

# Depression in the Medical Setting: Biopsychological Interactions and Treatment Considerations

Dwight L. Evans, M.D.; Jeffrey P. Staab, M.D., M.S.; John M. Petitto, M.D.;  
Mary F. Morrison, M.D.; Martin P. Szuba, M.D.; Herbert E. Ward, M.D.;  
Barbara Wingate, M.D., M.S.W.; M. Philip Lubert, M.D.;  
and John P. O'Reardon, M.D.

This article examines depression in 6 medical conditions: coronary artery disease (CAD), cancer, human immunodeficiency virus (HIV) infection, Parkinson's disease, pain, and the sex hormone changes of aging. Research is beginning to define specific biological and psychological mechanisms underlying the adverse interactions between depression and these medical conditions. Antidepressant medications, psychosocial therapies, and hormonal manipulations are effective in reducing depressive symptoms. Specific psychosocial interventions may increase longevity in CAD and cancer and may enhance quality of life in HIV infection. Newer antidepressants appear to be safer and better tolerated than older agents for medically ill patients, but do not appear to be as effective for neuropathic pain. Dopamine agonists may benefit depression associated with Parkinson's disease. Hormone replacement therapy may improve subsyndromal depressive symptoms in postmenopausal women and may enhance antidepressant response for older women with major depression.

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**D**epression is a common illness. According to the National Comorbidity Survey, the 30-day prevalence of major depression in the general population of the United States is 5%.<sup>1</sup> In some groups of medically ill patients, the burden of medical disease pushes the prevalence of depression to more than 50%.<sup>2</sup> Rates of depression increase with acuity of medical care, ranging from a low of 9% in general outpatient environments to 30% or more in acutely hospitalized patients.<sup>3</sup> Despite its common occurrence, depression often is overlooked in medically ill patients. Frequently, the classic signs and symptoms of depression (e.g., dysphoria, demoralization) are overshadowed by vague nonspecific somatic complaints that are ascribed to medical illnesses or side effects of medications. For example, in a study of 3299 elderly patients seen in a primary care clinic over a period of 12 months, depressed patients had much higher rates of fatigue, dizziness,

headache, abdominal pain, and back pain than nondepressed patients.<sup>4</sup> Screening tools have been developed to assist clinicians in detecting depression in the medically ill. These instruments do not depend on physical symptoms to make the diagnosis of depression, so they are most helpful when somatic complaints could arise from either depression or medical illness.<sup>5</sup>

The consequences of overlooked or ineffectively treated depression can be grave. Approximately 15% of patients with untreated major depression commit suicide.<sup>6</sup> Furthermore, a growing body of evidence suggests that depression may accelerate the progression of medical illnesses, producing mortality rates that are higher than expected from the medical conditions alone.<sup>3,7</sup> For example, elderly nursing home patients with major depressive disorder and 2 or more significant medical illnesses had a 59% higher probability of death than similarly ill but nondepressed patients ( $p < .05$ ).<sup>7</sup> Depression also exacts a high price in morbidity and economic cost. In one managed primary care setting, the average annual cost for patients with depression was approximately 1.5 times greater than for an age- and sex-matched cohort of patients without depression even after adjustment for severity of medical illness.<sup>8</sup> Less than 25% of the higher cost was due to mental health treatment. The remainder was due to a generalized increase in health care utilization that could not be attributed to a specific cost segment (i.e., laboratory, pharmacy, etc.). Depressed patients used more medical resources across the board than their nondepressed counterparts.

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From the Department of Psychiatry, University of Pennsylvania School of Medicine (Drs. Evans, Staab, Morrison, Szuba, Wingate, Lubert, and O'Reardon), Philadelphia, and the Department of Psychiatry, University of Florida College of Medicine (Drs. Petitto and Ward), Gainesville.

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Reprint requests to: Dwight L. Evans, M.D., Department of Psychiatry, University of Pennsylvania School of Medicine, 300 Blockley Hall, 423 Guardian Dr., Philadelphia, PA 19104.

This article reviews several aspects of depression in the medically ill. Six medical conditions—coronary artery disease (CAD), cancer, human immunodeficiency virus (HIV) infection, Parkinson's disease, pain, and sex hormone changes with aging—serve as models for examining (1) the increased morbidity and mortality associated with depression in the medically ill, (2) specific biological and psychological mechanisms by which depression and medical conditions exacerbate one another, and (3) the efficacy of antidepressant therapies in patients with medical illnesses. In CAD, cancer, and HIV infection, depression may increase the progression of the comorbid medical condition. For CAD, the biological link between depression and higher cardiac morbidity may be dysregulation of autonomic tone in the electrical conduction system of the heart (i.e., abnormal heart rate variability). Psychologically, negative affective states often precede ischemic events. In cancer and HIV infection, depression appears to have adverse effects on immune system functioning. Several studies suggest that effective psychosocial treatment programs decrease CAD risk factors<sup>9-11</sup> and mortality rates, and increase longevity in cancer patients.<sup>12</sup> Antidepressant medications successfully reduce depressive symptoms in medically ill patients, but data are scarce on the relationships between effective pharmacotherapy and mortality rates or longevity.

As many as one half of all patients with Parkinson's disease suffer from major depression. However, they may be more susceptible to antidepressant side effects and have more difficulty with drug-drug interactions than other patient populations. Dopamine agonists, which have some antidepressant activity, may be useful for Parkinson's disease patients with depression, but further studies of this topic are needed. A growing body of data indicates that selective serotonin reuptake inhibitors (SSRIs) and other new antidepressants are effective, better tolerated, and safer than older agents for patients with medical illnesses. However, the newer SSRIs do not appear to have the analgesic properties of tricyclic antidepressants (TCAs) when treating neuropathic pain. The possible connections between sex hormones and depression remain controversial. Estrogen replacement therapy relieves subsyndromal depressive symptoms in postmenopausal women. However, it does not relieve the mood symptoms of major depressive disorder. Interestingly, estrogen replacement therapy may increase the response of older women to SSRIs. There are limited data on the antidepressant efficacy of replacing other hormones that normally decline with age.

## INTERACTIONS BETWEEN DEPRESSION AND MEDICAL CONDITIONS

### Coronary Artery Disease

Depression is common in patients with CAD. Fifteen percent to 25% of cardiac patients suffer from major de-

pression.<sup>13-15</sup> This rate is 3 times higher than in the general population and greater than that seen in patients with other chronic medical conditions.<sup>16</sup>

