Treatment Considerations for Depression in Patients with Significant Medical Comorbidity

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In addition to being a strong psychological stressor in itself, medical illness is associated with risk factors that predispose patients to develop coexisting depression. Patients with conditions such as cancer, cardiovascular disease, and neurologic disorders are particularly prone to depression because these illnesses are severe, chronic, and often fatal. Because an antidepressant may exacerbate an underlying illness, leading to more serious side effects, agents with a poor tolerability profile or that act at multiple receptor sites should be avoided. In many cases, this precludes the use of tricyclic antidepressants and monoamine oxidase inhibitors, and favors the use of selective serotonin reuptake inhibitors and other new antidepressants because they have fewer anticholinergic, cardiac, or cognitive adverse effects. Depressed medically ill patients clearly benefit from antidepressant therapy. Because mental health influences prognosis and treatment outcome, primary care physicians should maintain a high index of suspicion for depression in patients with significant medical illness and aggressively treat the condition when indicated.

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Major depression is responsible for more days in nonpsychiatric hospitals and more days home from work than any other chronic illness except for severe, unstable coronary artery disease.[1] Even though at least 8 million people in the United States become depressed in any given year,[2] only one third to one half of those with major depressive disorder are properly diagnosed.[3] Family physicians have an increased burden to care for these patients because 3 of every 4 mental health visits present initially to the primary care setting.[4]

There is a trend toward increased prevalence of major depression in primary care clinics (5% to 10%) and inpatient medical wards (10% to 14%) compared with community samples (2% to 4%) (Figure 1).[5] In view of these statistics, it is not surprising that patients with chronic medical conditions, such as cancer, chronic lung disease, and arthritis, have a significantly higher lifetime prevalence of psychiatric disorders (46% to 60%) compared with patients with none of these conditions (33%; $P<.001$).[6] Thus, the prevalence of depression in medically ill primary care patients underscores the need for recognition and treatment of depression in the family medicine setting.

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RISK FACTORS

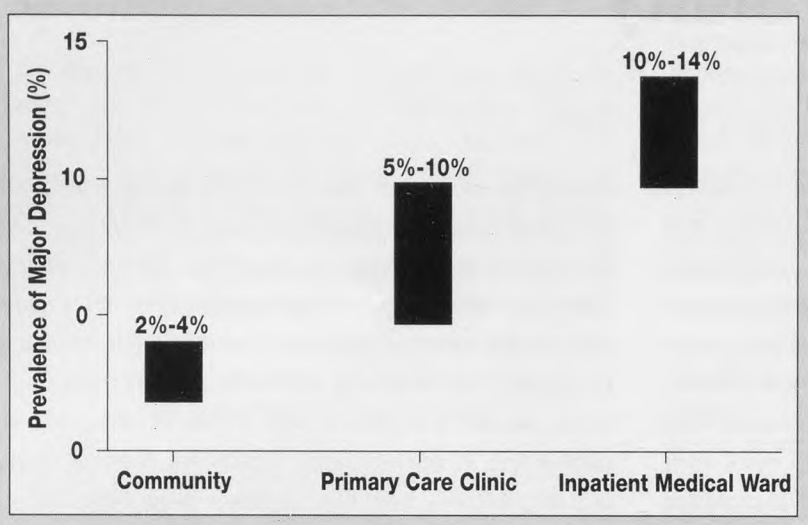
Some medical disorders have clearly been associated with higher incidences of depression. These include cancer (1% to 50%),[7,8] stroke (25% to 30%),[9-11] coronary heart disease (18% to 50%),[12-14] and Parkinson's disease (4% to 70%).[10,15-17] These epidemiologic data concur with the results from other studies, demonstrating that severe or chronic diseases are associated with a higher prevalence of depression.[6,18] Medically ill patients who are over 70 years of age,[19] hospitalized,[20,21] or institutionalized[22] are also more likely to develop depression.

