms²⁷⁷ (level 3).

5. The combination of TCAs and SSRIs has been suggested for resistant depression in patients with epilepsy²⁷⁸ (level 4).

6. There are no published controlled data available on the efficacy of psychosocial interventions in the treatment of depression associated with epilepsy. Several psychosocial interventions, such as relaxation therapy, CBT, and biofeedback, and educational interventions have been used to reduce depression and seizure frequency and improve quality of life, but a Cochrane systematic review of these studies found no reliable evidence to support the use of these interventions.²⁷⁹ Two open, controlled trials, however, found CBT to be effective in reducing depression among patients with epilepsy^{280,281} (level 3).

Treatment recommendations. Current evidence supports adoption of the following recommendations:

1. Because depression is more highly prevalent in patients with recurrent seizures than in seizure-free patients, the first step in the effective treatment of comorbid depression with epilepsy is to control the seizures with AEDs.

2. Seizure-free patients also are at risk in special situations. Even after the postsurgical control of seizures, patients who underwent anterotemporal lobectomy were at greater risk of depression.²⁸² The appearance of depression in patients with better seizure control with AEDs (forced normalization) has been reported.²⁸³

3. Anticonvulsants with potential depressogenic properties or increased suicidal risks (GABAergic AEDs with no serotonin reuptake inhibition) such as phenobarbitone, primidone, tiagabine, vigabatrin, felbamate, and topiramate should be avoided, if possible. If the onset of depression is temporally related to the initiation or upward titration of dose of these AEDs, then lowering the dose or switching to anticonvulsants with mood-stabilizing properties such as lamotrigine, valproic acid, and carbamazepine has been recommended (level 4).²⁵⁴ If potential depressogenic AEDs produce the best seizure control, the depressive episodes triggered by these AEDs can be symptomatically treated with antidepressants.²⁵⁴

4. Selection of antidepressants: SSRIs with minimal P450 enzyme pharmacokinetic interactions, including citalopram, escitalopram, and sertraline, that can be used safely in combination with AEDs are recom-

mended as second-line treatment since these medications have only level 3 evidence.^{273,274,284} However in the absence of first-line treatment recommendations, these medications should be considered the preferred choice. Switching to venlafaxine (75 to 225 mg) can be tried as third-line treatment if SSRI treatment fails.²⁵⁴ The antidepressants with the strongest proconvulsive properties, such as bupropion, maprotiline, and amoxapine, should be avoided. TCAs and MAOI antidepressants are considered only in the treatment of resistant depression; otherwise, treatment with TCAs should be avoided because of drug interactions, which result in decreases in epileptic threshold. Polypharmacy of antidepressants, higher doses of antidepressants, and rapid titration should be avoided to prevent decreases in the seizure threshold.

5. Lamotrigine as monotherapy or add-on treatment can be considered as second-line treatment for unipolar depression associated with epilepsy (level 3). Evidence for BD depression comorbid with epilepsy is not available.

6. Other considerations for resistant depression include the following:

CBT in combination with SSRIs can be tried in patients who fail to improve with SSRI monotherapy.

Supplementation with folate can be considered, as folate deficiency associated with the use of AEDs may contribute to depression.²⁶²

ECT can be considered for resistant depression associated with epilepsy, as it has both anticonvulsive and antidepressant effects.^{285,286} Similarly, VNS can be considered to treat both resistant MDD and BD depression associated with controlled or intractable epilepsy.^{287,288}

Osteoporosis

Osteoporosis is a chronic disease that affects approximately 26% of women age ≥ 65 .^{289,290} A 50-year-old woman has approximately a 40% chance of sustaining an osteoporotic fracture^{291,292} and a 14-year-old girl has a 17% chance of sustaining a hip fracture at some point in her lifetime.²⁹³ One of the few illnesses with a greater disease burden than low bone-mineral density (BMD) is MDD; it has been projected that MDD will be the greatest cause of disability worldwide by 2020.²⁹⁴ This is not simply attributed to psychiatric morbidity, and in fact, MDD has been linked to a host of physical illnesses, mitigated to a large extent by side effects of pharmacotherapy.²⁹⁵ Recent evidence highlights the fact that impaired bone health may soon be joining this growing list.

