Annals of Clinical Psychiatry, 19[4]:289–303, 2007

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230701653542

informa
healthcare

Medical Co-Morbidity in Depressive Disorders

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Background. *Depression is much more prevalent among those with chronic medical conditions compared to the general population of the United States. Depression is recognized as a cause of increased morbidity and mortality and has been associated with higher health care costs, adverse health behaviors, significant functional impairment, lost work productivity, occupational disability and increased health care utilization.*
Method. *Searches of Medline, OVIDMedline, PubMed and PsycINFO of all English-language articles published between 1966 and 2007 were conducted using the keywords mood disorders, medical comorbidity, depression, antidepressant therapy. Supplemental references were manually extracted from relevant articles and chapters. Reviews of mechanistic studies and open label and randomized controlled trials of depression in patients with medical co morbidities were reviewed.*
Results. *Depressive disorders are prevalent among the medically ill and the relationship between depression and medical illness may be bidirectional. Antidepressant medications are effective in the treatment of depression in the medically ill.*
Conclusions. *Depressive disorders can adversely impact the course of medical illnesses. Available antidepressant treatments are effective for the treatment of depression in the medically ill. Early identification and treatment of depression in medical illness can positively influence medical outcomes and quality of life.*

Keywords Mood disorders, Medical comorbidity, Depression

INTRODUCTION

Despite available effective treatments for depressive disorders, the psychosocial and medical burden of depression is increasing. The World Health Organization projects that depression will continue to be prevalent, and by the year 2020, will remain a leading cause of disability, second only to cardiovascular disease (1,2).

Current evidence suggests that depression is much more prevalent among those with chronic medical conditions compared to the general population of the United States (3). Depression is also recognized as a cause of increased morbidity and mortality in chronic medical illness (4). The presence of depression with a medical illness has been associated with higher healthcare costs, adverse health behaviors, significant functional impairment, lost work productivity, occupational disability, and increased health care resource utilization (4).

A growing body of evidence also points to a bidirectional relationship between depression and medical illness, suggesting that depression may be a cause and a consequence of some medical illnesses, such as cardiovascular disease, HIV/AIDS, cancer, epilepsy and stroke (5).

Despite the evidence and the availability of effective treatments for depression in the medically ill, these patients frequently suffer needlessly with untreated depression. Barriers to treatment include the diagnostic challenges of identification of

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depressive symptoms in the presence of multiple somatic and cognitive symptoms, many of which occur with the illness itself or due to the medications used to treat the illness (6) as well as patient, family and clinicians expectation that depressed mood is a predictable response to living with a serious illness.

This article will review several aspects of depression in individuals living with chronic medical conditions, focusing on some of the conditions for which the relationships between depression and the existing medical conditions have been well established; specifically, cardiac conditions, cancer, human immunodeficiency virus (HIV) infection and neurologic disorders (Alzheimer's, Parkinson's, and epilepsy). We will review the efficacy of antidepressant medications in these medically ill populations and provide recommendations for treatment.

Cardiac Disease

Depression has been implicated as an important risk factor for coronary artery disease and also is common in patients with cardiac disease with prevalence rate estimates in individuals with coronary artery disease (CAD), unstable angina, acute myocardial infarction (MI), congestive heart failure (CHF) or coronary artery bypass graft surgery (CABG) in the range of 17–27% (7)—a rate significantly higher than the general population.

Furthermore, depression has been implicated as an independent cardiac risk factor. Frasure-Smith and colleagues, in a relatively large clinical study observed that patients with major depression experience elevated mortality rates from cardiovascular disease. These investigators found depression to be a significant predictor of mortality (P <. 001) in 222 patients, 6 months following myocardial infarction (MI), even after adjusting for other risk factors such as left ventricular dysfunction and previous MI (8). Multiple logistic regression analyses described a strong association between depression and 18 month cardiac mortality, even after controlling for other predictors of mortality (9). In another study examining the five year risk of cardiac mortality in relation to depressive symptoms after MI, the presence of depression or depressive symptoms increased the risk of cardiac death by > 3.5 fold (10).

Depression has also been shown to increase risk for onset of coronary artery disease by 1.64 fold (95% confidence interval (CI), 1.41–1.90) (1) and incident IHD by 1.5–2 fold (11).

Evidence also suggests that the presence of depression impacts outcomes of individuals undergoing cardiac surgery. Depression predicts recurrent cardiac events at 12 months post coronary artery bypass graft (CABG) (12). In a study of 817 patients undergoing CABG, Blumenthal and colleagues showed that moderate to severe depressive symptoms on the day prior to surgery or mild depression persisting from baseline to 6 month follow up after surgery was a predictor of mortality over mean follow up of 5.2 years, with hazard ratio's of greater than 2.0 (13).

Mechanisms of Co-Morbidity

Although the mechanisms linking depression to cardiovascular diseases are unknown, evidence suggests many potential biological and psychosocial factors. Biological theories implicate the hypothalamic-pituitary-adrenocortical axis, sympathomedullary hyperactivity and autonomic nervous system activity as demonstrated by reduced heart rate variability and platelet mechanisms (14).