DIAGNOSIS

It is expected that patients will react to a serious medical illness with some degree of demoralization or dysphoria. It is important to note, however, that noncompliance with or disregard for medical treatment by patients is a significant indicator of depression.[18] The diagnosis of depression should also be considered when somatic symptoms are out of proportion to the illness or when the symptoms have a

FIGURE 1

Relationship between the prevalence of depression and medical illness. Based on data from Katon and Schulberg.[5]



significant impact on functional status.[18] Somatic complaints that are exaggerated relative to the patient's medical illness or that are persistent or unresponsive to treatment are an indication that depression may underlie the medical illness.[20] The presence of a prior depressive episode or a positive family history for affective disorder should also raise the level of suspicion for depression. According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[23] patients may be diagnosed with a Major Depressive Disorder if at least five symptoms are present over a 2-week period. One of the diagnostic symptoms must be either a depressed mood or the loss of interest or pleasure. Symptoms that may be present nearly every day include a depressed mood, diminished interest or pleasure in most activities, significant weight loss or weight gain (eg, change of more than 5% of body weight), insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, decreased ability to think or concentrate, or recurrent thoughts of death or suicidal ideation.

Differential Diagnosis

Depression may coexist with medical illness. However, depression may also be a psychological response or a direct effect of a physical illness. Diagnosing depression in medically ill patients is further complicated by medication side effects or symptoms of the illness that mimic depression. For example, insomnia, anorexia, and fatigue are features that can be attributed to either a medical illness or depression.[24] Mood Disorder Due to a General Medical Condition is a disorder described in the DSM-IV as a persistent mood disturbance caused by the direct physiological effects of a general medical condition. Symptoms associated with the mood disturbance may include a depressed mood, diminished interest in activities, or elevated or irritable mood.[23] Specific symptoms that differentiate depression from manifestations of medical illnesses include suicidal feelings, a sense of failure or hopelessness, the feeling of being punished, diminished social interest, crying, indecision, and dissatisfaction (Table 1).[25-27] Psychomotor retardation (with the exception of hypothyroidism and Parkinson's disease) and feelings of guilt and self-reproach are other features of depression that are not usual consequences of medical illnesses.[26]

According to DSM-IV, a Substance-Induced Mood Disorder is a persistent mood disturbance that is associated with the direct physiological effects of a substance (ie, a drug of abuse, a medication, other somatic treatment for depression, or toxin exposure).[23] Thus, reviewing the medication profile can uncover potential iatrogenic sources of depression. Although a myriad of drugs have side-effect profiles that resemble depression,[28] drugs of abuse (eg, opiate, marijuana, and alcohol), antihypertensives (eg,

TABLE 1

Discriminators of Depression from Medical Illness

- Guilt and self-reproach
- Psychomotor retardation
- Recurrent suicidal thoughts (except for dialysis and HIV)
- Sense of failure
- Loss of social interest
- Feeling punished
- Persistent dissatisfaction
- Indecision
- Recurrent or persistent episodes of crying

HIV denotes human immunodeficiency virus. Based on data from Camaron[25]; Cassem[26]; and Clark, Cavanaugh, Gibbons.[27]

reserpine, propranolol, and methyldopa), and corticosteroids are frequently implicated (Table 2). If drug-induced depression is suspected, substituting an alternative agent or discontinuing the drug altogether will quickly uncover a drug-related side effect.[29]

Age may be helpful in determining whether depression or a physical illness is the primary disorder. Depression is more likely to develop in patients who are young (usually in their third decade of life) compared with older patients who develop medical illnesses (usually in their fifth decade of life).[25] Depression and medical illness may develop concurrently, but it is also possible that depression is masking a newly developing medical condition, such as Huntington's disease, multiple sclerosis, Cushing's disease, Parkinson's disease, systemic lupus, and human immunodeficiency virus (HIV) encephalopathy.[26] For example, spontaneous crying is indicative of severe depression, but it can also be a manifestation of neurologic disease.[30] To reduce the potential for misdiagnosis, case finding for depression in medically ill patients should be based primarily on the psychological state. Physical symptoms should be used only to support the diagnosis of depression after more specific screening methods have been utilized.