Risk factors for depression in patients with CAD are similar to those found among noncardiac patients and include female sex, prior history of mood disorder, family history of psychopathology, recent stressful life events, and a sense of being out of control of one's life.<sup>14,15,17,18</sup> Not surprisingly, depression also is associated with the severity of medical illness, particularly infarct size and functional disability, in patients with CAD.<sup>14,15</sup> This might raise a question about depression being an epiphenomenon of CAD, but substantial research has established depression as an independent cardiac risk factor. In patients discharged from the hospital following a myocardial infarction (MI), post-MI depression was a significant predictor of cardiac mortality at 6 months (adjusted odds ratio [OR] = 4.29, 95% confidence interval [CI] = 3.14 to 5.44)<sup>19</sup> and 18 months (adjusted OR = 6.64, 95% CI = 1.76 to 25.09),<sup>20</sup> even after accounting for the effects of typical cardiac risk factors such as left ventricular dysfunction and previous MI. Depression also appears to be a risk factor for a first MI. In a follow-up to the Baltimore cohort of the Epidemiologic Catchment Area study, 1551 subjects without cardiac symptoms in 1981 were surveyed again in 1994. Sixty-four reported MIs. After controlling for other cardiac risk factors, the adjusted odds ratio for an MI in subjects who had major depression in 1981 was 4.54 (95% CI = 1.65 to 12.44).<sup>21</sup> Similar results were obtained in a study of 730 Danish men and women.<sup>22</sup> Perhaps even more provocative is the finding that an increase in depressive symptoms may foreshadow an MI, stroke, or death. In a multicenter study of systolic hypertension in elderly adults, 4367 men and women aged 60 years or older were assessed every 6 months for an average of 4.5 years using the Center for Epidemiological Studies Depression scale (CES-D). After multivariate correction for demographics and other risk factors, every 5-unit increase in CES-D score from baseline carried an 18% increased risk of MI or stroke and a 25% increased risk of death.<sup>23</sup>

The mechanisms underlying the increase in cardiovascular risk with depression are unknown. Investigations point to several psychosocial issues and an increasing number of potential biological factors. Post-MI patients with depression were less adherent to exercise programs and more likely to continue smoking than their counterparts without depression.<sup>24,25</sup> Poor social support increased the risk of death in men with known ischemic heart disease during a 5-year follow-up period in one study<sup>25</sup> and in men and women within 6 months of an MI in another investigation.<sup>26</sup> High levels of hopelessness predicted incident MI during a 6-year study of 2428 middle-aged men.<sup>27</sup> Several negative affective symptoms including anxiety, anger attacks,<sup>28</sup> hostility,<sup>29</sup> frustration, sadness, and tension<sup>30</sup> also have been linked to biological risk factors for CAD.

Depressed outpatients with high levels of anxiety had higher serum cholesterol levels and a greater likelihood of prolonged QTc intervals than nonanxious depressed patients. Those with anger attacks also had higher cholesterol levels.<sup>28</sup> In 42 CAD patients, hostility was positively correlated with minutes of ischemia during ambulatory electrocardiographic (ECG) monitoring.<sup>29</sup> A second ambulatory ECG study found that negative emotional states preceded episodes of ST-segment depression. Myocardial ischemia was more than twice as likely to occur during the hour following high levels of frustration, sadness, or tension than during less stressful periods of the day.<sup>30</sup> Cardiac patients with depression also were found to have elevated levels of 2 platelet activation factors, potentially increasing their risk of thrombosis.<sup>31</sup> 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. Negative affective states have substantial impact on sympathetic and parasympathetic tone. Low heart rate variability is a significant risk factor for death following an MI.<sup>32</sup> Patients with CAD and depression had lower heart rate variability than patients with CAD but no depression.<sup>33</sup> Finally, depression appears to compound the negative impact of other cardiac risk factors. For example, the highest death rate (60%) in patients at 18 months post-MI was in a subgroup with more than 10 premature ventricular contractions (PVCs) per hour and a Beck Depression Inventory (BDI) score greater than 10.<sup>20</sup>

The relationship between CAD and depression is clearly complex. Not only does depression affect the incidence and course of CAD, but a body of evidence demonstrates that in elderly patients cardiovascular disease can be etiologic in the onset of depressive illness. The vascular hypothesis of depression posits that vascular insults precipitate depressive episodes in a subset of elderly patients, particularly those with a late onset of the first affective episode.<sup>34</sup> The same arteriosclerotic disease that is manifest in the heart as CAD can lead to mini-infarcts in the brain which are manifest as clinical depression.<sup>35</sup> Consistent with this is the finding in a study of 15,186 patients seen in a general medical practice over a period of 1 year that patients with vascular disease had a significantly higher rate of depression than patients without vascular disease.<sup>36</sup>

## Cancer

The prevalence of depression among cancer patients varies with the type of malignancy, ranging from 1% in lymphoma patients on a waiting list for bone marrow transplantation to approximately 50% in patients with pancreatic cancer. Overall, the rate of major depression in cancer patients is estimated to be 24%.<sup>37</sup> An additional group of patients suffer from depressive symptoms that do not meet the full criteria for a major depressive episode. For example, in a group of 83 women with primary or re-

current gynecologic cancers, 23% had major depression and an additional 24% were diagnosed with dysthymia or an adjustment disorder.<sup>38</sup> Among cancer patients, depression is correlated with hospitalization, poor physical function, low quality of life, and a lack of social support.<sup>39-42</sup> Depression is increased in cancer patients with poor pain control.<sup>43</sup> It is less frequent in those whose cancer is in remission.<sup>40</sup> Despite the common occurrence of major and subsyndromal depression among cancer patients, few receive specific antidepressant treatment. Prior to the introduction of SSRIs, a study of hospitalized patients at the Memorial Sloan-Kettering Cancer Center revealed that only 3% received an antidepressant.<sup>44</sup> Treatment rates are likely to have increased in the decade since that study, but there is no indication that they match the prevalence of depression in the cancer population.

## HIV Infection and Acquired Immunodeficiency Syndrome

The prevalence of depression may be increased in some groups of HIV-infected individuals. Although a community-based survey did not find a general increase in depression among those infected with HIV,<sup>45</sup> a number of clinical studies have found a relatively high prevalence of depression in HIV-infected homosexual men. For instance, at time of entry into a longitudinal cohort study, it was found that 29% of HIV-positive and 45% of HIV-negative gay men had a past history of major depression.<sup>46</sup> These rates exceed the lifetime prevalence of depression established by the Epidemiologic Catchment Area community sample for a comparable demographic group. The rates of major depression at the time of entry into the study and at 6-month follow-up were 8% and 10% respectively for HIV-positive men and 3% and 11% respectively for HIV-negative men. Other studies<sup>47-49</sup> also have found higher lifetime rates of major depression in HIV-infected and uninfected gay men.

Whether the presence of HIV infection itself increases the rate of major depression is still debated. One study<sup>50</sup> found that depression increased just prior to the development of acquired immunodeficiency syndrome (AIDS). By contrast, a recent study<sup>51</sup> found that rates of syndromal depression were stable longitudinally despite HIV-illness progression in a group of homosexual men that were assessed over 9 semiannual visits. This again suggests that select subgroups of HIV-infected individuals may be vulnerable. Either way, the presence of depression may have an impact on HIV-disease progression. Two recent studies<sup>52,53</sup> found evidence for depression being linked with increased risk of disease progression. A study<sup>52</sup> among 395 homosexual and bisexual men infected with HIV found that most acute and chronic concurrent health conditions were not significant predictors of disease progression after controlling for immune status. However, 2 factors—depression and smoking—were found to be asso-

ciated with higher risk of progression to an AIDS diagnosis. Men with symptoms of depression had a relative hazard ratio of 1.4 (95% CI = 1.00 to 2.08) for progression to a diagnosis of AIDS. Congruent with this, a prospective cohort study<sup>53</sup> of 402 homosexual and bisexual men found that depressive affect (as measured on the affective subscale of CES-D scale) was associated with increased mortality risk (adjusted risk ratio = 1.67, 95% CI = 1.01 to 2.78). Even though a meta-analysis<sup>54</sup> of 19 published studies concluded that depressive symptoms were not associated with objective indicators of accelerated HIV progression, this may not be the case for major depressive disorder and should prompt a careful screening for the presence of depression in all HIV-positive individuals. It is important to bear in mind that although psychological disturbances and major depression can present as the initial manifestation of conditions such as destruction of the thyroid gland by Kaposi's sarcoma<sup>55</sup> or AIDS encephalitis,<sup>56</sup> controlled longitudinal studies indicate that complaints of fatigue and insomnia in asymptomatic HIV-infected men are likely related to psychological disturbances and major depression.<sup>57</sup>