Hypothalamic-pituitary-adrenal axis dysregulation has been identified in about half of patients with major depression, with or without CAD (15,16). Glucocorticoids, which are elevated in depressed states, mobilize free fatty acids resulting in inflammation of the endothelium and clotting (1,15–17).

Higher levels of plasma norepinephrine have been found in depressed subjects in response to cold or orthostatic challenge. These stressors may enhance platelet activity by inhibiting eicosanoid synthesis and stimulating platelet derived growth factor formation (16–18).

Cardiac patients with depression were also found to have elevated levels of two platelet activation factors, beta-thromboglobulin and platelet factor 4 (19,20) suggesting a heightened susceptibility to thrombus formation in response to thrombogenic stimuli.

Inflammatory cytokines have also been found to be elevated in patients with CAD, and the extent of elevation of specific markers such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-alpha) and C reactive protein (CRP), predicts coronary and cerebrovascular disease events and progression of heart failure (21,22). Depression has been associated with increases in circulating levels of IL-6 and CRP (23).

The most important biological link between depression and CAD may be heart rate variability, a measure of the balance between sympathetic and parasympathetic inputs to the cardiac conduction system. A high degree of heart rate variability (HRV) is observed in normal hearts with good cardiac function, whereas HRV can be significantly decreased in patients with severe CAD or heart failure (24). Heart rate variability may diminish in depression, even in the absence of coronary disease (25). Reduced heart rate variability may contribute to ventricular arrhythmias and sudden cardiac death (26) and has been associated with greater blood pressure variation, more commonly found in depressed patients (24). Depression appears to worsen the impact of other cardiac risk factors. A meta-analysis of psychosocial risks for cardiac mortality found that the highest death rate (60%) for patients at 18 months post MI, was in a subgroup with more than 10 premature ventricular contractions (PVC's) per hour and a Beck Depression Inventory (BDI) score greater than 10 (9).

Behavioral factors may also contribute to the increased risk for cardiac disease with depression. Post MI patients may be less adherent to exercise programs, smoking cessation programs, dietary changes, aspirin and antihypertensive therapies and cardiac rehabilitation programs (27–31). Several negative affective symptoms including anxiety, anger attacks (32),

hostility (33) frustration, sadness, and tension (34) also have been linked to biological risk factors for CAD.

Cancer

Depression appears to be more common in patients with cancer than in the general population (35,36) and has been estimated to be up to 4 times greater than population estimates (37). However, exact prevalence estimates are difficult to ascertain as the available studies have examined diverse malignancy groups, variable clinical staging, small sample sizes and non-standardized definitions of depression (38). Overall, the rates of major depression in cancer patients are estimated to be 24%, with prevalence rates reported to range from 1.5% to 50% (39). Many factors influence prevalence rates of cancer including the type of cancer, diagnostic criteria, disease severity, and type of treatment (Table 1) (36). Limited data exists regarding prevalence rates for depression in cancer patients who are children, elderly or minority populations.

Depression has been associated with a poorer prognosis and increased morbidity (38). The relationship between cancer and depression is complicated. Depression may occur with cancer due to stress related to the cancer diagnosis and treatment, medications, underlying neurologic or medical problems, nutritional or endocrine disturbances, brain metastasis or recurrence of a pre-existing affective disorder (40) or, antineoplastic therapies (41). Additionally, patients with depression might be poorly adherent to cancer treatment regimens or might engage in adverse health behaviors (38). Depression has also been associated with immunosuppression, which might increase cancer risk in susceptible individuals (42,43).

Table 1 Factors that Affect the Prevalence of Depression in Patients with Cancer

Type of Cancer
Pancreas>oropharynx>breast>colon>gynecologic>
Lymphoma>gastric>leukemia
Severity of Disease
Chemotherapeutic Regimen
Interferon alpha
Interleukin-2
Amphotericin-B
Cycloserine
Glucocorticoids
L-asparaginase
Leuprolide
Procarbazine
Tamoxifen
Vinblastine
Vincristine
Surgery Type
Mastectomy> breast conversation
Depression Diagnostic Criteria

Adapted from Raison and Miller, 2003 (36)

Mechanisms of Co–Morbidity

Psychosocial factors that may contribute to depression in those with neoplastic disorders have been the focus of much research, with newer efforts focusing on the biological mediators of depression in those with neoplastic disorders. Evidence suggests that release of pro-inflammatory cytokines during tissue damage and destruction and its associated inflammation can have a substantial impact on neurotransmitter function, neuroendocrine function and behavior (44,45). These behavioral changes are called the "sickness syndrome" and are characterized by anhedonia, cognitive dysfunction, anxiety, irritability, psychomotor slowing, anergia, fatigue, anorexia, sleep alterations and increased sensitivity to pain (46). These symptoms overlap with those of major depression.