TABLE 2

Medications That May Induce Depression

Cardiovascular drugs
α-methyldopa
Reserpine
Propranolol
Guanethidine
Clonidine
Thiazide diuretics
Digitalis
Hydralazine
Procainamide

Antineoplastics
Azathioprine
6-Azouridine
L-asparaginase
Bleomycin
Cisplatin
Cyclophosphamide
Doxorubicin
Mithramycin
Vinblastine
Vincristine tranquilizers

Anti-Parkinsonian drugs
Amantadine
Bromocriptine
Levodopa

Antipsychotic drugs
Haloperidol
Fluphenazine

Sedative and antianxiety drugs
Benzodiazepines
Barbiturates
Choral hydrate
Ethanol

Anticonvulsants
Carbamazepine
Ethosuximide
Phenobarbital
Phenytoin
Primidone

Sedatives/tranquilizers
Barbiturates
Benzodiazepines
Ethanol
Major and minor

Anti-inflammatory/ anti-infective agents
Nonsteroidal anti-inflammatory agents
Ampicillin
Cycloserine
Dapsone
Griseofulvin
Isoniazid
Co-trimoxazole
Ethambutol
Disulfiram
Sulfonamides
Metoclopramide
Metronidazole
Nalidixic acid
Nitrofurantoin
Procaine penicillin
Streptomycin
Tetracycline

Stimulants
Amphetamines (withdrawal)
Caffeine
Cocaine (withdrawal)
Methylphenidate

Hormones
Oral contraceptives
ACTH (corticotropin)
Glucocorticoids
Anabolic steroids

Others
Cimetidine
Disulfiram
Methysergide
Phenylephrine
Ranitidine

Reproduced from Valente et al, 1994, with permission.[28]

Other Affective Disorders

Adjustment Disorder

Medically ill patients with depressive features, such as flat mood, tearfulness, or hopelessness, who do not meet the DSM-IV criteria for major depression may be suffering from an adjustment disorder. Adjustment disorder with depressed mood develops due to a maladaptive response to a stressful life event (eg, marital difficulties or a disabling general medical condition).[31] Once the stressor or its consequences have been removed, the adjustment disorder resolves within 6 months. Treatment consists of identifying the stressor, relating the symptoms to the stressor, and providing social support.[32] Because depressive features of affective disorders can develop into a full-blown major depression, patients should be continually assessed for changes in symptom severity.

Dysthymia

Dysthymia is another affective disorder that commonly occurs in patients with medical illness. Dysthymia is a milder, but more chronic, form of depression that is present for a majority of days during at least a 2-year period in adults.[23] Dysthymia usually begins insidiously during childhood or adolescence and, in children, continues for a least 1 year.[33] Even though it is considered to be less severe than major depression, untreated dysthymia causes a greater degree of physical and social impairment compared with many other chronic medical illnesses, such as hypertension and diabetes.[34]

IMPACT ON MEDICAL ILLNESS

Depressed medically ill patients perceive their general health as poor and tend to amplify somatic symptoms of their medical illness. As patients become less cooperative and motivated, the recovery period is prolonged and the likelihood for a positive outcome is decreased. Unrecognized depression may appear to be a worsening medical condition that leads to costly and unnecessary diagnostic tests and medications. Even if the medical condition is properly treated, severe limitations in physical function may persist if the depression does not remit.[35] This can eventually lead to increased mortality either by suicide or by worsening medical disease[36-38] and to an increased risk of substance abuse.[6] Other consequences of untreated depression include social and family dysfunction, failure to advance in school, and loss of productivity at work.

TREATMENT OPTIONS IN THE MEDICALLY ILL

Treatment options for depressed patients with severe medical comorbidity include nonpharmacologic approaches, medication, and a combination of medication and psychotherapy. One advantage of nonpharmacologic therapy is the lack of side effects that are commonly associated with antidepressant medications. Psychotherapy (eg, cognitive, interpersonal, and behavioral therapy) may be effective in patients with mild to moderate depression. However, it should be noted that many patients are unable to comply with or complete the full course of psychotherapy.[39] Patients who do not respond to nonpharmacologic therapy may respond to a combination of medication and psychotherapy or to medication alone.