### Parkinson's Disease

Major depression occurs in 40% to 50% of patients with Parkinson's disease,<sup>58-61</sup> making it the most common neuropsychiatric manifestation of Parkinson's disease. The presence of depression in Parkinson's patients poses an added burden to the underlying illness. A diagnosis of depression in patients with Parkinson's disease is associated with greater memory and language impairment than in Parkinson's patients without depression.<sup>62</sup> Depression impairs motor performance in patients with Parkinson's disease independent of motivational factors.<sup>63,64</sup> Many have speculated that the increase in motor impairments with depression is due to additive prefrontal cortical hypo-function seen on functional neuroimaging studies.<sup>65,66</sup> Other studies have shown that depression in patients with Parkinson's disease is associated with poor function in activities of daily living when compared with matched control groups without depression.<sup>61</sup>

### Pain

Pain frequently accompanies both medical illnesses and depression. Furthermore, the co-occurrence of depression and medical illness may exacerbate pain symptoms.<sup>1,67</sup> The causal relationship between pain and depression remains an intriguing area of research.<sup>68</sup> Two studies<sup>69,70</sup> examined the onset of depression and pain. In about half the cases, depression and chronic pain developed together. Another 40% the time, pain occurred first. Only infrequently did depression precede chronic pain. Therefore, it is not a simple matter to conclude that the psychosocial burden of pain and its attendant disability lead to depression. The neurobiological relationships be-

tween pain and depression are not known. Anatomically, the sensory disturbances in chronic pain are understood better than the affective or motivational components. It is speculated that the affective components are mediated via neural pathways linking the posterior portion of the ventral medial thalamic nucleus to the limbic system.<sup>71</sup> Interestingly, serotonin and norepinephrine—the neurotransmitters most associated with depression—play key roles in pain modulation.<sup>72</sup>

### Sex Hormone Changes With Aging

**Estrogen.** Although depression is often seen in the elderly patient, the prevalence of major depression is significantly lower in the healthy geriatric population than in younger people.<sup>73</sup> However, even in the elderly, women are 2 to 3 times more likely to have major depression than men. Prevalence rates for depression in the healthy geriatric population are 1.4% for women and 0.4% for men.<sup>73</sup> The epidemiology of depression in the elderly has not been studied as extensively as in younger populations, and gender differences have been barely studied in this age group. Cyclical sex steroid changes are hypothesized to contribute to the increased prevalence of depression in younger age groups. In postmenopausal women, there are data from epidemiologic and clinical studies suggesting that low estrogen contributes to increased depressive symptoms and a lack of antidepressant response.

In a community population of 1190 white women 50 years and older, 25% of the women were using estrogen.<sup>74</sup> In this cross-sectional study, mean depressive symptom scores increased steadily with age in the untreated women, while no significant increase in mean depressive scores with age was seen in the estrogen-treated group. This finding is consistent with the hypothesis that ongoing estrogen deficiency increases the likelihood of developing depressive symptoms in the postmenopausal age range and that estrogen therapy is protective. However, in the youngest group (50–59 years), women treated with estrogen had significantly higher depression scores than untreated women of the same age. The reason for this is not known.

**Estrogen and serotonin.** Several investigators have hypothesized that the correlation between low estrogen levels and depression is mediated by effects on serotonin. The effect of estrogen on peripheral serotonin markers has been studied. Nondepressed women after bilateral oophorectomy were given supraphysiologic doses of estrogen to study the relationship between depressive symptoms, estrogen levels, and platelet <sup>3</sup>H-imipramine binding.<sup>75</sup> Indeed, variations in mood scores were coincident with changes in estrogen levels and <sup>3</sup>H-imipramine binding. Although all mood scores were in the normal range, hormonal therapy was associated with a more positive mood and fewer depressive symptoms than placebo. Urinary 5-hydroxyindoleacetic acid levels (5-HIAA), a serotonin metabolite, were determined before and after estrogen

treatment in postmenopausal women in an open study. Both oral and transdermal estradiol produced increases in 5-HIAA excretion, with the greatest increases in 5-HIAA excretion in the transdermal estrogen group. Postmenopausal women were given the serotonin agonist *m*-chlorophenylpiperazine (*m*-CPP) to probe serotonergic function.<sup>76</sup> Postmenopausal women demonstrated blunted cortisol responses to *m*-CPP in comparison with premenopausal women, and estrogen replacement increased the cortisol response to *m*-CPP in postmenopausal women, suggesting that low serotonin responsivity in postmenopausal women may account for a vulnerability to depressive symptoms and that estrogen can improve serotonin responsivity.<sup>77</sup>

**Dehydroepiandrosterone.** Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) are the most abundant steroids in humans and decrease dramatically with aging.<sup>78</sup> DHEA has attracted recent attention because of its correlation with successful aging and the suggestion that it may have protective effects on diabetes, cancer, aging, and autoimmune disease.<sup>79,80</sup> DHEA has long been of interest to psychiatrists, who used it as early as 1952 for the treatment of neurasthenia.<sup>81</sup> Data in children and adolescents with major depression suggest that there may be subtypes of major depression with low morning DHEA, high morning cortisol, or both abnormalities.<sup>82</sup> It remains to be determined whether there are subtypes of major depression with low DHEA among older adults and whether this might have significance for the pathogenesis of depression or its treatment. In a case series of older people (age range, 51–72 years) with major depression and low DHEA or DHEA-S levels, subjects took DHEA 30 to 90 mg/day orally for 4 weeks and had significant improvements in depressive symptoms.<sup>83</sup> Increases in serum DHEA and DHEA-S levels were correlated with improvements in depression scores. The antidepressant effect of DHEA may result from an antiglucocorticoid effect. DHEA administration was associated with a reduction in 4 p.m. serum cortisol levels in a dose-dependent fashion ( $r = -0.78$ ,  $p < .04$ ).<sup>84</sup> In another study, older subjects were given 50 mg/day of DHEA in a randomized placebo-controlled crossover trial to study effects of DHEA on aging-associated catabolism.<sup>77</sup> Standard psychiatric measures were not used. Sixty-seven percent of men and 84% of women perceived an increase in physical and psychological well-being. Subjects reported improved quality of sleep, feeling more relaxed, increased energy, and better ability to handle stress during DHEA replacement. These 2 small studies suggest that replacement DHEA may have beneficial effects on depressive symptoms, but confirmation of this observation requires larger studies with standard psychiatric measures. In addition, there may be a role for DHEA in conjunction with conventional antidepressants to improve efficacy in treatment-resistant depression in elderly patients. However, this has not been studied.

