New Indications for Antidepressants

Alan F. Schatzberg, M.D.

The second and third generation of antidepressants, i.e., the selective serotonin reuptake inhibitors, nefazodone, venlafaxine, and mirtazapine, are proving to be useful in a variety of seemingly diverse disorders, including most anxiety disorders. In addition to receiving approval from the U.S. Food and Drug Administration (FDA) for major depressive disorder, some of the newer antidepressants have received FDA approval for other disorders, e.g., generalized anxiety disorder (venlafaxine), bulimia nervosa (fluoxetine), obsessive-compulsive disorder (fluvoxamine, paroxetine, sertraline, and fluoxetine), social phobia (paroxetine), panic disorder (sertraline, paroxetine), and posttraumatic stress disorder (sertraline). In controlled studies, these agents have also shown usefulness in premenstrual dysphoric disorder, borderline personality disorder, obesity, smoking cessation, and alcoholism. This article describes the new and potential indications for recently developed antidepressants and the studies that suggested these indications. *(J Clin Psychiatry 2000;61[suppl 11]:9–17)*

The second and third generation of antidepressants, including the selective serotonin reuptake inhibitors (SSRIs), nefazodone, venlafaxine, and mirtazapine, which are approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder, are also likely to be useful in a variety of other seemingly diverse disorders including most anxiety disorders. Some newer antidepressants have, in fact, already received FDA approval for indications other than depression such as generalized anxiety disorder (venlafaxine), bulimia nervosa (fluoxetine), obsessive-compulsive disorder (fluvoxamine, paroxetine, sertraline, and fluoxetine), social phobia (paroxetine), panic disorder (sertraline, paroxetine), and posttraumatic stress disorder (sertraline). Furthermore, in controlled studies, these agents have shown usefulness in a variety of other psychiatric disorders including premenstrual dysphoric disorder (PMDD), borderline personality disorder, obesity, smoking cessation, and alcoholism. As evidence mounts for the efficacy of these second- and third-generation antidepressants across a broad spectrum of psychiatric disorders, their use is likely to continue to increase.

MECHANISMS OF ACTION IN ANTIDEPRESSANTS

A description of the neuroanatomy of the serotonergic neurotransmission system provides a basis for understanding the broad efficacy of antidepressants and the differences among these agents. Serotonergic neurons originate in specific locations in the brain stem raphe region, but then project widely throughout the central nervous system (CNS). Projections to the frontal cortex mediate mood, projections to the hypothalamus mediate appetite and sleep, and those to the amygdala regulate anxiety and fear responses. Serotonin (5-HT) also has a role in aggression, sexual behavior, and pain. In short, altering serotonergic neurotransmission with medication affects a wide range of human functions. The SSRIs, which block the reuptake of serotonin, were developed on the theory that they would be effective for patients with disorders characterized by marked dysfunction of the serotonin system and would be devoid of the toxic adverse effects of the older tricyclic antidepressants (TCAs), which affect both the noradrenergic and serotonergic systems.

However, it has become clear that there are important relationships between the serotonergic and noradrenergic neurotransmitter systems. Serotonin reuptake inhibition is probably only the first step of a cascade of neuronal events that ultimately leads to antidepressant and antianxiety effects. Projections of serotonergic neurons from the midbrain raphe area to the noradrenergic nucleus locus ceruleus probably play an important role in the regulation of mood and anxiety. The next generation of antidepressants—nefazodone, venlafaxine, and mirtazapine—like the TCAs, have actions on both the serotonergic and noradrenergic systems, but lack the anticholinergic and cardiovascular adverse effects of the older agents. Nefazodone blocks 5-HT_{2A} receptors and inhibits serotonin uptake as well as modestly inhibiting norepinephrine uptake; venlafaxine increases both norepinephrine and serotonin as a function of reuptake inhibition; and mirtazapine, an antagonist of presynaptic α_2-adrenoceptors and heteroreceptors, increases both norepinephrine and serotonin

From the Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, Calif.