Selecting an antidepressant is more of a challenge in the setting of medical illness because care must be taken to avoid agents that exacerbate the medical condition. Other factors to consider include potential antidepressant drug interactions and the effect of impaired renal, hepatic, or gastrointestinal (GI) function on drug metabolism and elimination. In some cases, antidepressant side effects can be exploited to provide a therapeutic benefit to both the depressive and medical illnesses. Antidepressant therapy should be tailored to the individual patient based on tolerability, prior response, and the potential clinical advantage that can be derived from the side effects of the drug. Based on these factors, treatment recommendations for various medical conditions are provided below (Table 3).

Neurological Disorders

It has been postulated that some central nervous system (CNS) disorders are associated with neurotransmitter imbalances that precipitate depression. Regardless of the mechanism, depression is a common consequence of neurological illnesses, such as Parkinson's disease, multiple sclerosis, and stroke.[26] Because of the impact on quality of life and ability to function normally, the choice of an antidepressant in this patient population is mainly directed toward avoiding agents with anticholinergic and orthostatic properties.

Stroke patients are usually elderly and have suffered some degree of cerebral insult. Thus, tricyclic antidepressants (TCAs) are less desirable because patients are more sensitive to the anticholinergic, sedative, and orthostatic side effects.[40] The monoamine oxidase inhibitors (MAOIs) also are not used because of orthostasis. Besides headache, the other commonly reported side effects of the selective serotonin reuptake inhibitors (SSRIs), namely nausea, sleep disturbance, and sexual dysfunction, do not exacerbate neurologic conditions and are safer to administer in stroke patients. The lower incidence of anticholinergic and orthostatic effects associated with the secondary amine TCAs (eg, desipramine and nortriptyline) also makes these agents an option.

Stroke patients or other patients with insult to the brain should not receive agents with notable seizure-inducing properties, such as bupropion, maprotiline, or clomipramine.[41] For cases in which hepatic enzyme-inducing antiepileptics (eg, phenytoin and

TABLE 3

Antidepressant Treatment Recommendations for Various Medical Conditions

Medical Condition	Antidepressant of Choice	Drugs to Avoid
Neurological disorders		
Parkinson's disease	Bupropion, venlafaxine	TCAs, MAOIs, SSRIs (if coprescribed with selegiline)
Stroke	SSRIs, possibly secondary amines	TCAs, MAOIs, bupropion
Alzheimer's dementia	SSRIs, nefazodone, venlafaxine	TCAs, bupropion, and fluoxetine if dementia accompanied with agitation
Cancer		
Severe cancer pain requiring opiates	TCAs, but watch for constipation	MAOIs
Cachexia	Sertraline, paroxetine, trazodone, nefazodone, TCAs, venlafaxine	Fluoxetine
Nausea	No specific advantages	Bupropion, SSRIs, venlafaxine
Endocrine disorders	No specific advantages	No specific disadvantages
Cardiac disease	SSRIs, bupropion, nefazodone	TCAs, venlafaxine in patient with high blood pressure, SSRIs with type IC antiarrhythmics (eg, encainide and flecainide)
Allergic conditions	No specific advantages	Coprescribing SSRIs, nefazodone, and fluvoxamine with terfenadine, astemizole

MAOIs denotes monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.
Based on data from Haig[7]; Cummings[15]; Reynolds[40]; Cunningham[41]; Schowersky and deVries[42]; Raskind[43]; Guze and Gitlin[44]; Maguire et al[45]; Jackson et al[46]; Glassman et al[47]; Veith et al[48]; McElroy et al[49]; Ragheb[50]; and DeVane.[51]

barbiturates) are added to preexisting TCA therapy, increased TCA doses may be needed to compensate for decreased serum concentrations. The SSRIs, particularly fluvoxamine and fluoxetine, may inhibit cytochrome P450 3A4 and 2C, resulting in increased levels of carbamazepine and phenytoin, respectively.[52] Therefore, selection of an agent in patients with seizure potential should take into consideration the antidepressant side-effect and drug-interaction profiles.

