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REVIEW ARTICLE

The CANMAT task force recommendations for the management of patients with mood disorders and comorbid medical conditions: Diagnostic, assessment, and treatment principles

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BACKGROUND: Medical comorbidity is commonly encountered in individuals with major depressive disorder (MDD) and bipolar disorder (BD). The presence of medical comorbidity has diagnostic, prognostic, treatment, and etiologic implications underscoring the importance of timely detection and treatment.

METHODS: A selective review of relevant articles and reviews published in English-language databases (1968 to April 2011) was conducted. Studies describing epidemiology, temporality of onset, treatment implications, and prognosis were selected for review.

RESULTS: A growing body of evidence from epidemiologic, clinical, and biologic studies suggests that the relationship between medical illness and mood disorder is bidirectional in nature. It provides support for the multiplay of shared and specific etiologic factors interlinking these conditions.

CONCLUSION: This article describes the complex interactions between medical illness and mood disorders and provides a meaningful approach to their comorbid clinical diagnosis and management.

KEYWORDS: major depressive disorder, mood disorder, bipolar disorder, comorbidity, medical illness

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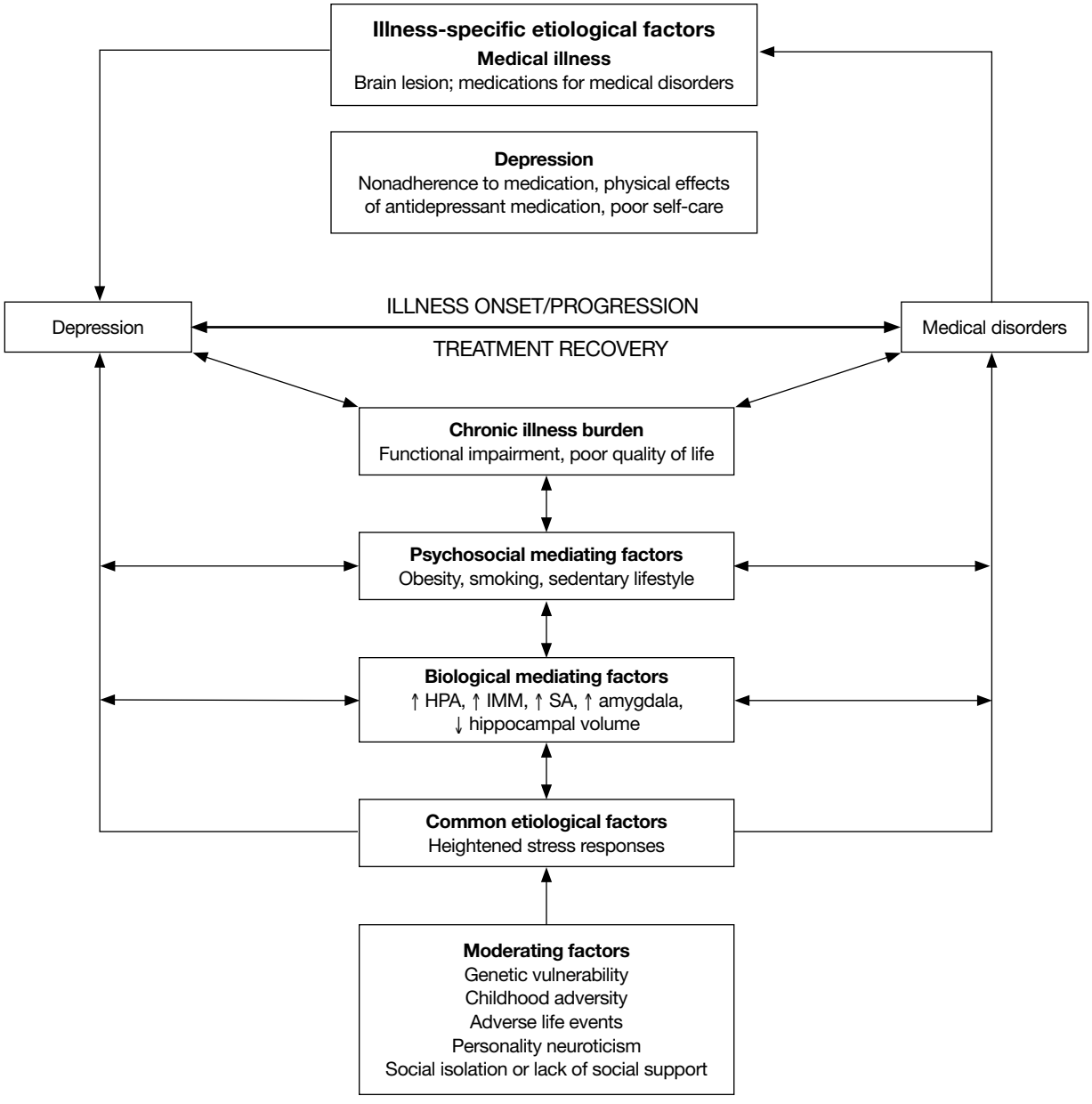
INTRODUCTION