Several pathways by which pro-inflammatory cytokines may cause depression or sickness have been suggested. Pro-inflammatory cytokines have been shown to alter the metabolism of monoamines impacting mood, specifically norepinephrine, serotonin and dopamine (44). They have been reported to stimulate the hypothalamic-pituitary-adrenal axis through activation of corticotrophin releasing hormone(CRH) (47,48). Cytokines may induce resistance of nervous, endocrine and immune system tissues to circulating glucocorticoid hormones stimulating the glucorticoid resistance found in depressed patients (49). Proinflammatory cytokines may induce enzymes that metabolize tryptophan, the primary precursor of serotonin (50). They may inhibit pathways involved in thyroid hormone metabolism resulting in euthyroid sick syndrome, which is characterized by normal TSH and T4 levels and reduced T3 levels in the early stages, and by normal TSH, reduced T3 and T4 in the later stages (51).

Although depressive symptoms are very responsive to antidepressant treatments, the neurovegetative symptoms described in the sickness syndrome have been less responsive to antidepressant treatments and require a different treatment approach (52). Evidence suggests that prophylactic interventions for cancer patients before the initiation of interventions that might induce depressive symptoms such as disfiguring surgeries or chemotherapies could be more effective than the current practice of targeting depression treatment after the onset of symptoms (36).

HIV/AIDS

Depression is one of the most common psychiatric disorders observed in people infected with HIV. Earlier prevalence estimates showed wide variations, with estimates ranging from 4–22% in HIV seropositive men and between 2% and 18% for HIV seropositive women (53,54). Although an earlier community based survey did not find an increased prevalence of depression among those infected with HIV (55), a number of clinical studies have found high rates of depression among HIV positive gay men (54,56–58). Earlier controlled studies

found that the prevalence of major depression and other mood disorders was higher among asymptomatic HIV-seropositive men than in the (59, 60) general population (61,62) but was similar to that of HIV-seronegative gay men (58,61,63,64).

Most of the earlier prevalence studies focused on HIV-seropositive men, (65–67) even though women make up 50% of new cases of HIV infection worldwide and women account for more (56) than 16% of all cases of HIV infection in the United States (68). Estimates of depression among HIV seropositive women have ranged from (69,70) 1.9% to 35% in clinical samples and from 30% to 60% in community samples (58,71). More recent studies with large sample sizes and controlled study designs have reported that HIV (66,67) positive women are at significantly greater risk for major depressive disorder (72) than demographically matched HIV negative women. Ickovics and colleagues reported chronic depressive symptoms in 42% and intermittent depressive symptoms in 35% of a sample of 765 HIV positive women (60). Recent studies suggest prevalence rates close to 20% for HIV seropositive women. In a clinical study of 93 HIV-seropositive women and 62 HIV seronegative women, Morrison and colleagues found the prevalence of major depressive disorders was significantly higher among HIV-positive women than among HIV-negative controls (19.4% vs. 4.8%) (73). Depression, depressive symptoms and psychological stress are associated with poor adherence to antiretroviral treatment, deterioration in psychosocial functioning, more rapid progression of HIV/AIDS and higher mortality (60,63–65,67,74–76). Evidence also suggests that endocrine/immune system changes associated with depression might affect HIV entry and replication, thereby increasing the risk of HIV infection (72,77–79).

Mechanisms of HIV Effect and Depression

Although a considerable body of evidence supports the relationship between depression and HIV disease progression, the mechanisms mediating these relationships remain unclear. Although studies suggest that poor health habits might account for these findings, support for the impact of these behaviors on psycho immune relationships is lacking (60,65,72,76).

Most HIV literature has focused on the hypothalamic-pituitary axis (HPA) and sympathetic nervous systems as possible mediators based on animal and human research linking immune status changes to dysregulation of these systems (80,81). Some evidence suggests that cortisol is positively related to stress and depression in HIV (79) and that cortisol may alter immune response by promoting viral replication (78), altering programmed cell death and cytokines secreted (77,78), changes that have been associated with HIV disease progression. Increased sympathetic activity via norepinephrine has been shown to affect HIV replication. Cole et al. demonstrated that higher baseline levels of sympathetic nervous system activity in HIV+ gay men predicted poorer suppression of plasma RNA viral load and worse CD4+ T-cell recovery after receiving HAART compared with men with lower levels of activity (82). The neuropeptides substance P has also been implicated as a potential mediator of psychological distress upon HIV disease progression. A substance P antagonist has been efficacious in the treatment of depression (83), and substance P may be involved in the modulation of HIV infection. Plasma levels of substance P are higher in HIV-infected persons and area associated with decreased NK cell populations (84,85). Alterations in functioning of killer lymphocytes (natural killer and cytotoxic T-lymphocytes) associated with depression might diminish host defenses against HIV infection, which might be a mechanism by which depression might influence HIV disease progression (72,86,87). Stressful life events, poor social support and chronic depression have been associated with more rapid declines in CD4 lymphocyte counts (74,88,89) and progression to AIDS (60,72,76).