The pathophysiology of Parkinson's disease is attributed to decreased dopamine, norepinephrine, and serotonin and to increased acetylcholine levels in the CNS. The anticholinergic effects of the TCAs may improve impaired motor function, but they can also aggravate other Parkinsonian symptoms, such as cognitive deficits, constipation, somnolence, and urinary retention.[15] Some patients already receiving anticholinergic agents, such as benztropine and trihexyphenidel, may not be able to tolerate the additive anticholinergic symptoms when TCAs are coprescribed. In addition, TCA-induced orthostatic hypotension increases the risk for falls in elderly patients with an unsteady gait. Another limitation of TCA therapy in patients with Parkinson's disease is a drug interaction with levodopa. It is important to optimize levodopa absorption so that the maximum amount is available for conversion to dopamine. Consequently, drugs that decrease the absorption of levodopa, such as the TCAs, should be avoided.

Another strategy that can be used to optimize dopamine concentrations in the CNS is to avoid dopaminergic blocking agents, such as amoxapine.[41] Conversely, antidepressants that block dopamine uptake (eg, bupropion and venlafaxine) may have dual therapeutic benefit by being effective for depression in addition to augmenting other coprescribed drug therapies for Parkinson's disease, such as levodopa and amantadine. Improvement of serotonin imbalances by the SSRIs may also be advantageous in ameliorating Parkinsonian as well as depressive symptoms. Case report data suggests a possible association between fluoxetine and extrapyramidal symptoms, which may offset this

clinical benefit.[53-56] Drug treatment options for Parkinson's disease include the monoamine oxidase B inhibitor selegiline. Addition of a serotonergic drug to a regimen with an MAOI could potentiate a serotonergic syndrome leading to delirium, coma and, in some cases, death. This interaction has occurred after concomitant use of sertraline and selegiline.[42] Because other antidepressants have similar effects on serotonin receptors in the brain, they should all be suspected of having the same drug interaction potential with selegiline.

Depression is not an expected psychological consequence of Alzheimer's dementia. Distinguishing between the diagnosis of depression as opposed to dementia is confusing because many of the characteristic symptoms overlap (eg, sleep and appetite changes, loss of interest in usual activities, and psychomotor agitation or retardation).[57] If depression is present, improved motivation and functional and cognitive status will become evident with treatment. Agitated patients may benefit from the sedative properties of TCAs or trazodone. However, drugs with sedative properties may actually worsen cognitive impairment in patients with dementia.[41] This is a result of the anticholinergic properties of TCAs, which induce confusion, short-term memory loss, poor concentration and attention, and disorientation and delirium.[43] Because of the activating properties of fluoxetine[58-60] and bupropion,[61,62] some primary care physicians avoid using them in patients with dementia accompanied by agitation. In the elderly, the SSRIs may be better choices because their selective mechanism of action results in milder, better tolerated side effects. Other agents that do not have negative cognitive effects include nefazodone and venlafaxine.

Cancer

Depression in cancer patients may be due to biologic changes caused by the disease.[63] On the one hand, a developing cerebral metastasis or paraneoplastic syndrome can cause CNS or endocrine disturbances that present as a subclinical depression. Also, the emotional stress of coping with cancer may be the catalyst for depression. Cancer patients at increased risk for depression include those who need multiple courses of poorly tolerated chemotherapy, who have recurring disease, or who have a poor prognosis.[18] TCAs are clinically useful in this patient population because their therapeutic benefits extend beyond their efficacy in depression. Coprescribing TCAs with opiates is common clinical practice even in patients with no depressive symptoms. This combination has been effectively used to provide equipotent pain relief with a lower opioid dose. Patients with insomnia or diarrhea caused by radiation therapy may also benefit from the sedative and anticholinergic side effects of TCAs.[7] In patients with cachexia, fluoxetine, which has been associated with weight loss, should be avoided. Instead, some physicians have found that weight-neutral agents (eg, sertraline and paroxetine)[44] or weight-promoting agents (eg, doxepin, imipramine, and amitriptyline) are useful.