The comorbidity between depression and medical illness has become an increasingly important clinical and global public health issue. Several medical conditions are associated with increased risk of depression,

FIGURE 1
Interactions between depression and medical disorders



HPA: hypothalamic-pituitary-adrenal; IMM: immunomodulator; SA: striatal activity.

which responds less robustly to antidepressant treatment when medical illness coexists. Conversely, depression is associated with increased morbidity, mortality, and chronic disease burden in patients with medical disorders.[1] The comorbidity model conceptualizes the coexistence of depression and medical illness, elucidating a definable relationship between these conditions. This model emphasizes a bidirectional association, with each condition having a negative impact on the onset, course, prognosis, and treatment of the other.[2]

TABLE 1
Depression as a risk factor for the development of medical illness

Medical illness	Comments
Coronary artery disease/ischemic heart disease	Depression increases the risk by 1.5 to 2 fold[3]
Ischemic stroke	Depression increases the risk by 1.8 fold[4]
Epilepsy	Depression increases the risk by 4 to 6 fold[5]
Alzheimer's disease	Depression increases the risk by 2.1 fold[6]
Diabetes mellitus (type II)	Depression increases the risk by 60%[7]
Cancer	Depression and life stressors increase the risk by 1.35 to 1.88 fold[8,9]
HIV	Bipolar spectrum conditions (hyperthymic/cyclothymic) may increase the risk for HIV infection[10]

HIV: human immunodeficiency virus.

A growing body of evidence provides support for the multi-play of shared and specific etiological factors interlinking both medical and mental illness (**FIGURE 1**).

Comorbid bidirectional relationship

Depression as a risk factor for the development and progression of medical illness. Several epidemiologic studies suggest that prior episodes of depression may be an important risk factor for the onset of diseases such as coronary artery disease, stroke, diabetes mellitus, and epilepsy (**TABLE 1**).[3-10] There is also evidence that depression adversely affects medical outcomes (**TABLE 2**).[11-17] Approximately 52% to 78% of studies showed an association between depression and increased mortality rates, even after controlling for the confounding effects of medical disease severity.[2,18] Comorbid depression is associated with increased use of medical resources and costs, amplification of physical symptoms, additive functional impairment, and poor quality of life.[2,19,20] Depression likely increases medical morbidity through biological mechanisms such as increases in hypothalamic-pituitary-adrenal (HPA) axis activity, sympathetic stimulation, pro-inflammatory cytokine levels, and behaviors such as nonadherence to medical treatment regimens, neglect of self-care, physical inactivity, poor diet, and substance use.[2]

Medical illness as a risk factor for the development and progression of depression. Medical conditions likely contribute to the development of depression through direct physiological mechanisms (eg, brain injury and thyroid deficiency) and stress-related physiologic mechanisms (eg, increased activation of HPA and the immunologic system) associated with the physical condition or disability. HPA axis overdrive and elevated levels of pro-inflammatory cytokines are found in several medical conditions, including cardiovascular disease, stroke, and cancer. Besides biologic factors, psychosocial factors related to illness burden and disability also may contribute to depression related to medical illness.[2] The relative contributions of these mechanisms may vary from person to person. The presence of medical illness may negatively influence the prognosis of comorbid depression. Studies comparing treatment outcome in major depressive disorder (MDD) with or without comorbid medical illness suggest that depression in the medically ill may respond poorly or slowly to antidepressants and have higher relapse rates.[21]