**Testosterone.** Testosterone levels in men decrease progressively with age. At 80 years, the mean testosterone level is about 60% of the mean level at age 20 to 50 years.<sup>85</sup> Hypogonadal men are thought to derive benefit from androgens in terms of resumption of secondary sexual characteristics as well as improvement in libido, penile erections, energy, and mood.<sup>86</sup> With a 40% decline in testosterone, one could argue that many geriatric men are hypogonadal. In one study, endogenous testosterone levels in aging men were inversely correlated with depressive symptoms.<sup>87</sup> However, in a double-blind, placebo-controlled trial in 56 elderly men, testosterone supplementation did not improve mood.<sup>88</sup> Women also experience a decline in testosterone with age. Even in premenopausal women, there is a decrease in testosterone levels such that levels of testosterone are about half as high in women in their 40s as in their 20s.<sup>89</sup> Testosterone has been given to older women by gynecologists for disorders of libido and mood, but this has received little systematic study.<sup>90</sup> In surgically menopausal young women, a beneficial effect on depressive symptoms was reported after treatment with estrogen, androgen, or a combined estrogen-androgen preparation.<sup>75</sup> Certainly, if testosterone is to be given to women, its effects should be carefully studied.

#### TREATMENT OF DEPRESSION IN PATIENTS WITH MEDICAL COMORBIDITY

Once depression is recognized in the medically ill, it must be safely and effectively treated. Underlying medical problems increase the complexity of pharmacotherapy, but the key to success is an adequate dose and duration of antidepressant medication just as it is for patients without medical comorbidity. In the last decade, clinical practice has shifted away from TCAs and monoamine oxidase inhibitors (MAOIs) to SSRIs and other newer agents. The older antidepressants are unquestionably effective and their safety and side effect profiles are well known. However, their adverse effects present greater problems in the medically ill than they do in medically healthy individuals. Several case series have documented TCA discontinuation rates as high as one third in medically ill patients because of adverse effects.<sup>91,92</sup> Delirium occurred in 16% of medically compromised patients on low-dose imipramine or doxepin (mean  $\pm$  SD dose =  $57 \pm 29$  mg/day).<sup>93</sup> TCAs double the risk of hip fracture in elderly patients, either because of sedation or orthostasis or both.<sup>94</sup> Data are only beginning to emerge on the safety and effectiveness of newer classes of antidepressants in patients with a variety of medical conditions. The following sections will examine these data in the case of the 6 medical conditions that are the subject of this review. The effectiveness of psychological therapies that have been developed to treat depression in the medically ill will also be discussed. Specific intervention programs have been proven to decrease

depressive symptoms and improve functional capabilities, and there is a small amount of evidence that they may decrease medical morbidity and mortality.

### Coronary Artery Disease

The pathophysiologic links between depression and CAD have not been elucidated fully, but the goals of aggressive psychiatric intervention for patients with CAD and depression are clear: curtail morbidity and mortality and enhance function. A recent review of cardiac rehabilitation programs found that they reduce cardiac risk factors, improve physical function, and diminish levels of anxiety, depression, and somatization.<sup>9</sup> Psychosocial interventions add to the benefits of standard cardiac rehabilitation. In a meta-analysis of 23 controlled studies, patients who received psychosocial interventions (e.g., individual and group psychotherapy, stress management) in conjunction with standard cardiac rehabilitation had greater reductions in systolic blood pressure, heart rate, and serum cholesterol than patients who received standard rehabilitation alone. Furthermore, patients enrolled only in the standard program had a higher 2-year mortality rate (adjusted OR = 1.70, 95% CI = 1.09 to 2.64) and a greater likelihood of additional cardiac events (adjusted OR = 1.84, 95% CI = 1.12 to 2.99).<sup>10</sup> The Recurrent Coronary Prevention Project demonstrated a 44% reduction in reinfarction and a decrease in psychological risk factors such as hostility, impatience, depression, and anger when post-MI patients received psychosocial treatments.<sup>11</sup> Thus, the most favorable outcomes for patients who have suffered an MI are obtained by comprehensive programs that integrate psychosocial interventions with standard cardiac rehabilitation protocols. These programs successfully reduce both traditional risk factors (e.g., excess weight, hypertension, elevated serum lipids, lack of exercise) and psychological risk factors (e.g., depression, anger, hostility, social isolation) for elevated morbidity and mortality following an MI. A combined risk factor reduction program for healthy men also reduced a wide range of risk factors for CAD.<sup>95</sup>

Data on the risks and benefits of psychopharmacotherapy for patients with CAD and depression are incomplete. Early investigations using older antidepressants were contradictory, leading to divergent opinions about their safety.<sup>96,97</sup> Studies using newer agents are just beginning to be published. Before the introduction of the SSRIs, few physicians would prescribe antidepressants to patients with a recent MI.<sup>98</sup> Many physicians considered MAOIs and TCAs to be contraindicated for patients within 6 months of an MI and for those with poor myocardial function.<sup>97</sup> MAOIs were avoided because of their dietary restrictions, potential medication interactions, and tendency to cause orthostatic hypotension. TCAs were prescribed infrequently due to concerns that cardiovascular side effects such as increased heart rate, orthostatic hypotension, and intraventricular conduction delays would aggravate

the condition of patients with CAD. In one study, 7 (22%) of 32 geriatric patients developed major cardiac side effects during a 37-week trial of low-dose amitriptyline, imipramine, or nortriptyline. Five of those 7 had preexisting cardiac disease.<sup>99</sup> However, imipramine proved to be effective and well-tolerated in a short study of 12 men who developed depression following MI or cardiac bypass grafting. Depression rating scale scores were improved significantly after 4 weeks. No conduction abnormalities were found and only 1 subject dropped out due to orthostatic hypotension.<sup>100</sup>

Recent research is more consistent than these earlier studies and strongly suggests that TCAs may increase morbidity and mortality in patients with CAD by adversely affecting cardiac conduction. Two large studies investigating the suppression of asymptomatic ventricular ectopy in post-MI patients (Cardiac Arrhythmia Suppression Trials [CAST] I and II) were halted early because of an increased risk of sudden death in patients receiving class 1 antiarrhythmic medications.<sup>101,102</sup> A meta-analysis of 4 smaller studies also found an increase in mortality with quinidine, a type 1A agent.<sup>103</sup> These findings raised considerable concern about using TCAs in patients with CAD because TCAs possess type 1A antiarrhythmic activity.<sup>104</sup> Direct evidence of the adverse effects of TCAs on cardiac conduction was obtained in a series of laboratory studies in dogs. Amitriptyline, imipramine, and clomipramine slowed cardiac conduction in infarcted regions of dogs' hearts. At higher doses, imipramine prolonged the QRS interval. Amitriptyline prolonged the PR, QRS, and QT intervals, slowed conduction in unaffected heart tissue, and increased the frequency of arrhythmias induced by electrical stimulation.<sup>105,106</sup> Finally, in 2 studies of medically healthy depressed patients, TCAs decreased heart rate variability.<sup>107,108</sup> In patients with CAD, this could aggravate a risk factor for sudden cardiac death after MI. Taken altogether, these data suggest that the negative impact of TCAs on the cardiac conduction system may outweigh their effectiveness against depression in patients with CAD. Therefore, TCAs should be used only with caution in cardiac patients. The safety of MAOIs has not been examined systematically in patients with CAD. However, their side effect profiles and potential interactions with cardiovascular medications could argue against their use in this patient population.