Although the TCAs are effective for treating depression and other symptoms associated with cancer, side effects can still be problematic and result in a high rate of noncompliance.[45,64] Anticholinergic side effects, such as constipation and dry mouth, can be troublesome for patients recovering from GI surgery or stomatitis. Electrocardiographic changes associated with TCAs may potentiate the cardiotoxicity of doxorubicin. Therapeutic doses of meperidine used within 14 days of an MAOI have resulted in an opiate overdosage syndrome characterized by symptoms of coma, severe respiratory depression, cyanosis, and hypotension.[65] As a result, MAOIs should be administered with caution, if at all, to cancer patients who are receiving opiates for chronic pain management.[41] The use of morphine or fentanyl is preferred over meperidine in patients receiving MAOIs.

Nausea is a frequent complication of cancer resulting from GI oncologic processes or emetogenic chemotherapy. This undesirable aspect of the disease needs to be taken into consideration when prescribing antidepressants associated with nausea, such as the SSRIs, bupropion, and venlafaxine. Nausea associated with SSRI therapy is generally transient, dose-dependent, and tends to resolve after several weeks of therapy. Patients who are particularly troubled by nausea may choose to take their dose in the evening or switch to an alternate SSRI and then to an alternate class of antidepressants. Although TCAs may be appropriate in some situations, overall, the SSRIs, trazodone, nefazodone, or venlafaxine are preferred in cancer patients because of the lower risk for complicating side effects and the decreased potential for lethality in overdose situations.

Endocrine Disorders

Corticosteroid abnormalities have a number of biological effects on the CNS that commonly precipitate depressive disorders. Almost every endocrine disease has been associated with depression, but only a few (eg, Cushing's syndrome, Addison's disease, hyperthyroidism, hypothyroidism, and hyperprolactinemic amenorrhea) cause symptoms that reach the intensity of a major depressive disorder.[66] Clinical response to treatment and specific disease-related features can be used to determine whether endocrine disease or depression is the primary disorder. For example, depression in Cushing's syndrome responds poorly to antidepressant drugs but improves rapidly with steroid inhibitors. Furthermore, patients with Cushing's syndrome rarely experience major psychiatric disturbances other than affective disorders (eg, depression and related anxiety and irritable mood). Because stressful life events can induce both depression and pituitary-adrenal imbalances, it is possible that these disorders may coexist with no physiological link.[67] It is recognized that hormone imbalances can cause depression, but physiologic changes can also be indirectly responsible for depressive symptoms; for instance, contending with the social stigma of acromegaly or hirsutism may be the source of depression. Therefore, not all cases of depression coexisting with endocrine disorders will resolve once the hormonal imbalances are corrected. It is possible that personal distress may be the actual source of depression, in which case, treating the condition with an antidepressant is appropriate.