Shared etiological mechanisms in the comorbidity of depression and medical illness. Heightened stress responses—increased activation of HPA and the immunologic system—may serve as both a cause and consequence of depression and chronic medical illness. Genetic vulnerability, childhood adversity, stressful life events, personality disposition, and lack of social support are all known to trigger the stress reaction and to increase the risk of depression (**FIGURE 1**). Several recent studies also have shown that early adverse psychosocial experiences such as maltreatment, social isolation, socioeconomic disadvantage, and perinatal problems (eg, low birth weight and preterm birth) increase the risk of depression and comorbid medical conditions.[22-24] Individuals with early adverse events may have enduring immune and HPA axis abnormalities that confer vulnerability both to depression and medical illness. The functional impairment associated with certain medical illnesses also may increase the physiological stress response, which, in turn, may worsen depression and physical health outcomes.[2]

Contribution of medications to the comorbidity of depression and medical illness. Pharmacologic treat-

ment of depression may contribute to, or complicate, a coexisting medical condition. Evidence from large epidemiological studies suggests that selective serotonin reuptake inhibitors (SSRIs) may increase the risk of gastrointestinal and subcutaneous bleeding, probably due to their antiplatelet activity,[25] and have been linked to osteoporosis as well.[26] There is also evidence that tricyclic antidepressants (TCAs) may cause orthostatic hypertension, decreased heart-rate variability, and QT prolongation.[27] Bipolar disorder treatment, such as the anticonvulsants valproate and carbamazepine, have been linked to bone loss, ovarian problems, hematological abnormalities, and liver problems. Similarly, the mood stabilizer lithium is known to impact thyroid and renal function[28] (**FIGURE 2**).

Conversely, comorbid depression could be related to medications used to treat physical illness. Corticosteroids, cancer chemotherapeutic agents (eg, vincristine, vinblastine, and procarbazine l-asparaginase interferon), and antihypertensive medications (eg, reserpine, methyldopa, and β-blockers) have all been implicated in the pathogenesis of depression.[29,30]

Variations in comorbid relationships. It is crucial for clinicians to understand the nature of the bidirectional relationship between a medical illness and depression. The etiological factors contributing to comorbid depression may vary from person to person. In the comorbid bidirectional model, the role of depression as a cause and/or consequence of medical illness is variable. Furthermore, depression may serve as a risk factor for a medical condition as well as for comorbid depression in the same patient.

For example, the literature suggests that antecedent depression increases the risk of stroke[4] and post-stroke depression.[31] It is also possible that in a given patient the bidirectional relationship between a medical illness and depression may be asymmetrical, and psychosocial factors may predominate in the etiology of comorbid depression. Hence, the evaluation of the patient-specific relationship between 2 conditions and etiological factors for comorbidity are vital for individualized treatment.

TABLE 2
Depression as a risk factor for poor medical outcomes in patients with existing medical illnesses

Medical illness	Findings
Cardiovascular disease	Depression increases cardiac mortality by 3.5 to 4 fold and predicts poor prognosis in patients with pre-existing coronary disease[11]
Stroke	Depression increases mortality by 3.4 fold and adversely affects functional recovery[12,13]
Epilepsy	Depression increases burden from seizures and decreases quality of life[14]
Diabetes mellitus	Depression increases the earlier onset of vascular complications, functional disability, and death[15]
Cancer	Depression increases mortality by 2.6 fold[16]
HIV	Depression is associated with illness progression to AIDS and higher mortality rates[17]