Presented at the planning roundtable "New Strategies for Improving Treatment of Depression," which was held October 15, 1999, in San Francisco, Calif., and supported by an unrestricted educational grant from Bristol-Myers Squibb.

Reprint requests to: Alan F. Schatzberg, M.D., Department of Psychiatry and Behavioral Sciences, Stanford University Room 3201, Stanford, CA 94305-5548.

neurotransmission without affecting the reuptake of these neurotransmitters.

It is now widely believed that the increase in synaptic serotonin and norepinephrine produced by antidepressants leads to the phosphorylation of transcription factors within postsynaptic neurons in the brain. These transcription factors are then able to bind to promoter regions on genes. The result is activation of previously latent genes. This process takes several weeks and may explain the workings of antidepressants at a fundamental level.

Antidepressants may differ in efficacy for some psychiatric conditions because of their diverse mechanisms of action. For example, panic disorder probably responds slowly to SSRIs because serotonin is involved in panic disorder only indirectly, and it may take several weeks for the direct effect of SSRIs on the serotonin system to have a secondary effect on norepinephrine.[1] SSRIs and clomipramine are generally more effective in obsessive-compulsive disorder (OCD) than TCAs and monoamine oxidase inhibitors (MAOIs). Bupropion, which does not affect serotonin, is effective in smoking cessation. Many depressive disorders and anxiety disorders have been linked to serotonergic dysregulation, but response to specific antidepressants may depend on the specific serotonergic receptor targeted by the agent.

NEW INDICATIONS FOR ANTIDEPRESSANTS

Generalized Anxiety Disorder

For a long time, it was assumed that only benzodiazepines and buspirone were effective in generalized anxiety disorder (GAD) and that antidepressants had the potential to worsen GAD. Both assumptions are probably incorrect. Although benzodiazepines and buspirone are clearly effective for GAD, evidence for the efficacy and possible superiority of some antidepressants is growing, and in 1999, venlafaxine became the first antidepressant to be approved for the treatment of GAD. The efficacy of paroxetine, mirtazapine, and nefazodone in GAD has also been reported.

Venlafaxine was significantly more effective than placebo and superior to buspirone in a recent study of 365 outpatients who met DSM-IV criteria for GAD.[2] The patients were treated with 75 or 150 mg/day of venlafaxine extended release (XR), 30 mg/day of buspirone, or placebo for 8 weeks. On a variety of outcome measures, both venlafaxine dosages were significantly more efficacious than both placebo and buspirone.

The SSRI paroxetine and the TCA imipramine were superior to a benzodiazepine in a 4-week study of 81 patients with a DSM-IV diagnosis of GAD.[3] About two thirds of the patients who completed the study improved greatly or moderately with all 3 drugs, but by the fourth week of treatment, both paroxetine and imipramine resulted in more improvement than the benzodiazepine.

In a preliminary open study,[4] 15 to 45 mg/day of mirtazapine was administered to 10 patients with major depression and comorbid GAD for 8 weeks. Significant improvements on the Hamilton Rating Scale for Anxiety (HAM-A), the Hamilton Rating Scale for Depression (HAM-D), and the Beck Depression Inventory (BDI) began during the first week and continued throughout the study.

Nefazodone was also reported useful in an open 8-week study of 21 patients who met DSM-IV criteria for GAD.[5] The usual starting dose was 25 to 50 mg/day, which was titrated over 2 to 3 weeks to a maximum of 600 mg/day given in divided doses. Twelve of the 15 patients who completed the trial were rated as either very much or much improved as assessed by the HAM-A, and none of the patients was rated as worse. Six months later, 6 of the 9 responders available for follow-up were still taking nefazodone with anxiolytic effects.