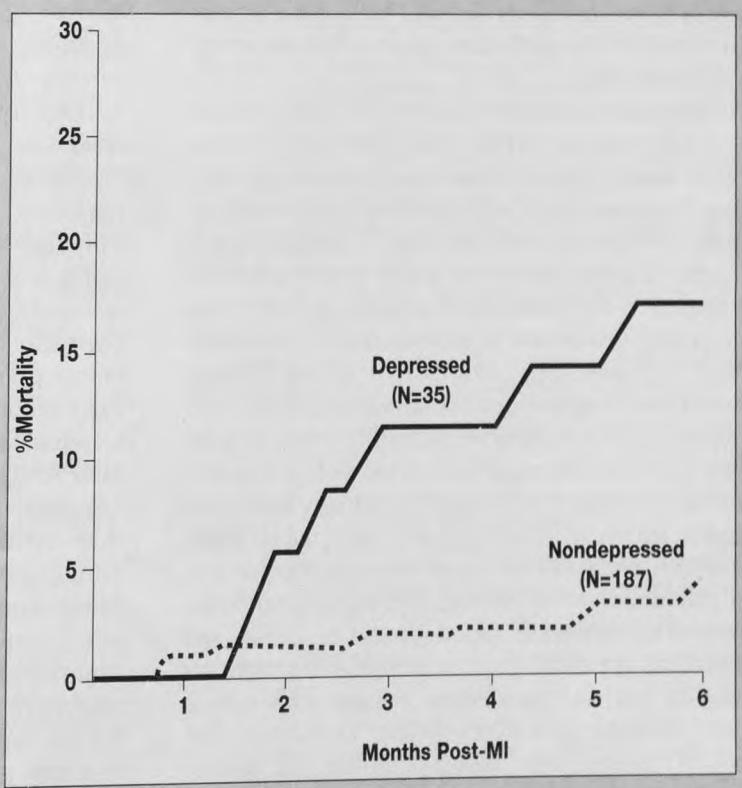
Cardiac Disease

Loss of control over important aspects of life, such as employment, independence, or anxiety about recurrent cardiac events, contributes to the prevalence of depression in patients with myocardial infarction (MI), congestive heart failure, coronary bypass surgery, and other cardiac conditions. Because untreated depression prolongs recovery and increases the risk of cardiac death, there is a compelling rationale to treat depression in patients with preexisting heart disease.[13] Even after controlling for other clinical variables, such as the degree of cardiac impairment and previous MIs, depression itself is a significant risk factor for dying in the 6 months after an MI (Figure 2).[68] It is recommended that TCAs be avoided in this patient population because they slow cardiac conduction and cause greater postural blood pressure changes.[46] Another precaution associated with TCA therapy is a potential drug interaction with warfarin. Because anticoagulation with warfarin in the post-MI phase is becoming common practice, primary care physicians will need to be more cognizant of this drug interaction and the associated increased risk for hemorrhagic events.

Patients with cardiac conduction disease are particularly prone to the unpredictable and even fatal antiarrhythmic effects of TCAs. An important implication of this antiarrhythmic effect is the potential for high TCA concentrations to induce ventricular

FIGURE 2

Depression is a significant risk factor for mortality in the 6 months after myocardial infarction (MI). Reproduced from Frasure-Smith et al, 1993, with permission.[68]



arrhythmias. Thus, it is advisable that other antidepressants be used in place of TCAs so that the potential for cardiac complications can be avoided, especially in patients with suicidal tendencies. TCAs taken with sympathomimetic amines can also result in tachycardia, arrhythmias, and hypertension. Because some of these products are available as over-the-counter purchases in the form of decongestants or weight-loss products, patients can precipitate this reaction inadvertently if not properly warned. More severe, life-threatening hypertensive crises can occur if MAOIs are taken with sympathomimetic amines or tyramine-containing foods. Therefore, it is best to avoid the likelihood of these serious events occurring by selecting antidepressants that are not associated with adverse cardiac events, such as the SSRIs, bupropion, or nefazodone.

TCA-induced orthostatic effects also increase in frequency and magnitude with worsening left-ventricular function. In one study, approximately 50% of patients with congestive heart failure experienced such severe orthostatic hypotension with imipramine therapy (drops in systolic blood pressure of up to 44 mm Hg) that they withdrew from the 3-week trial.[47] Nortriptyline causes less orthostatic hypotension compared with imipramine, amitriptyline, and desipramine,[47,48,69,70] and is a rational choice in the rare cases when a TCA is considered necessary.