Neurological Disorders

High rates of depression have been noted in many neurological disorders, specifically cerebrovascular disease (90), Alzheimer's disease (91), Parkinson's disease (92), Multiple Sclerosis (93) and epilepsy (94). The relationships between neurological disorders and depression are complicated and bidirectional. Development of depression could be due to the stress of illness or due to the consequence of the neurological disease itself (95). In addition to the adverse impact upon quality of life and cognitive functioning, epilepsy has been associated with a significant increase in suicide rates (96). The presence of depressive disorders in patients with Parkinson's disease has been identified as one of the most important reversible risk factors that affects functioning and quality of life (92). Studies suggest improvements of cognitive impairments with treatments following post-stroke depression (97) pointing to the importance of identifying and treating patients with comorbid depression and neurological disorders.

Depression is also one of the most common non-cognitive symptoms of Alzheimer's disease (91,98). Additionally, the occurrence of late onset depression and reversible cognitive impairment associated with depression has been shown to correlate highly with an eventual diagnosis of Alzheimer's dementia (99). Depression in AD has been associated with more nursing home placements (100), rapid cognitive decline and increased mortality (101).

High rates of depressive disorders have also been found in patients with Multiple Sclerosis (MS). Up to 50% of patients with MS will have a depressive disorder as part of an active exacerbation of illness or during the chronic course of the illness (93).

Pathogenesis of Depression in Neurological Disorders

The pathogenic mechanisms underlying these relationships are not known. Some studies suggest that post-stroke mood

disorders may be caused by cerebral ischemic changes, while other studies suggest that mood symptoms might be associated with lesion localization, i.e., post-stroke depression might be associated with left sided lesions (90,102). Others however, have not supported these findings (103). Depression might be a risk factor for stroke for susceptible individuals by the same mechanistic pathway as those postulated for coronary artery disease and atherosclerosis, specifically by increasing platelet reactivity (104,105), and adrenocortical hyperreactivity (106) which leads to atherosclerosis and stroke (107). Depression might also be a consequence of underlying neurodegenerative processes in Alzheimer's Disease (95), and Parkinson's disease (108), and genetically predisposed individuals with Alzheimer's Disease might be at increased risk for depression (91).

Management and Treatments of Depressive Disorders in the Medically Ill

Effective treatments are available for depressed individuals with chronic medical conditions. A number of well-controlled studies have demonstrated the efficacy of antidepressants and psychotherapy in treatment of depression in medically ill patients (5,38). Selective serotonin reuptake inhibitors (SSRIs), heterocyclic antidepressants, tricyclic antidepressants (TCAs) and psychostimulants have been used in the treatment of depression with comorbid medical illness. A recent meta-analysis of treatment outcomes suggests that SSRIs, TCAs and other antidepressants improve depressive symptoms in patients with a wide range of physical illnesses significantly more often than does either placebo or no treatment (109).

Unfortunately, this growing body of evidence has not necessarily translated into better treatments for those with medical-psychiatric comorbidites. Failure to recognize the symptoms of depression in this population continues to be a serious problem (38). A significant contributor to missed diagnosis appears to be the difficulty of distinguishing the symptoms of depression from those of the illness itself.

The diagnosis of depressive disorders in the medical population is fraught with difficulty for a variety of reasons. The classic signs and symptoms of depression such as dysphoria, demoralization, fatigue, pain, psychomotor retardation, anorexia and insomnia can be attributed to the medical illness itself or side effects of treatments. A syndrome of "demoralization" has been described in the literature that is associated with life-threatening medical illness, disability or bodily disfigurement, fear, loss of dignity and social isolation. Demoralization consists of hopelessness, loss of meaning and existential distress expressed as a desire or death that might be expressed as suicidality. Demoralization is conceptualized as distinct from depression, thus thoughts of death and the desire for hastened death may be reported by patients with advanced medical disease in the absence of depressed mood, and may not be a reliable sign of a depressive disorder (110,111). Physical suffering or disability may cause loss of interest or diminished capacity to experience pleasure in many activities. Additionally, depressive symptoms may manifest in atypical or masked forms including the amplification of somatic symptoms and noncompliance with or refusal of medical treatments (112, 113).

Several screening instruments are available to help the clinician make a diagnosis of depression in the presence of medical symptoms, including the Center for Epidemiologic Studies Depression (CES-D) scale (111), the Hospital Anxiety and Depression Scale (HADS) (114), the Beck Depression Inventory II (BDI II) (115), and the Patient Health Questionnaire (PHQ) (116).

Recent critical reviews of depression screening suggest that these efforts have resulted in greater recognition of depressive disorders in the medically ill, but not necessarily in better management of depression or improved outcomes (117). Nonetheless, recognition is essential given the consequences of overlooked or ineffectively treated depression. Approximately 15% of all patients with untreated major depression die from suicide (118) and carefully controlled studies suggests an increased risk of suicide in several medical conditions including cancer (119), multiple sclerosis (120) and Huntington's chorea (121).