Obsessive-Compulsive Disorder

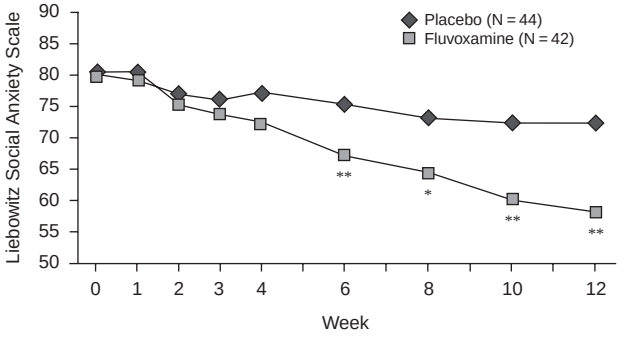
Obsessive-compulsive disorder has moved from a tight, neat syndrome to a spectrum of overlapping impulsive, preoccupation, and neurologic (motoric) disorders. The preoccupation disorders include body dysmorphic disorder, depersonalization, anorexia nervosa, and hypochondriasis; the impulsive disorders include sexual compulsions, trichotillomania, pathological gambling, kleptomania, and self-injurious behavior; and the neurologic behaviors include Tourette's disorder, Sydenham's chorea, torticollis, and autism.[6] These various syndromes have all been shown to have effects that are mediated by serotonergic agents.

At present, the most efficacious pharmacologic treatments for OCD are antidepressants that inhibit serotonin reuptake. One TCA, clomipramine, and 4 SSRIs, fluvoxamine, fluoxetine, paroxetine, and sertraline, are approved by the FDA for use in patients with OCD.[7] In most anxious patients, the starting doses of antidepressant medications are often lower than for depressed patients. However, many clinicians find that patients with OCD ultimately require fairly high doses of antidepressants. Although OCD is hypothesized to be a manifestation of primary serotonin dysregulation, multiple neurotransmitters (particularly those associated with serotonergic and dopaminergic activity) are most likely involved in the etiology of the disorder. A fuller understanding of the mechanism of action of antidepressants and of the actual neurotransmitter and receptor abnormalities in various psychiatric illnesses is essential to address these various issues.

Studies comparing SSRIs in the treatment of OCD show few differences among the agents. There were no significant differences in antiobsessional effects in 31 patients who underwent a 10-week randomized study with fluvoxamine, paroxetine, or citalopram treatment.[8] Flament and Bisserbe[9] reported that clomipramine is as efficacious as fluoxetine or fluvoxamine in one-on-one comparative studies.

The dual-action antidepressants have also been studied in patients with OCD. In an 8-week open trial of nefazodone treatment in 18 patients with DSM-III-R major depressive episodes, 9 of whom had comorbid OCD, a trend toward antiobsessional responses was seen in the patients with OCD.[10] Although a significant reduction in depressive and anxiety symptoms was observed in treatment completers, no differences were found between patients with and without comorbid OCD.

Figure 1. Mean Scores on the Liebowitz Social Anxiety Scale for Subjects in a 12-Week Placebo-Controlled Study of Fluvoxamine for Social Phobia[a]



[a]Adapted from Stein et al.,[13] with permission. Data presented are from last observation carried forward for all evaluable patients. Differences in change from baseline between the placebo and fluvoxamine groups were analyzed by means of 2-way analyses of variance (df = 1,78).
*p < .05.
**p < .01.

Social Phobia

The recent FDA approval of paroxetine for social phobia has brought this disorder to the forefront. Although primary care physicians often resist identifying and treating what they term "shyness," many individuals with the disorder, which has a prevalence of 7.1%,[11] are heavily impaired. MAOIs and benzodiazepines are effective in social phobia, but neither class is widely used, and recent research provides evidence for the efficacy of the serotonergic agents, which have a more favorable side effect profile than the MAOIs and are devoid of the risks of dependence and abuse liability associated with the benzodiazepines.

Placebo response rates are often low in early studies of a new treatment. Stein et al.[12] reported the efficacy of 20 to 50 mg/day of paroxetine for social phobia in a 12-week trial (N = 183). Mean total scores on the Liebowitz Social Anxiety Scale were reduced significantly from 78.0 to 47.5 in the paroxetine-treated patients, while scores in the placebo-treated patients decreased from 83.5 to 68.9 (nonsignificant). This low placebo response tends to increase in later studies of a disorder because the severity of illness of the population being studied generally decreases the longer an illness is studied.