Other patients who need careful consideration are those with borderline or unstable hypertension. Higher doses of venlafaxine (eg, 37.5 mg or greater) have been associated with small but clinically significant increases in blood pressure.[49,71] The likelihood for this adverse effect to occur is unpredictable because it is not related to any patient-specific characteristic, such as age, sex, or renal or hepatic function.[72] Consequently, alternatives to venlafaxine should be considered for hypertensive patients who cannot tolerate additional increases in blood pressure. TCAs should also be avoided in hypertensive patients because they interact with many antihypertensive agents to either increase (eg, guanethidine, clonidine, and methyldopa) or decrease (eg, β-blocker, calcium channel blocker, diuretics, angiotensin-converting enzymes) blood pressure.[50] SSRIs and bupropion are considered the first-line treatment for patients with cardiac disease because they have a more favorable side-effect profile. They have minimal effects on pulse, blood pressure, and cardiac conduction due to their low affinity for muscarinic, histaminergic, and α-adrenergic receptors. Still, SSRIs should not be administered concomitantly to patients being treated with type IC antiarrhythmics (eg, encainide, flecainide, and propafenone)[51] because SSRIs block the metabolism of these antiarrhythmics (via inhibition of cytochrome P450 2D6), resulting in high concentrations and, possibly, treatment-emergent arrhythmias. Bupropion may be a better choice in these circumstances. However, these cases are seldom managed in the family practice setting because these patients often require specialized care from cardiologists.

CONCLUSIONS

Treating depression in patients with significant medical comorbidity is further complicated by physiologic changes, drug interactions, and drug side effects that are not present in physically healthy but depressed patients. In the past, physicians have often hesitated to prescribe antidepressant therapy for fear that side effects would exacerbate the underlying medical condition. Today, newer antidepressants with specific mechanisms of action represent a significant advance in the treatment of medically ill patients. Because they are well tolerated and do not increase morbidity, these agents offer a rational treatment option for the medically ill depressed patient.

Drug interactions can also determine the choice of an antidepressant. Because there are now several antidepressants available from which to choose, drug interactions can often be avoided. Although this review covered only the disease states in which depression occurs most commonly, family physicians should be aware that antidepressants interact with other drugs that are commonly prescribed. For example, nefazodone and fluvoxamine are contraindicated for therapy with terfenadine and astemizole because of the risk of fatal arrhythmias. The mechanism for this drug interaction has been implicated to be the same as that which has occurred when ketoconazole is administered with these antihistamines. Fluvoxamine also increases theophylline levels, which requires close monitoring during concomitant therapy. Thus, it is good practice to continually review each patient's medication profile before beginning or changing his or her antidepressant therapy.

Depression should not be dismissed by the

patient and primary care physician as an understandable or normal reaction to the individual's disease. If untreated, it can hinder the recovery process and increase morbidity and mortality. The burden of a mood disorder to the patient, to his or her family, and to society is unnecessary because depression is a highly treatable disease. Approximately 80% to 90% of cases resolve with appropriate treatment.[73] Therefore, family physicians should not hesitate to provide counseling, support, and medication when depression is present. An increased awareness of the indirect or covert manifestations of depression in the medically ill will enable rapid diagnosis and effective therapy.

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DISCUSSION

Dr Richardson: Most patients in primary care come in with a hybrid of medical problems, and it is easy to forget about the depressive component. Sometimes we shy away from working up depression because we are consumed with the patient's multiple problems. However, it could be that depression is presenting in the form of somatic symptoms. If we would simply spend a few minutes to screen for depression, we might save ourselves a lot of time in the long run. It could be that once we treat the depression appropriately, all the patient's physical symptoms will disappear.

Dr De Wester: I think an example of this is in the demented patient. These patients have been on multiple medications chronically, and we always meet a lot of resistance anytime we try to change anything or add anything new to their medication regimen. A common misconception is that dementia is a natural process of growing old, but we all know that pseudodementia is a common way for depression to present in the elderly. I think as long as you use a safe agent and monitor the patient's response, a trial with an antidepressant is justified.

Dr McCoy: These examples emphasize the point that family doctors should remember that depression in medical illness can occur coincidentally, can be a true symptom of the medical disorder, or can be a secondary or functional reaction to impairment. There are quick and easy screening methods that can be used to discriminate depression from medical illness, and I think it would really be worth our time to perform them. Once we identify and treat the depression, it could curtail the number of patients who repeatedly return to the office with illegitimate medical complaints and save us from having to perform unnecessary tests and procedures. It may also improve the condition of patients with true medical illnesses because they start feeling better about themselves and less handicapped by their medical illness.