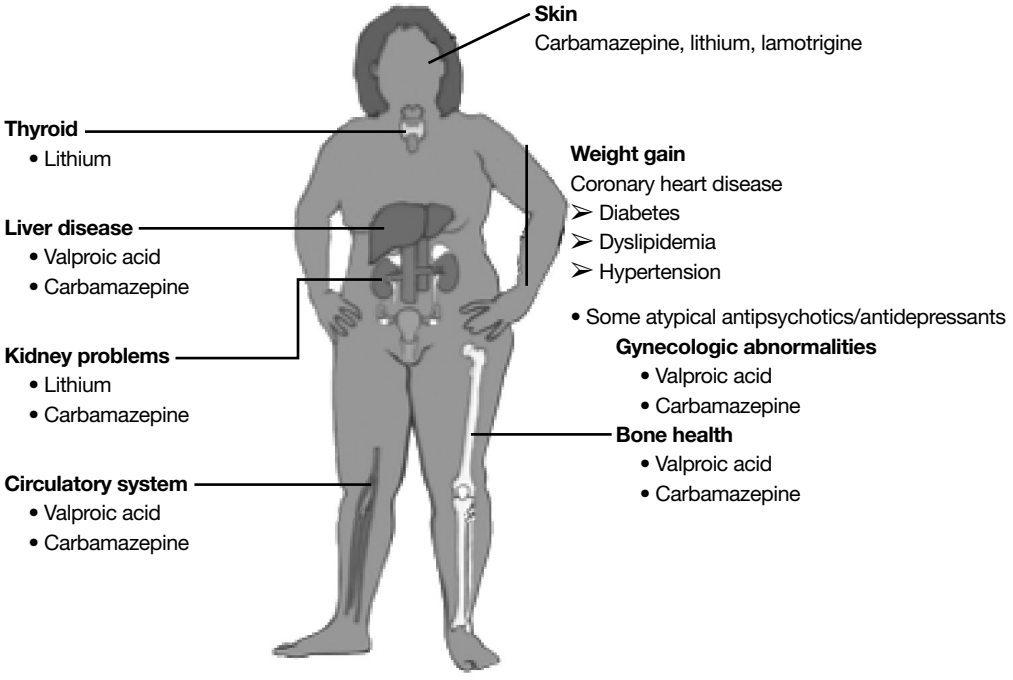
AIDS: acquired immune deficiency syndrome; HIV: human immunodeficiency virus.

Clinical diagnosis of depression in the medically ill

Depression due to a general medical condition is considered secondary depression, meaning that the depression is physiologically caused by the medical illness. Secondary depression is different etiologically from depression without medical illness, which is known as primary depression. However, in exploring this relationship, investigators have found few or no differences in the clinical presentation and course of primary vs secondary depression,[32-34] questioning the nosological status of secondary depression as a distinct clinical entity. Both share common etiological mechanisms such early life stress and genetic/familial predisposition,[22,35-37] and primary depression may increase the risk of depression secondary to medical illness.[31] Hence, the evaluation of depression in the context of a comorbidity model is crucial for proper management. The current understanding is that depression comorbid with a medical disorder represents a continuum of depressive diathesis. Because the distinction between primary and secondary depression remains blurred, depression in the context of medical illness is commonly referred to as comorbid depression or depression associated with medical illness.

The essential first steps in the management of depression comorbid with a medical disorder are the correct diagnosis of depression in the medically ill, and, conversely, an awareness of medical illness in patients with depression. Clinically, it often is difficult

FIGURE 2
Body systems at risk of medication side effects



Source: Adapted from Taylor V, Schaffer A. Guidelines for the safety monitoring of patients with bipolar disorder. Mood and Anxiety Disorders Rounds. 2010;1(4):1-6.

to differentiate some symptoms related to medical diseases, such as anorexia, weight loss, sleep disturbances, decreased libido, fatigue, and anhedonia, from the vegetative symptoms of depression. The presence of symptoms such as guilt, worthlessness, and suicidal ideation are more common in MDD than as part of a sickness syndrome, helping to guide a diagnostic approach.[38] Cohen-Cole and colleagues[39] suggested 4 approaches to assess depression in the medically ill. In the "inclusive approach" all depressive symptoms are counted, irrespective of whether they are related to medical illness. In the "exclusive approach" the non-discriminatory somatic and vegetative symptoms are excluded and only depression-specific mood and cognitive symptoms such as anhedonia, feelings of guilt, hopelessness, worthlessness, and suicidality count toward a diagnosis of depression. In the "etiological approach" a symptom is counted only if it is determined not to be caused by the medical illness, while in the "substitutive approach" the psychological symptoms—mood and cognitive symptoms—replace the vegetative symptoms.