Once depression is recognized, the challenge for clinicians will be to identify effective treatments whose mechanisms of action and side effect profiles will not exacerbate the co-existing medical condition. The key to success is an adequate dose and duration of antidepressant medication just as it is for patients without medical co morbidities.

Selective Serotonin Reuptake Inhibitors

SSRIs are generally regarded as first-line treatment for depression in those with medical conditions, due to their relative safety and tolerability. Several double blind, randomized controlled trials have demonstrated the effectiveness of SSRIs in the treatment of depression in individuals with cardiac disease (122), stroke (123), Alzheimer's disease (124,125), diabetes (126), multiple sclerosis (127), cancer (128), and HIV/AIDS (129,130). Open label studies demonstrate improvement of depression despite no observed change in motor function in patients with Parkinson's disease (131).

Recent studies suggest that the benefits of SSRI treatment may extend beyond their positive effects on depression to improvements (132) in co-existing medical illnesses as well. Fluoxetine has been shown to improve glycemic control in patients with diabetes mellitus (126), and in individuals with cardiac disease, SSRIs may be have cardiac safety (122,133). Paroxetine, sertraline and venlafaxine have been shown to effectively reduce the intensity and frequency of hot flashes in women with breast cancer who develop chemical menopause associated with tamoxifen use (134–137).

Although the SSRIs are effective and generally well tolerated, their adverse effects may add to the already existing physical problems. For most individuals, the SSRI side effects

are transient, lasting 3–7 days after starting the medication or increasing the dose. The short-lived adverse effects include nausea, headache, sedation, diarrhea, constipation, tremor, and nervousness. Longer-term effects include sexual dysfunction, dry mouth, sweating, insomnia and potential weight gain. Rare but potentially serious side effects of SSRIs include the syndrome of inappropriate antidiuretic hormone secretion and platelet dysfunction leading to bleeding (138). Some studies suggest that the SSRIs may worsen the motor symptoms in patients with Parkinson's disease (139).

Strong considerations must be given to the potential for drug interactions in this population. For example, the presence of hepatic disease may affect metabolism and excretion of SSRIs and significantly alter their pharmacokinetics (140).

Other Newer Antidepressants

In addition to the SSRIs, a diverse group of other antidepressants have become available in the last 15 years, including venlafaxine, duloxetine, buproprion, mirtazapine, the recently released selegeline transdermal patch, nefazodone (no longer available in many countries outside the US), and moclobemide (not available in the US). These agents are commonly used as alternative treatments to SSRIs, albeit less evidence exists for their safety and efficacy in medically ill patients.

Venlafaxine and Duloxetine are serotonin and norepinephrine reuptake inhibitors, which appear to have greater efficacy, greater likelihood of producing remission, and greater improvement of painful physical symptoms in those with depression. Venlafaxine also has the potential to cause sweating and nausea early in treatment and to cause hypertension that may persist throughout the course of treatment (141). Overall, they are well tolerated. Venlafaxine is available in immediate release and extended release formulations. Its side effect profile is similar to that of the SSRIs with the exception of its association with increased blood pressure at doses above 150 mg daily. Duloxetine, a newer dual action agent, has been approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy. Duloxetine has not been associated with the elevations in blood pressure noted with venlafaxine, however it has been shown to increase the risk of elevation of serum transaminases and bilirubin, and should not be used in individuals with hepatic insufficiency, end stage renal disease requiring dialysis, or severe renal impairment (creatinine clearance<30mL/min).

Mirtazapine increases norepinephrine and serotonin concentrations through blockade of inhibitory alpha-2 adrenergic receptors on both serotonergic and noradrenergic neurons. It does not appear to cause nausea, insomnia, anxiety or sexual dysfunction. Additionally, it has been associated with minimal drug interactions (142). It is moderately sedating and tends to cause more long-term weight gain than other antidepressants. As a result of its serotonin receptor blocking anti-emetic effects, it may be helpful for medically ill patients experiencing nausea (143). Its sedative and appetite simulating effects may improve insomnia and anorexia in patients who experience these symptoms as part of their medical illnesses.

Bupropion is a norepinephrine and dopamine modulator. Its efficacy and safety has been demonstrated in double blind, randomized controlled trials and open trials in patients with cardiac disease (144). It is not sedating, does not cause sexual dysfunction and has few cardiac effects. Side effects include agitation and insomnia. Bupropion has been reported to cause hypertension without affecting heart rate in some individuals (145) Bupropion causes a dose-related lowering of the seizure threshold and may precipitate seizures in susceptible patients receiving dosages above 450 mg/day (57). Given the above, it is recommended that single doses greater than 150 mg and daily doses greater than 300 mg be avoided in patients with brain tumors and a history of seizures.

Nefazadone is another dual action agent whose mechanisms of action involve antagonism of serotonin and norepinephrine, however, its precise mechanism of action is unknown (146). Potential severe hepatotoxicity with nefazadone has led to a black box warning in the United States and its removal from the market in a number of countries, and it should not be used in those with preexisting liver disease (147).