A small but increasing amount of data suggests that SSRIs are safe and effective for treating depression in patients with CAD. Their cardiovascular side effect profile is quite favorable with little to no anticholinergic or  $\alpha_1$ -adrenergic activity. There are no data regarding serious cardiac side effects, except for isolated case reports of bradycardia and atrial fibrillation with fluoxetine.<sup>109-111</sup> The SSRIs also do not appear to aggravate cardiac risk factors. Fluvoxamine had no impact on cardiac conduction parameters in post-MI dogs.<sup>112</sup> Fluvoxamine<sup>107</sup> and paroxe-

tine<sup>107,108</sup> had no deleterious effect on heart rate variability in humans. In the first study to compare a TCA with an SSRI in patients with CAD, nortriptyline and paroxetine were equally efficacious for the treatment of depression. However, 7 (18%) of 40 patients treated with nortriptyline experienced adverse cardiac events (sinus tachycardia, angina, increased ectopy) compared to only 1 (2%) of 41 patients treated with paroxetine. That patient was restarted on paroxetine after an angioplasty of the circumflex artery relieved his unstable angina.<sup>113</sup> These findings are consistent with preclinical data supporting SSRIs as a safer alternative to TCAs.

Although the SSRIs appear to be free of adverse cardiac effects, they have the potential to interact with a variety of cardiovascular medications. All 4 SSRIs show in vitro inhibition of one or more isoenzymes in the cytochrome P450 system.<sup>114-117</sup> Fluoxetine is a potent inhibitor of cytochrome P450 2D6 and 2C9, a mild inhibitor of 3A3/4, and a moderate inhibitor of 2C19. Sertraline is a moderate inhibitor of cytochrome P450 2D6 and may affect the 3A3/4 and the 2C family. Paroxetine is a potent inhibitor of 2D6 but does not appear to affect other cytochrome P450 isoenzymes. Fluvoxamine strongly inhibits cytochrome P450 1A2, 3A3/4, and the 2C family. Many common cardiovascular medications are metabolized by cytochrome P450 isoenzymes including  $\beta$ -blockers, calcium channel blockers, antiarrhythmic agents, warfarin, and CoA reductase inhibitors.<sup>112-123</sup> Systematic in vivo pharmacologic investigations of the potential interactions between these cardiovascular medications and the SSRIs have not been performed, although in some instances case reports suggest possible adverse effects. For example, heart block<sup>124</sup> and bradycardia<sup>125</sup> were reported with fluoxetine plus propranolol or metoprolol. Until more data are available, careful monitoring of patients taking cardiovascular medications is prudent when an SSRI is prescribed. Another potential source of drug-drug interactions is the displacement of medications that are highly bound to plasma proteins. Fluoxetine, sertraline, and paroxetine are more than 95% protein bound and may compete with other highly bound drugs such as warfarin.

Less is known about the risks and benefits of nefazodone, bupropion, venlafaxine, and mirtazapine for patients with CAD. Nefazodone is a potent cytochrome 3A4 inhibitor.<sup>126</sup> Bupropion, venlafaxine, and mirtazapine do not appear to substantially inhibit the cytochrome P450 system.<sup>127,128</sup> Like the SSRIs, all of these medications have lower anticholinergic activity than the TCAs. In medically healthy depressed patients, no changes were reported in heart rate or cardiac conduction with any of these drugs.<sup>128-130</sup> However, bupropion and venlafaxine increased diastolic blood pressure by an average of 7 mm Hg after 4 to 6 weeks of treatment.<sup>129,130</sup> Diastolic blood pressure changes were dose-related with venlafaxine. At doses above 200 mg/day, 5.5% of patients had an increase of 15

mm Hg or more from baseline or had a diastolic blood pressure greater than 105 mm Hg.<sup>129</sup> Mirtazapine produced weight gain in 10% of patients.<sup>131</sup> It also decreased heart rate variability, but to a lesser degree than did imipramine.<sup>107</sup> Bupropion is the only one of these antidepressants that has been studied to date in patients with heart disease. In 36 patients with major depression and left ventricular dysfunction or cardiac conduction abnormalities, bupropion did not affect heart rate, ejection fraction, cardiac conduction, or ventricular arrhythmias. However, 2 patients developed clinically significant hypertension and 1 patient had orthostatic hypotension.<sup>131</sup>

Some depressed patients with CAD may require electroconvulsive therapy (ECT). The indications for ECT in depressed patients with CAD are no different than those for depressed patients without CAD and include severe depression, medication resistance or intolerance, catatonia or other severe medical/psychiatric conditions, and patient preference.<sup>132</sup> Patients with CAD can undergo ECT successfully, although they have an increased risk of developing ischemia or arrhythmias during the procedure.<sup>133</sup> Pretreatment with labetalol can reduce these risks by controlling tachycardia, hypertension, and PVCs.<sup>134</sup>

## Cancer

Psychosocial interventions and antidepressant medications have been studied in depressed patients with cancer. Several studies suggest that psychosocial treatments improve survival, reduce depressive symptoms, and enhance coping skills. For example, a structured intervention program that included health education, problem-solving skills, stress management, and social support reduced both depressive symptoms and mortality in postoperative malignant melanoma patients. Six months after completing the psychosocial treatment program, participants reported less depression ( $p = .017$ ), fatigue ( $p = .022$ ), and confusion ( $p = .013$ ) on the Profile of Moods State than a control group who did not receive psychological intervention. During a 6-year follow-up period, participants in the psychosocial program had a mortality rate of 8.8% (3 of 34) compared with 29.4% (10 of 34) for the control group ( $p = .03$ ).<sup>135</sup> The improvement in depression was associated with an increase in large granular lymphocytes, natural killer (NK) cells, and natural killer cell activity (NKA).<sup>136</sup> In animal models of cancer spread, more large granular lymphocytes and higher NKA correlate with resistance to metastases.<sup>137</sup>

Psychotherapy also improved cancer survival in women with advanced breast cancer. Fifty women with metastatic breast cancer underwent weekly group psychotherapy for 90 minutes and were taught self-hypnosis for pain control in addition to their oncological regimens. Their survival was twice that of a control group who received only usual oncological care (36.6 vs. 18.9 months,  $p < .0001$ ).<sup>12</sup> The differences in survival between the 2

groups became apparent only after 20 months. These studies suggest that well-organized psychosocial interventions may be effective for treating mild-to-moderate depression in cancer patients. Over the long run, they also have a substantial positive impact on survival through unknown mechanisms that may be related to an enhancement of immune function.

A number of antidepressant medication trials in cancer patients are beginning to emerge. Two controlled investigations and 1 uncontrolled study demonstrated a reduction in depressive symptoms and improvement in quality of life for depressed patients with cancer. A double-blind trial compared mianserin, a tetracyclic antidepressant with a low incidence of anticholinergic and cardiovascular adverse effects, with placebo in women with major depression and breast cancer.<sup>138</sup> At 28 days of therapy, the 36 women who received mianserin had significantly lower Hamilton Rating Scale for Depression (HAM-D) scores than the 27 women who received placebo (8.19 vs. 13.2,  $p < .01$ ). Mianserin was tolerated well in 6 women during the first week of therapy with mild sedation as the only major side effect. A recent study<sup>139</sup> achieved similar results. Mianserin was studied in patients with breast cancer (stage I or II, without metastases) using a randomized double-blind placebo-controlled design. Fifty-five women meeting DSM-III criteria for depression participated in the study. The 21-item HAM-D scale was used to assess efficacy. A trend favoring mianserin emerged by day 14. At days 28 and 42, significantly larger reductions in HAM-D scores were found in the mianserin treatment group.