Among these approaches, the inclusive approach is considered to be the most appropriate in the clinical setting for optimal patient care, whereas the exclusive approach is appropriate for research studies. While the inclusive approach may lead to overdiagnosis of depression in clinical practice, this risk appears to be small compared with the risk of depression underdiagnosis. For example, in stroke patients, the standard inclusive approach showed specificity in the range of 95% to 98% and sensitivity of 100% in the diagnosis of post-stroke depression compared with other approaches.[40] The inclusive approach also has more clinical utility than other approaches because it discourages simple dichotomies between vegetative symptoms due to depression and medical illness. Data support a common biological basis of these symptoms, such as elevation in immunological markers in both depression and medical illness independently, as well as higher immunological disturbance in patients with both conditions compared with patients with a medical disorder without depression.[38] Adjustment disorder

with depressed mood and subsyndromal depression may evolve into MDD in vulnerable patients who are at increased risk for depression. The foregoing patients will require longitudinal evaluation.

The factors that suggest a medical illness may be a cause or contributor to depression include a temporal relationship between the illnesses, an atypical clinical picture of depression that includes cognitive impairment and personality changes,[41] the presence of other emotional syndromes such as emotionalism, catastrophic reaction,[42] depression improving with the treatment of medical condition,[43] worsening of depression with worsening of medical disorder, and poor response to antidepressant treatment.[21,44] Depression emerging after initiation of medications that are known to cause or contribute to depression, or presence of worsening depression with an increase in medication dosage, may suggest that medication could be a contributing factor for comorbid depression in medically ill patients. Consistent with the biopsychosocial model and multifactorial origin of comorbid depression in the medically ill, the presence of severe physical disability and psychosocial stressors associated with a medical condition could be a risk factor for comorbid depression. This should be considered in the diagnostic formulation of depression in the medically ill.

Conversely, the factors that suggest depression may be a contributor to the onset of medical illness include a history of depression prior to the onset of illness, research supporting a link between antecedent depression and medical illness, and the biological plausibility of etiologically linking depression to the medical illness. The factors that suggest that depression may be a contributor to medical illness progression include clinical history suggesting worsening of medical illness after the onset of depression, improvement in the medical illness following improvement in depression, evidence of poor compliance with medications for medical illness, and lack of adherence to diet and exercise regimens due to poor motivation, physical inactivity, increased smoking and drinking, and overeating in the context of depression. Furthermore, the presence of side effects of antidepressants and mood stabilizers may complicate the course and treatment of physical illness.

Screening instruments

A key component of accurate diagnosis is the use of depression screening instruments in specialized medical clinics (eg, neurology, cancer, cardiology) to promote early detection. Several clinician-administered and self-reported depression rating scales are commonly used for screening for depression associated with medical conditions[45] (**TABLE 3**).

Although these screening scales are not diagnostic instruments, they have clinical utility in routine screening for depression in specialized medical clinics. Scales that rely less on physical symptoms, such as the Beck Depression Inventory for Primary Care (BDI-PC), were found to be useful in screening for depression in medically ill patients.[46] The 9-item Patient Health Questionnaire is an especially useful clinical instrument for primary care physicians in diagnosing depression as well as assessing depression severity, because it includes symptom assessment and functional impairment to make a tentative diagnosis of depression.[47,48] Routine screening with simple probing questions about mood also would help detect depression in the severely medically ill and single-item interviews such as "Are you depressed?" or "Do you often feel sad or depressed?" have been shown to be useful in screening for depression in terminally ill and stroke patients.[49,50] These brief measures could be important tools for screening for depression both in the severely medically ill and in patients with communication deficits; the use of a visual analogue mood scale in screening for depression in stroke patients with aphasia and cognitive impairment is not recommended due to low sensitivity of the measure.[51]

Treatment considerations

Treatment of depression in medically ill patients should be comprehensive and collaborative in nature, involving primary care, medical specialists, nurses, psychologists, and social workers. Once the diagnosis of depression is established, the treatment should focus both on the psychiatric diagnosis as well as the contributing medical illness and related causative factors. Proper pain management and the treatment of medical conditions such as hypothyroidism and vitamin deficiencies, for example, may improve the depression comorbid with these disorders. In chronic medical conditions, depression should be treated with antidepressants and psychotherapy in accordance with current depression guidelines.