Evidence suggests that moclobemide may reduce depressive symptoms in patients with Alzheimer's disease (148). Open trials suggest the effectiveness of mirtazapine and mianserin in patients with cancer (149) and HIV/AIDS (150) and nefazadone (151) paroxetine (129,152) and bupropion (153) in individuals with HIV/AIDS.

Tricyclic Antidepressants (TCAs)

The older antidepressants are unquestionably effective and their safety and side effect profiles are well known. They have been proven effective in the treatment of depression in patients with cerebrovascular disease, Alzheimer's disease, Parkinson's disease, cancer, HIV/AIDS, epilepsy, chronic pain and diabetes (38). Nonetheless, the last decade has seen a movement away from TCAs and monoamine oxidase inhibitors to SSRIs and newer agents. TCAs are strong antagonists of cholinergic, histaminic and alpha-adrenergic receptors and can affect cardiac conduction, contributing to their ability to present greater problems for medically ill patients than for the nonmedically ill. Several case series have documented TCA discontinuation rates as high as one third in medically ill patients because of adverse effects (154,155). In one study, delirium occurred in 16% of medically compromised patients on low dose imipramine or doxepin (156). TCAs have been reported to double the risk of hip fracture in elderly patients, either because of sedation or orthostasis or both (157). Monoamine Oxidase inhibitors (MAOIs) were the first generation of consistently effective oral antidepressants. The MAOIs, phenelzine and tranyclcypromine, have the potential for hypertensive reactions following the ingestion of foods containing high levels of

tyramine such as aged cheeses, meats, wines and medications such as over the counter sympathomimetics (e.g., decongestants, appetite suppressants) and stimulants (e.g., caffeine). Potentially fatal serotonin syndrome may occur when SSRIs, venlafaxine, duloxetine, mirtazepine or nefazadone are combined with MAOIs. General anesthetics are difficult to administer to patients taking these medications as well as pressor agents such as dopamine, dobutamine and other sympathomimetics. MAOIs must be discontinued at least two weeks before administration of any of the above drugs, making it difficult to use these medications in individuals with chronic medical illness (158).

Psychostimulants

Methylphenidate and dextroamphetamine have been used to treat depression in patients with various medical conditions, either as single agents or in combination with antidepressant medications. However, only a few controlled studies of their use in medically ill patients are available. Psychostimulants have been used in the treatment of depression HIV/AIDS (159–161), stroke, and cancer (162) and have been reported to improve mood, initiative and energy. They are generally well tolerated with mild dose related side effects of agitation, nausea and insomnia. Rarely, psychotic symptoms or tachycardia and hypertension may occur. They may be useful due to their rapid onset of action in elevating mood, increasing appetite, and diminishing fatigue (163), but only limited data support these effects.

St. John's Wort (Hypericum Perforatum)

St. John's Wort is a popular herbal supplement marketed for the treatment of depressed mood. Its mechanism of action is uncertain, but it is known to increase serotonin and norepinephrine activity, which may cause sinus tachycardia and gastrointestinal distress. It is a photosensitizer and may cause sun induced skin rash, neuropathy and possibly increased incidence of cataracts. It induces CYP3A4 and has the potential to interact with medications metabolized by this enzyme to lower drug levels and decrease the therapeutic effect of some medications including digoxin and cyclosporine. It also induces renal P-gp drug transport systems, increasing renal elimination of several drugs, including digoxin and cyclosporine. St. John's Wort may induce serotonin syndrome in combination with other serotonergic drugs (164). St. John's Wort has been shown to reduce indinavir levels in HIV positive individuals significant enough to cause drug resistance and treatment failure in open studies (165).

Antidepressant Treatments for Specific Diagnostic Groups

The relationship between depression and cardiac disease has been an area of great interest due to the reported relationships between coronary artery disease (CAD), depression and mortality. The efficacy and safety of SSRIs in the treatment of cardiac patients with depression have been evaluated in two large randomized controlled trials. The Sertraline Antidepressant Heart Attack Trial (SADHART) (122) and the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trials (166). The SADHART trial randomized 369 patients with major depression after hospitalization for unstable angina or acute MI in a double blind study to receive treatment with sertraline, 50–200 mg/day or placebo. The primary goal of the trial was to assess the safety of sertraline treatment with a secondary goal of estimating the effect on cardiac outcomes. While the trial was not powered to determine effects on morbidity and mortality (i.e., only seven deaths occurred during the follow up period), sertraline was superior in absolute numerical terms to placebo in the rate of recurrent MI, mortality, heart failure and angina. Limited data from the SADHART study also suggests a potential cardioprotective effect of sertraline in the treatment of this population, although these data require confirmation by larger prospective trials (122).