The quality of life of 22 female cancer patients with major or minor depression was examined in an uncontrolled study of antidepressant medications.<sup>140</sup> Women were divided into 2 groups, those having received an adequate antidepressant trial—defined as a TCA dose equivalent to at least 150 mg/day of imipramine for 4 or more weeks—and those without adequate antidepressant treatment. Patients who were treated adequately had significantly lower posttreatment HAM-D scores than those with poor medication management (8.6 vs. 12.7,  $p = .008$ ). Adequately treated patients also had a better quality of life as measured with the Psychosocial Adjustment to Illness scale ( $p = .012$ ). Importantly, patients with minor depression appeared to benefit from adequate antidepressant therapy.

Another study<sup>141</sup> yielded less robust effects when evaluating the efficacy of fluoxetine in cancer patients with mild-to-moderate depression or adjustment disorder according to DSM-III criteria. In this 14-site trial, 91 patients were randomly assigned in double-blind fashion to receive either 20 mg/day of fluoxetine or placebo. Based on the a priori response criterion of a reduction in Hospital Anxiety and Depression Scale (HADS) scores to below 8, there was no significant difference between the 2 groups. However, the authors found fluoxetine to be more effective

than placebo in improving global psychological adjustment as measured by the Revised Symptom Checklist (SCL-90-R). They concluded that their findings were consistent with previous positive reports for antidepressant pharmacotherapy in oncology.

At this juncture, antidepressant choice for cancer patients is guided more by anecdote than clinical research. More data should be forthcoming from clinical trials that are underway, including a comparison of paroxetine, desipramine, and placebo in breast cancer patients with depression or adjustment disorder with depressed mood.

### HIV Infection and AIDS

A comparative analysis of the efficacy of antidepressant agents in HIV-infected individuals has been published.<sup>142</sup> These data show that response rates for standard antidepressants ranged from 70% to 74% compared with 33% for placebo. Imipramine<sup>143</sup> was effective in 97 HIV-infected patients in a randomized placebo-controlled trial. At 6 weeks, the response rates were 74% for the imipramine group and 26% for the placebo group. No changes in CD4<sup>+</sup> helper/inducer cell counts were found in imipramine-treated subjects. However, adverse side effects led to discontinuation of imipramine within 6 months. In a comparison of desipramine versus methylphenidate in a treatment trial of 15 subjects, both agents showed approximately a 50% response rate. However, subjects treated with desipramine experienced more adverse side effects including dry mouth, anxiety, and insomnia.<sup>144</sup> In an open trial<sup>145</sup> assessing the efficacy of dextroamphetamine in 24 individuals with AIDS who exhibited debilitating low energy and a DSM-III-R depressive disorder diagnosis, 75% of the subjects responded to treatment. Improvement in mood and energy coincided with one another, and analyses revealed significant reductions in HAM-D scores by as early as a week or two. Although systematic follow-up evaluations were not available, treatment effect (improved mood and energy) was maintained for up to 2 years. Placebo-controlled trials will be important to follow-up of this promising observation.

In a study<sup>146</sup> related to the one described above, HIV-infected depressed subjects who failed imipramine treatment (e.g., subjects who relapsed, did not tolerate side effects, nonresponders) were enrolled in a 12-week open trial of fluoxetine. Although the baseline levels of depression severity in HAM-D score were lower in the latter study (12.5) compared with the imipramine study (15.8), 83% of subjects treated with fluoxetine (15–60 mg/day) responded and exhibited significant reductions in HAM-D scores. Fluoxetine treatment did not alter CD4<sup>+</sup> counts. The authors noted that fluoxetine was tolerated better than imipramine. Interestingly, they also found that all 7 patients treated with the combination of fluoxetine and dextroamphetamine (5–25 mg/day) responded over the 12-week course of study.



A preliminary double-blind study<sup>147</sup> found that cocaine-dependent, HIV-infected subjects with comorbid depression responded to fluoxetine with improvement in depression and decreased levels of cocaine consumption and craving. A study of sertraline also has been conducted to determine the efficacy of the drug in the treatment of depression in HIV illness.<sup>148</sup> In an open trial of 28 depressed HIV-infected subjects, a 70% response rate was observed among subjects who completed the 8-week open trial. Side effects resulted in a loss of 18% of the total sample. Sertraline did not alter either CD4<sup>+</sup> cell counts or NK cell counts. In a 6-week open trial<sup>149</sup> of paroxetine (20 mg/day) in 10 HIV-positive patients with major depression, significant improvement in HAM-D scores was noted between weeks 2 through 6 of the study. In a 6-week open trial<sup>150</sup> of paroxetine, fluoxetine, and sertraline in 33 symptomatic HIV-infected individuals with depression, 73% completed the trial and 83% of those subjects were responders. Most of the subjects who dropped out of the study did so because of complaints of agitation, anxiety, and insomnia during weeks 1 through 3. They found that depression, as well as somatic symptoms perceived to be related to HIV infection, improved with SSRI treatment. Differences in the efficacy between the 3 SSRIs could not be reliably ascertained because of the design and small sample size, although the authors suggested that fluoxetine was the most effective and best tolerated.

### Parkinson's Disease

Several studies have indicated that depression in Parkinson's disease is grossly underrecognized and undertreated.<sup>59,151-153</sup> To date, there have been few systematic investigations of the efficacy of antidepressant treatment in Parkinson's patients. A meta-analysis by Klaassen et al.<sup>154</sup> found that the limited number of placebo-controlled studies that had been done by 1995 contained various methodological flaws. These investigations failed to provide sufficient detail about blinding, included some patients with Parkinson's disease but no depression (or depression but no Parkinson's disease), and had small patient numbers. As a result, few conclusions may be drawn about the efficacy of traditional antidepressants in patients with Parkinson's disease.

Cummings<sup>60</sup> reviewed 4 early double-blind studies of the efficacy of imipramine, nortriptyline, desipramine, and bupropion in the treatment of depression in Parkinson's patients. These compounds had mixed success. For example, nortriptyline relieved depression, but did not affect the motoric manifestations of the Parkinson's disease.<sup>155</sup> Bupropion, which possesses indirect dopaminergic activity, improved depression in about 42% and Parkinson's motor symptoms in about 50% of Parkinson's disease patients with depression.<sup>156</sup> Later studies have not advanced methodological design or evaluated the newer antidepressants in depressed patients with Parkinson's disease.