A recent report of fluvoxamine in social phobia[13] also produced a striking reduction in scores on the Liebowitz Social Anxiety Scale in the fluvoxamine-treated patients (mean dose = 202 mg/day), but little change in the placebo-treated group (Figure 1). Psychosocial impairment including work, social life, and family life disruption, as assessed by the Sheehan Disability Scale, also improved with fluvoxamine treatment. Scores on the Sheehan Disability Scale provide a corollary to patient self-report of reduced anxiety. In another double-blind, placebo-controlled study, van Vliet et al.[14] reported substantial improvement in 46% of patients receiving 150 mg/day of fluvoxamine versus 7% of those receiving placebo. Sertraline has also been found useful in a double-blind, placebo-controlled study of social phobia. Sertraline (maximum mean dose = 134 mg/day) was more effective than placebo in 12 patients.[15]

Dual-action antidepressants have been found effective in social phobia. Venlafaxine has been used particularly in SSRI nonresponders. At doses ranging from 112.5 mg/day to 187.5 mg/day, venlafaxine improved social phobia in 12 nonresponders to SSRIs as evidenced by decreasing scores on the Liebowitz Social Anxiety Scale.[16] Kelsey[17] also reported improvement in 8 of 9 patients, most of whom were SSRI nonresponders, who were treated openly with venlafaxine. The authors cautioned that the starting dose in social phobia should be smaller than that recommended by the manufacturer.

Nefazodone has also been recently reported useful in social phobia. Worthington et al.[18] conducted a clinical case study in which 5 consecutive patients meeting DSM-IV criteria for generalized social phobia were treated with 200 to 600 mg/day of nefazodone for 3 months. Three patients completed 3 months of treatment, and analysis of endpoint data demonstrated significant improvement on a variety of outcome measures. In another open study, Van Ameringen et al.[19] started 23 patients with a DSM-IV diagnosis of generalized social phobia on treatment with 100 mg/day of nefazodone, which was increased as necessary on the basis of clinical response and side effects. Sixteen of the 21 patients who completed the trial were considered to be responders on measures of social anxiety, social phobic avoidance, depression, and social functioning.

Panic Disorder

Many physicians consider the SSRIs, either alone or in combination with high-potency benzodiazepines, to be first-line therapy for the management of panic disorder. The SSRIs have well-established efficacy and safety profiles in the treatment of panic disorder including those patients with comorbid depression, social phobia, or OCD. Studies of panic disorder are increasingly using not only the frequency of panic attacks as measures of drug efficacy but also symptom improvement and quality-of-life measures that can be determined by a variety of assessment tools.

Paroxetine was the first SSRI to receive FDA approval for the specific treatment of panic disorder. Oehrberg

and colleagues[20] studied the efficacy and tolerability of paroxetine compared with placebo in patients who also received standardized cognitive therapy. Nearly 90% of the paroxetine-treated patients were responders, significantly more than in the placebo arm. In another study, Ballenger et al.[21] tested 3 doses of paroxetine—10, 20, and 40 mg/day—against placebo. The 40-mg/day paroxetine dose proved significantly more effective than placebo, and more than 80% of the patients became panic-free.

Sertraline was the second SSRI approved by the FDA for the treatment of panic disorder, and it is an effective agent for a range of symptoms that include panic attacks, phobic avoidance, and overall disability. In a randomized double-blind trial of sertraline in 168 patients with a DSM-III-R diagnosis of panic disorder with or without agoraphobia, the drug was significantly more effective than placebo in decreasing the number of panic attacks.[22] Sertraline-treated patients also had significantly more improvement than placebo in scores on the Quality of Life Enjoyment and Satisfaction Questionnaire (patient global evaluation) and the Clinical Global Impressions (CGI) Severity of Illness and Global Improvement scales.