The ENRICHD trial randomized 2481 post-MI patients with depression or low perceived social support to a 6 month course of either cognitive behavioral therapy (CBT) or usual care (both of which included antidepressant treatment), for the purpose of evaluating the effect of treatment on reinfarction rates and mortality. The CBT intervention was not found to be effective in reducing mortality; however, there were improvements in the depression and social support scores for those in the intervention group when compared to those in the usual care group. This study also suggests that sertraline may have some impact on all cause mortality as all cause mortality was only 7.4% of the intervention group compared with 15.3% of the without drug therapy and 10.6% in those treated with TCAs respectively. The absence of randomization to antidepressant treatments in this study requires caution in the interpretation of these results, but suggests that further study of these relationships are indicated. (Writing Committee for the ENRICHD Investigators 2003). TCAs are not considered first line therapies in patients with heart disease because they are type IA antiarrhythmics which might increase mortality in those with IHD (167,168).

Cancer

A number of antidepressant treatment trials in depressed patients with cancer have demonstrated the effectiveness of TCAs and SSRIs. (128,169–171). Mirtazapine and mianserin have shown promising results in open trials (149,172,173) While TCAs are equally effective for the treatments of depression in this population, SSRIs are the first line antidepressants prescribed in cancer settings because they are effective and have few sedative and autonomic side effects. Antidepressants like Mirtazapine that can cause weight gain may be advantageous in anorexic-cachectic cancer patients, but are not a good

choice in those gaining weight from steroids or from chemotherapy (149). The SSRIs and venlafaxine have been found to reduce both the number and intensity of hot flashes and night sweats in non-depressed women who become menopausal after chemotherapy for breast cancer or who have a recurrence of vasomotor symptoms when they discontinue hormone replacement therapy (135,174,175). The TCAs are used to treat both depression and neuropathic pain syndromes caused by cancer or its treatments. Nortriptyline and desipramine have fewer anticholinergic side effects than amitriptyline or imipramine.

Psychostimulants (methylphenidate, dextroamphetamine) can promote a sense of well being, treat depression, decrease fatigue, and improve cognitive function in patients with cancer. They may be used as adjuvants to potentiate the analgesic effects of opiods and to counteract their sedative effects (162).

Depression is a predictable side effect of some cancer treatments that activate the immune system. Interferon alpha has been associated with new onset depression and recurrent episodes of depression when used as a cancer treatment. Patients with advanced melanoma who were treated with a 12 month protocol of interferon alpha developed fatigue, anxiety, insomnia, depression and rarely mania (176) Paroxetine started at the time of interferon-alpha treatment, has been shown to reduce the incidence of depression (177). In this placebo-controlled study of patients with malignant melanoma, paroxetine was administered for two weeks before the start of interferon alpha treatment. Those receiving the antidepressant showed decreased rates of depression, anxiety and neurotoxicity. Additionally, paroxetine treatment significantly reduced the likelihood that alpha interferon therapy would have to be discontinued because of severe depression or related neurotoxic effects. Only 5% of patients treated with paroxetine discontinued interferon alpha treatment before 12 weeks compared with 35% in the placebo treated group. However, prophylactic use of antidepressants for cancer patients is not currently recommended.

In the only study comparing an SSRI to a TCA, Musselman and colleagues compared the efficacy and safety of paroxetine and desipramine with those of placebo in the treatment of women with breast cancer, stages I–IV and major depression. Using a double blind placebo controlled design, 35 women were randomized to a 6 week trial of paroxetine, desipramine or placebo. Mean changes in Hamilton depression and anxiety scale scores, and CGI-S scores, the primary efficacy measures, were not significantly different for the paroxetine and desipramine groups than those for the placebo treated group. The small sample size limits interpretation of these data, suggesting need for further studies (178).

Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome

Numerous well designed studies have supported the effectiveness of TCAs (53,129,152,155,179–183), for treating depression in HIV infected adults. Head to head studies comparing TCAs and SSRIs have shown equal efficacy for both, but a less favorable side effect profile for TCAs. In one double blind, placebo controlled study comparing imipramine, paroxetine and placebo in 75 HIV-positive subjects, the 2 antidepressants were found to be equally effective when compared to placebo. However, the drop out rates due to anticholinergic side effects with imipramine were 48%, compared to 20% with paroxetine and 24% with placebo (129).

In another study examining the efficacy of SSRIs in HIV seropositive individuals, using a 6-week open trial design, paroxetine, fluoxetine and sertraline were compared in 33 symptomatic HIV seropositive subjects. Eighty three percent of the subjects reported improvements in depression and somatic symptoms related to HIV disease. Twenty-seven percent of the subjects dropped out of the study due to complaints of agitation, insomnia, and/or anxiety at weeks 1 and 3 (152). This study was not powered to determine differences in efficacy. Another small study examining the effectiveness of paroxetine in HIV-positive individuals with depression showed significant improvements in HAM-D scores between weeks 2 and 6 (182). Overall, these studies demonstrate the effectiveness of SSRIs in reducing depressive symptoms in HIV-seropositive individuals and indicate that they may be better tolerated than TCAs, supporting their use as first line agents for the treatment of depression in HIV-seropositive individuals.

Recent studies suggest that several of the newer antidepressant agents may be useful for the treatment of depression in this population. Open trials suggests that Nefazodone (151), sustained release bupropion (153), and mirtazapine (149) may be useful for the treatment of depression in HIV-seropositive individuals. Caution should be used with nefazodone in this population with high rates of hepatitis B and C, given reports of nefazodone induced hepatotoxicity (184).