In principle, the selection of antidepressants should be based on level 1 or 2 evidence, documenting the efficacy and safety of a particular antidepressant in comorbid depression. In the event that the available evidence is inadequate or inconclusive, clinicians need to counsel

TABLE 3
Screening instruments used for evaluating comorbid depression in patients with medical illness

Screening instrument	Method of administration	Administration time	Assessment
Hamilton Depression Rating Scale (HAM-D)	Clinician administrated	20 to 30 minutes	Severity of depression
Montgomery-Åsberg Depression Rating Scale (MADRS)	Clinician administrated	5 to 10 minutes	Severity of depression
Symptom Check List 90-Revision (SCL-90-R)	Self report	15 minutes	Screens depression/other psychiatric comorbidity
Brief Symptom Inventory (BSI) (Abbreviated SCL-90-R)	Self report	10 minutes	Screens depression/other psychiatric comorbidity
Illness Distress Scale (IDS)	Self report	5 to 10 minutes	Severity of physical and emotional distress
Psychological Distress Inventory (PDI)	Self report	5 minutes	Severity of distress
Carroll Depression Rating Scale (CDRS)	Self report	5 minutes	Severity of depression
Geriatric Depression Scale (GDS)	Self report	5 minutes	Severity of depression
Zung Depression Scale (Zung)	Self report	5 minutes	Severity of depression
Beck Depression Inventory for Primary Care (BDI-PC)	Self report	5 minutes	Severity of depression
Beck Depression Inventory–Fast Screen for Medical Patients (BDI-FS)	Self report	<5 minutes	Severity of depression
Depression in the Medically Ill scale (DMI-10)	Self report	5 minutes	Severity of depression
General Health Questionnaire (GHQ)	Self report	Dependent on the version	Severity of depression
Patient Health Questionnaire (PHQ-9)	Self report	<5 minutes	Presence of depression
Medical Outcomes Study Depression Questionnaire (MOS-DQ)	Self report	<5 minutes	Presence of depression
Hospital Anxiety and Depression Scale (HADS)	Self report	<5 minutes	Severity of depression
Centre for Epidemiological Studies Depression Scale (CES-D)	Self report	10 minutes	Severity of depression

Source: Reference 45.

patients about the uncertainty regarding the effective treatment and select a medication as suggested in the general guidelines for the treatment of depression without medical comorbidity.

Pharmacologic issues related to coexisting medical illness/medication. Drug-drug interactions and drug-illness interactions should be considered when treating a patient for depression comorbid with a medical condition. Certain SSRIs, such as fluoxetine and paroxetine, are potent inhibitors of cytochrome (CYP) 450 isoenzymes, especially CYP2D6. Coadministration of these SSRIs with antiarrhythmic agents, such as flecainide, mexiletine, and propafenone, which are metabolized by the same isoenzyme, may cause accumulation of toxic levels of the antiarrhythmic drug.[52] There also is risk of bleeding associated with concomitant use of anticoagulants (eg, aspirin, warfarin), nonsteroidal anti-inflammatory drugs, and SSRIs.[25] P-glycoprotein (Pgp) is responsible for the efflux of several anticancer and cardiac medications.[53] Paroxetine and sertraline are potent inhibitors of Pgp and may increase the levels of Pgp substrates such as digoxin, and anticancer medications.

Whenever possible, the dual roles of some medications used in psychiatry treatment should be capitalized on, such as lamotrigine for seizure control and depression in patients with epilepsy,[54] or TCAs in headache-prone patients because their antimigraine prophylaxis

effect.[55] Antidepressants that have negative effects on specific medical illnesses should be avoided. For example, imipramine should not be used in patients with cardiovascular disease because of its antiarrhythmic effect.[56]

Depression in medically ill patients may respond poorly to antidepressants,[44] and depressive relapses are more common in MDD associated with comorbid medical conditions.[21] However, because the evidence-based information for the treatment of resistant comorbid depression is lacking, such depression should be treated in accordance with the current guidelines for treatment-resistant depression. This includes consideration of somatic treatments such as electroconvulsive therapy, transcranial magnetic stimulation, or vagal nerve stimulation.

Psychotherapy, education, and case management should be considered in the treatment of mild to moderately depressed patients. Variation exists in the efficacy of specific psychotherapies for comorbid depression. Cognitive-behavioral therapy was found to be effective in the treatment of depression in post-myocardial infarction patients, whereas problem-solving therapy was found to be effective in patients with post-stroke depression.[57-59] Hence, evidence-based selection of specific psychotherapies may be warranted.

CONCLUSIONS

There is a clear and significant association between various medical conditions and mood disorders. This comorbidity needs to be accurately diagnosed and properly treated in order to ensure optimal patient outcome for both conditions. ■

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