SSRIs might be beneficial for patients with Parkinson's disease, because serotonin metabolism is affected by this illness.<sup>157</sup> Hauser and Zesiewicz<sup>158</sup> reported a drop in Beck Depression Inventory scores, but no change in Parkinson's motor symptoms in an open-label trial of sertraline up to 50 mg/day in 15 patients with Parkinson's disease and depression. Recently, Steur and Ballering<sup>159</sup> reported the results of open-label treatment of 10 depressed Parkinson's patients with either moclobemide (600 mg/day) or moclobemide plus selegiline (10 mg/day). Bradykinesia improved in all combination-therapy patients. Both groups showed an antidepressant effect after 6 weeks of treatment, although a greater effect was observed in the combination group. Levodopa has been reported to decrease depression in Parkinson's patients.<sup>151</sup>

There have been a number of investigations of dopamine metabolism in medically healthy individuals with major depression as well as studies of the antidepressant efficacy of dopaminergic agents. Some studies have found L-tyrosine (a precursor of dopamine) and levodopa to have antidepressant activity, especially in patients who have low levels of the dopamine metabolite homovanillic acid (HVA) in the CSF before treatment or in those who exhibit psychomotor retardation. This finding suggests that the dopamine system plays a role in depression.<sup>160</sup> Bromocriptine, priribedil, and pergolide have demonstrated antidepressant effects.<sup>160,161</sup> The highly selective dopamine auto-receptor agonist roxindole, which has a high affinity for dopamine receptors, exhibited significant antidepressant activity in an open-label study of 12 depressed inpatients. Eight of the patients who received roxindole experienced at least a 50% reduction in their HAM-D score after 1 month of therapy. Four of these patients showed a rapid response to treatment, with improvement in depressive symptoms occurring during the first 2 weeks of the study.<sup>162</sup>

The D<sub>2</sub>/D<sub>3</sub> dopamine agonist pramipexole also has been shown to have antidepressant effects. An open-label, dose-escalating study involving 26 patients with major depression evaluated the antidepressant efficacy and safety of pramipexole. Patients were given pramipexole for 28 days at a dose ranging from 1.75 to 9.0 mg t.i.d. Efficacy against depression was assessed using the HAM-D, the Montgomery-Asberg Depression Rating Scale (MADRS), and the Bech-Rafaelsen Melancholia Scale (BRMS). Depression scores decreased by a mean of approximately 30%, although up to one third of patients demonstrated reductions of 50% or more on the MADRS, results considered clinically meaningful. Only 5 patients failed to show a substantial reduction in the depression rating scale scores. Pramipexole was well tolerated in dosages up to 6.25 mg/day. Five patients elected to continue long-term pramipexole therapy beyond the study period, and adverse effects with extended treatment have not been reported.<sup>163</sup> This line of research raises the intriguing possibility that

dopamine agonists may offer additional treatment options for Parkinson's disease patients with major depression. Because of their specificity, dopamine agonists may demonstrate greater activity against depression associated with Parkinson's disease than nonselective dopamine agents. Controlled clinical trials testing this hypothesis have yet to be published.

ECT has been used successfully to treat both depression and the motor symptoms of Parkinson's disease.<sup>164</sup> Douyon et al.<sup>165</sup> showed that ECT was effective in improving motor dysfunction and mood in 7 depressed patients with Parkinson's disease who had failed to respond to traditional antidepressant medications. The investigators concluded that ECT improves Parkinson's symptoms and mood early in the treatment course. Some have suggested that the benefits associated with ECT are transient. It has been proposed that these benefits might be extended through maintenance ECT performed on an outpatient basis and titrated to keep patients symptom free. Several mechanisms have been postulated to account for the effectiveness of ECT in Parkinson's disease. These include enhanced responsiveness of central dopamine and norepinephrine to levodopa and dopamine agonists, increased blood-brain barrier permeability, and enhanced melatonin activity.<sup>166-169</sup> Transcranial magnetic stimulation, which appears to have antidepressant properties, also may provide some temporary benefit for Parkinson's motor symptoms.<sup>170</sup> Finally, one night of sleep deprivation—a potent stimulator of dopaminergic activity—has been shown to have a rapid, although short-lived, antidepressant effect.<sup>171</sup>

The need to treat depression associated with Parkinson's disease is clear, but treatment can have undesirable effects. In addition to the inherent side effects of antidepressant medications, the use of traditional antidepressants in Parkinson's disease is fraught with added risks. Antidepressants can be problematic because of their adverse effects on Parkinson's symptoms or because of interactions with the medications used to treat Parkinson's disease.<sup>172</sup> Numerous anecdotal reports of extrapyramidal symptoms associated with SSRIs raised concern about the possible worsening of Parkinson's symptoms in these patients. However, in a retrospective review, 20 of 23 Parkinson's disease patients who received fluoxetine up to 40 mg/day had no worsening of their Parkinson's symptoms.<sup>173</sup> There is cause for concern when SSRIs, including fluoxetine, sertraline, and paroxetine, are used in combination with MAOIs such as selegiline.<sup>174,175</sup> This combination may produce a serotonin syndrome characterized by diaphoresis, tremor, confusion, and fluctuating blood pressure. The serotonin syndrome can resolve on discontinuation of the offending agents along with supportive care as needed.

### Psychotropic Medications and Chronic Pain

Effective management of chronic pain is crucial to relieve suffering and improve patients' quality of life. Most

often, chronic pain conditions cannot be eliminated completely, but the distress and functional impairment that they cause can be ameliorated. Management of chronic pain is a multidisciplinary process, best addressed by a treatment team that includes medical and surgical specialists, anesthesiologists, psychiatrists and psychologists, physical therapists, and others. A number of controversies exist about the relative benefits of procedural interventions (e.g., surgery, localized injections), medication management, nonpharmacologic interventions (e.g., psychotherapies, physical therapy), and complementary treatments (e.g., acupuncture, therapeutic massage, and therapeutic touch). Within the realm of medication management, the appropriate prescription of narcotics is an unsettled issue. This section will provide a brief review of existing data on the use of nonnarcotic psychotropic agents and specific psychotherapies for the management of chronic pain.

A wide variety of medications have been reported to benefit patients suffering from chronic pain. Perhaps the best studied are the antidepressants, particularly the TCAs. There is a growing body of evidence that antidepressants reduce chronic pain even in the absence of major depression. The first report on the analgesic qualities of antidepressants was published in 1960,<sup>176</sup> describing the effectiveness of imipramine. A review of 40 subsequent studies in 1991 showed that 80% of studies found antidepressants to be more efficacious than placebo.<sup>177</sup> A 1992 meta-analysis of 39 placebo-controlled trials found that 74% of chronic pain patients treated with antidepressants experienced less pain than patients treated with placebo.<sup>178</sup> Both reviews discuss the challenge of drawing specific conclusions about the type and dose of antidepressant use from the myriad number of published reports. Problems include the wide diversity of pain symptoms and syndromes that were studied (e.g., headaches, fibromyalgia, lower back pain, facial pain, peripheral neuropathies, central pain, and cancer pain) as well as the variety and doses of medications that were compared. Nevertheless, there is broad agreement that TCAs have an important place in the management of chronic pain with or without depression. Dosages effective for analgesia generally are lower than those for management of depression (i.e., amitriptyline 25–75 mg/day), and onset of action is quicker.<sup>179</sup> The SSRIs have not proven to be as predictably useful as the TCAs for chronic pain problems.<sup>180</sup> The SSRIs have been most studied in neuropathic pain, a condition in which TCAs clearly are superior. Success has been reported with venlafaxine and nefazodone, but there are no systematic studies of these agents in chronic pain.<sup>181</sup>

The anticonvulsant/mood-stabilizing agents also are prescribed commonly for chronic pain. As is the case with the antidepressants, the analgesic properties of these medications do not depend on their effects on mood. Two older double-blind, placebo-controlled trials found that carbamazepine reduced the pain of diabetic neuropathy

thy.<sup>182,183</sup> More recently, gabapentin has gained popularity because of favorable initial reports about its efficacy and its relatively benign side effect profile. In open trials, gabapentin was at least partially helpful in relieving the neuropathic component of pain for the majority of 25 patients with multiple sclerosis<sup>184</sup> and 10 patients with head and neck pain.<sup>185</sup> Valproic acid and clonazepam have not been studied systematically, but the anecdotal experience<sup>181</sup> has not been favorable.