Epidemiology of comorbidity. The possibility of an association between SSRI use and low BMD has sparked a recent rise in studies investigating the clinical implications of antidepressant treatment on bone health. A number of large population-based studies have found associations between depression and bone density, specifically mediated by SSRI use.²⁹⁶⁻²⁹⁹ Not all studies investigating the association between SSRI use and BMD have found that SSRI use is associated with reduced bone density, and 3 small studies have demonstrated no connection.³⁰⁰⁻³⁰² Chronic use of mood stabilizers also may adversely affect bone density, although the relationship has not been fully elucidated. Bone homeostasis is a complicated and active process requiring parathyroid hormones, adequate serum calcium through intestinal absorption and renal reabsorption, and vitamin D. Putative mechanisms of bone loss include liver induction causing increased vitamin D breakdown, calcitonin deficiency, and effects on calcium absorption. Studies show decreased BMD with the use of benzodiazepines, carbamazepine, valproate, gabapentin, and oxcarbazepine.^{303,304} Lithium is less likely than some other medications to affect BMD in terms of bone turnover, but it causes increases in parathyroid hormone and affects renal calcium reabsorption, which leads to decreased mineral density.³⁰⁵

Etiologic mechanisms of comorbidity. A functional role for 5-HT in bone was first documented in 2001, when Blizotes and colleagues demonstrated the presence of neurotransmitters, receptors, and transporters in osteoblasts and osteoclasts.³⁰⁶⁻³⁰⁸ This work provided evidence of the role of serotonin in bone metabolism and a mechanism through which SSRIs may influence bone health.³⁰⁶

Depression also has been linked to decreased BMD in some,^{300-302,309} but not all,³¹⁰⁻³¹² studies. Several clinical studies examining BMD in depressed medication users and nonusers demonstrated that pharmacologic treatment may independently impact bone health, while physiologic and hormonal changes associated with depressive symptoms may magnify the adverse side effects of SSRIs.^{297-299,313,314} Therefore, it is possible that depression, in combination with pharmacotherapy, may have an additive negative effect on BMD.

Depression has been hypothesized to influence bone through inflammation, physical inactivity, falls, hypercortisolism, or hypogonadism. Another interesting and potentially modifiable link between bone and depression is vitamin D status. Decreased outdoor exposure associ-

ated with a mood disorder may result in lower vitamin D levels, but the few epidemiologic studies of vitamin D and depression have produced inconsistent results and generally have had substantial methodologic limitations. Recent findings from a randomized trial³¹⁵ suggest that high doses of supplemental vitamin D may improve mild depressive symptoms, but important questions regarding its efficacy in more severe depression remain.³¹⁶

Treatment recommendations. Current evidence supports adoption of the following recommendations:

1. The vastly growing body of research on mood disorders and their effect on bone health suggests that this relationship is complex, and interpreting these findings has proved to be challenging. Patients age >40 with long-term SSRI exposure (>2 years) should be routinely screened for bone density via dual-energy X-ray absorptiometry (level 2).

2. The data related to long-term use of some mood stabilizers are more definitive, however, and we know that exposure is directly related to decreased BMD. Patients receiving long-term exposure to these medications should be routinely screened for bone density (level 1).

3. For adults age >50 who are at moderate risk of vitamin D deficiency, supplementation with 800 to 1000 IU (20 to 25 mcg) of vitamin D₃ daily is recommended³¹⁷ (level 2).

CONCLUSIONS

Mood disorders are highly prevalent in patients with chronic medical conditions. Comorbid depression significantly increases disability, morbidity, and mortality in medically ill patients. This review summarizes the comorbid bidirectional relationship between mood disorders and several common medical conditions and provides evidence-based treatment recommendations. The most important message from the literature on treatment of depression in patients with comorbid medical conditions is that depression in medically ill patients is treatable. Failing to provide appropriate treatment to a medically ill patient with clinically diagnosed depression may adversely affect medical outcomes. Given the paucity of randomized controlled trials in this area, future studies are needed to examine the effect of treatment interventions on prevention and treatment of comorbid depression as well as medical outcomes. ■

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