Methylphenidate and dextroamphetamine have been used in the treatment of depression in chronic medical illness, and both have been studied in placebo-controlled trials in patients infected with HIV. These studies have demonstrated reductions in HAM-D scores as early as 2 weeks after initiating treatment (160) Stimulants improved mood, initiative, and energy (119,161). These medications appear reasonably well tolerated.

HIV associated reductions in testosterone levels have been correlated with changes in mood, appetite and sexual function (185). Studies examining the effects of testosterone supplementation (186) and treatment with the adrenal steroid dehydroepiandrosterone (DHEA) (186) have shown promise for improving mood, as well as anabolic and androgenic parameters.

The use of non-traditional agents such as St. John's Wort is best avoided in HIV seropositive individuals. An open label study revealed that the serum concentration of the protease inhibitor indinavir, metabolized by the CYP3A4 isoenzyme was markedly reduced by the administration of St. John's Wort, a CYP3A4 inducer (165). The effect was strong enough to potentially cause drug resistance and treatment failure. S-Adenysylmethionine (SamE) has been

studied in HIV + individuals with preliminary suggestions of efficacy (187).

The choice of an antidepressant agent in patients with HIV, as with other medical populations, should be guided by the potential for drug interactions, as described above, and potential positive or negative interactions between drug and disease. For example, SSRIs, which may cause loose stools, might be avoided in those with chronic diarrhea. Sedating antidepressants are not the best choice for individuals with lethargy. The anticholinergic effects of TCAs may increase the risk of oral candidiasis by causing xerostomia. Their propensity to cause orthostasis makes them a poor choice for patients with weakness or other risks for falls. On the other hand, appetite stimulating medications are most useful for those with cachexia or anorexia (188).

Neurologic Disorders

Strong evidence supports the effectiveness of available antidepressant treatments (123,189,190) for post-stroke depression including TCAs (123,189,191), SSRIs (123,190, 192), trazadone (193), psychostimulants (195), and ECT (195). In addition, two randomized controlled antidepressant trials suggest some benefit of SSRIs in the prevention of post stroke depression (102) (196). There have been few well-controlled trials for antidepressant treatments in AD. Existing trials have produced conflicting results for TCAs (197,198) and SSRIs (199–201). Two studies suggest that antidepressants may be effective for treating depressive symptoms in patients with dementia (202,203). The newer antidepressant agents, particularly the SSRIs are widely considered the first line treatment for AD due to their favorable side effect profiles (204). Classic Tricyclic antidepressants are usually not considered first line treatments because they have more adverse effects such as orthostatic hypotension, delays in cardiac conduction, anticholinergic effects, impaired cognition and delirium (205)

Although commonly used, limited data support the effectiveness of SSRIs or TCAs in the treatment of depression in patients with PD (139), while there have been case reports of exacerbation of motor symptoms with fluoxetine, citalopram and paroxetine (131,206,207). However, a recent meta-analsysis of antidepressant studies in PD found these medications to be efficacious and well tolerated in individuals with PD (208). Similarly, limited data exist for treatments of depression with epilepsy as well (94). Empirically based recommendations are that depression in this population be treated with current antidepressant treatments. While all antidepressants have some potential for lowering the seizure threshold, this risk is small and more common with TCAs than SSRIs or venlafaxine (94). Buproprion, maprotiline and amoxepine are the most likely antidepressants to trigger seizures and require greater caution in this population (209).

CONCLUSION

Depressive disorders are common among the medically ill contributing to morbidity and mortality that exceeds those predicted by the illnesses themselves. Depression is known to worsen medical prognosis, adversely impact adherence to treatment, reduce the quality of life and possibly hasten death from medical illness. As described above, we are just beginning to understand the role of depressive disorders in the pathogenesis of medical illness. Once recognized, depression should be aggressively treated in this population.

Antidepressant treatments can relieve suffering in depressed medically ill patients and significantly improve the quality of their lives. A growing body of evidence supports the effectiveness and safety of the SSRIs and the newer agents in the medically ill, making them the agents of choice in this population. There are safety concerns about the use of TCAs and MAOIs in medically ill patients, who are more susceptible to sedation, orthostasis, and drug interactions, making them less desirable agents, despite their efficacy.

Psychosocial interventions are well supported by the evidence as safe and effective treatments for depression in the medically ill. The most effective programs have been integrated into comprehensive medical/psychosocial programs for patients in specific medical groups. These programs have resulted in relief from depression, improved quality of life, improved adherence, and improved coping. Continued research will elucidate potential causal mechanisms, refine our understanding of current treatments and develop new treatment options for individuals living with chronic health conditions.

ACKNOWLEDGMENT

Dwight L. Evans, MD is a consultant to Abbott, AstraZeneca, Bristol Myers Squibb/Otsuka, Eli Lilly, Forest, Neuronetics, Pamlab, LLC. and Wyeth.

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