A number of psychological interventions including cognitive-behavioral therapy, biofeedback, relaxation therapy, and hypnosis have been employed in the treatment of chronic pain. A 1996 National Institutes of Health consensus conference reviewed the data on the efficacy of these interventions.<sup>186</sup> They found strong support for the effectiveness of well-structured relaxation therapy in reducing chronic pain associated with a variety of medical illnesses. Hypnosis was found to be effective in relieving cancer pain. The data on biofeedback and cognitive-behavioral techniques were positive but less robust.

### **Sex Hormones and Gender Factors in Treatment Response**

Sex steroids have important effects on the central nervous system and are known to affect mood.<sup>187</sup> However, the majority of the studies examining the relationships between depression and estrogen have been conducted in women with subsyndromal depressive symptoms; that is, the studies tracked dysphoria and related symptoms in women who generally did not have major depressive disorder. These investigations may provide insight into the relationship between estrogen and mood regulation, but should not be extrapolated directly to the treatment of women with mood disorders until more research is done in this group. In women with major depressive disorder, there is some evidence suggesting that elderly women are less likely to have an antidepressant effect from SSRIs.<sup>188</sup> An analysis of retrospective data indicated that estrogen therapy improved antidepressant response to SSRI medications. This section will review the data that currently are available on the use of hormones in patients with depression. Because there are few well-designed studies in this area, the potential uses of hormones—with or without antidepressant medications—for the treatment of mood disorders are still speculative.

The neuropsychiatric effects of estrogen replacement were studied prospectively in perimenopausal women with depression and no hot flashes. Preliminary results demonstrated significant improvement with estrogen compared with placebo in symptoms of tearfulness, emotional numbness, and mood instability and on BDI scores.<sup>189</sup> In another randomized study of surgically postmenopausal women without menopausal symptoms, BDI scores improved after each of 2 oral doses of estrogens but not after placebo.<sup>190</sup> Oral estrogen replacement, but not clonidine or placebo,

also reduced measures of depression and anxiety in non-surgical postmenopausal women.<sup>191</sup> A randomized placebo-controlled study investigated the effect of transdermal estradiol on quality of life.<sup>192</sup> The frequency of health-related quality-of-life complaints was significantly reduced after 3 months of estrogen replacement therapy. Oophorectomized women received supraphysiologic doses of either estrogen, androgen, or a combination and attained lower depression scores coincident with their higher plasma estrogen and testosterone levels.<sup>193</sup> When hormones were withdrawn, depression scores of all oophorectomized women were higher than those of the hysterectomy/no oophorectomy control group, although no scores were in the range of major depression. Thus, estrogens appeared to improve subsyndromal depressive symptoms in these women. The above studies suggest benefit from estrogen therapy on depressive symptoms, but their research designs often make interpretation of results difficult. The first study carefully separated the beneficial effects of estrogen on menopausal symptoms from an effect on depressive symptoms by excluding women with hot flashes. That study also included only perimenopausal women. However, most studies include both peri- and postmenopausal women or focus on only surgically menopausal women. These populations may be different in terms of their vulnerability to affective disorders.

A retrospective analysis of a large multicenter study suggested that depressed geriatric women on estrogen replacement therapy (ERT) experienced greater clinical improvement during treatment with fluoxetine than women not on ERT.<sup>194</sup> Fluoxetine-treated women not taking ERT showed no significant difference from placebo-treated women who also were not on ERT. Thus, estrogen status appears to be important to serotonergic antidepressant response in postmenopausal women. The importance of estrogen status to nonserotonergic antidepressant response in elderly depressed women is not yet known.

DHEA also may have beneficial effects on depressive disorders, particularly in depressed elderly patients with low endogenous DHEA. However, there are too few studies addressing its safety and efficacy. Testosterone is being used clinically to improve mood and libido in men and women. Yet more is known about the adverse effects of androgens on serum lipids and mood instability than about its usefulness as an antidepressant. Treatment with testosterone should be guided by well-designed future studies.

### **CONCLUSION**

Depression is quite common in the medically ill. The prevalence of major depression and subsyndromal depressive conditions in patients with active medical problems far exceeds that of the general population. However, depressive disorders often are underdiagnosed and inadequately treated. Furthermore, the negative impact that depression

may have on the morbidity and mortality of coexisting medical disease is only beginning to be investigated.

Antidepressant medications can alleviate depression and improve the quality of life for medically ill patients, but data are scarce about their effect on medical mortality. Studies are beginning to show that SSRIs are effective and well tolerated in depressed patients with comorbid medical conditions. Data on newer agents such as bupropion, venlafaxine, nefazodone, and mirtazapine are sketchy but promising. In contrast, there are increasing safety concerns about the TCAs and MAOIs in medically ill patients who are more susceptible to sedation, orthostasis, and drug-drug interactions. For patients with CAD and depression, TCAs actually may increase the risk of adverse cardiac events. The treatment of neuropathic pain runs counter to this trend. In this condition, low dose TCAs remain the antidepressant treatment of choice.

Several lines of research suggest that medications other than antidepressants may be effective for relieving depressive symptoms in patients with selected medical conditions. For example, ERT may decrease subsyndromal depression in perimenopausal women. Estrogen replacement alone is not effective for major depression, but it may enhance the antidepressant efficacy of SSRIs in older depressed women. Testosterone and DHEA also decline with age. Their potential use in depressed patients may be a fruitful area of investigation. Several studies have demonstrated antidepressant effects from dopamine agonists. These agents may offer dual benefits for depressed patients with Parkinson's disease, but again, more rigorous studies are needed.

Psychosocial interventions are safe and effective treatments for depression in the medically ill. The most successful psychosocial therapies are integrated into comprehensive medical/psychological programs for patients with specific medical diseases (e.g., cardiac risk reduction and rehabilitation, cancer treatment, HIV programs). For patients with CAD and perhaps cancer, psychosocial treatments may prolong survival. For those infected with HIV, they improve coping and quality of life. Future research should address the specific components of psychosocial therapies that are most effective and the mechanisms by which they have their positive impact. The cost-effective integration of psychosocial interventions with antidepressant medications also requires future study.

*Drug names:* amitriptyline (Elavil and others), bromocriptine (Parlodel), bupropion (Wellbutrin), carbamazepine (Tegretol and others), clomipramine (Anafranil), clonazepam (Klonopin), clonidine (Catapres), desipramine (Norpramin and others), dextroamphetamine (Dexedrine), doxepin (Sinequan and others), estradiol (Climera and others), estrogen (Premarin and others), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), imipramine (Tofranil and others), labetalol (Normodyne and others), levodopa (Larodopa), methylphenidate (Ritalin), metoprolol (Lopressor and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), pergolide (Permax), pramipexole (Mirapex), propranolol (Inderal and

others), quinidine (Cardioquin and others), selegiline (Eldepryl), sertraline (Zoloft), testosterone (Androderm and others), valproic acid (Depakene and others), venlafaxine (Effexor), warfarin (Coumadin).

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**DISCLOSURE OF OFF-LABEL USAGE**

The following agents mentioned in this article are *not* indicated for the primary treatment of major depression: estrogen replacement therapies, bromocriptine, piribedil, pergolide, roxindole, pramipexole.

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