Although fluoxetine is widely used for the treatment of depression and anxiety disorders, published studies are sparse on the efficacy of fluoxetine treatment in patients with panic disorder. In an open pilot study, Gorman et al.[23] reported complete cessation of panic attacks in 9 of 16 fluoxetine-treated patients who met DSM-III-R criteria for either panic disorder or agoraphobia with panic attacks. In an 8-week study, den Boer and Westenberg[24] found that patients treated with 150 mg/day of fluvoxamine experienced greater reductions in HAM-A scores compared with placebo or the 5-HT_2 antagonist ritanserin ($p < .001$). The success rate with fluoxetine appears to be greater with extended treatment and higher doses; furthermore, anxiety and activation may occur during the early weeks of treatment, which may contribute to a higher dropout rate.[25] Because panic disorder is a chronic, recurring illness, patients who have experienced previous relapses or those with comorbid conditions should be considered for long-term therapy.

The possibility that both serotonergic and noradrenergic activity are important in the pathophysiology of panic disorder raises the issue of the possible efficacy of dual serotonin/norepinephrine reuptake inhibitors, which affect both systems.[7] Papp and colleagues[26] conducted an open trial of venlafaxine in 13 patients with DSM-IV panic disorder; 10 patients completed the trial and all were responders. Because nefazodone demonstrates efficacy in the treatment of depression, an open 8-week trial was undertaken to assess the efficacy and safety of the drug in 14 patients with a primary diagnosis of DSM-III-R panic disorder and concurrent diagnoses of major depression, dysthymia, generalized anxiety disorder, and/or depression, not otherwise specified (presence of minor or reactive depressive symptoms).[27] A total of 10 of 14 patients showed a positive response to nefazodone as measured by decreased frequency and severity of panic attacks and improvement in HAM-D, HAM-A, CGI-Severity, and Sheehan Disability Scale scores. None of the patients withdrew because of side effects. Nefazodone was also used successfully to treat a patient (who could not tolerate SSRIs) with panic disorder not associated with depression.[28] A multicenter trial is currently underway evaluating the efficacy of nefazodone in patients with panic disorder.

Posttraumatic Stress Disorder

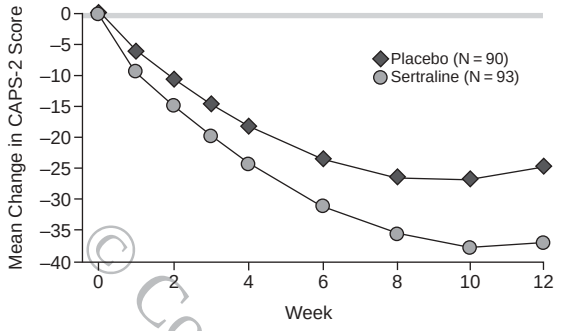
Patients with posttraumatic stress disorder (PTSD) may respond to pharmacotherapy in different ways, and it is unclear whether the different responses are related to gender, trauma type, or other factors. Many studies of PTSD have been conducted in war veterans who may constitute a treatment-refractory population. Moreover, PTSD is likely to be comorbid with affective disorders, other anxiety disorders, somatization, substance abuse, and dissociative disorders. Notwithstanding, although the controlled trials investigating the efficacy of medication in patients with PTSD are limited, there is increasing evidence that SSRIs are effective for the treatment of this disorder.[29] Additionally, the SSRIs seem to be more efficacious than the older antidepressants in relieving core symptom clusters—rather than isolated symptoms—of PTSD.

Sertraline was the first drug approved by the FDA for the treatment of PTSD. An open trial of sertraline was conducted in 64 combat veterans with PTSD and concurrent moderate-to-severe depression who had failed to respond to other antidepressants.[30] Twelve of 19 veterans responded positively to sertraline treatment and reported significantly reduced dysphoria, irritability, and anger. Another open clinical trial of sertraline in 5 adult rape victims showed a reduction in clinician-administered PTSD scale scores by 53%, and 4 of 5 participants responded positively to treatment.[31]

A recent large ($N = 187$) 12-week double-blind, placebo-controlled study[32] evaluated the efficacy and safety of sertraline in PTSD symptoms of moderate-to-marked severity. Mean baseline-to-endpoint changes on the Clinician-Administered PTSD Scale Part 2 (CAPS-2) were significantly greater ($p < .001$) for the sertraline-treated patients than for the patients who received placebo (Figure 2).

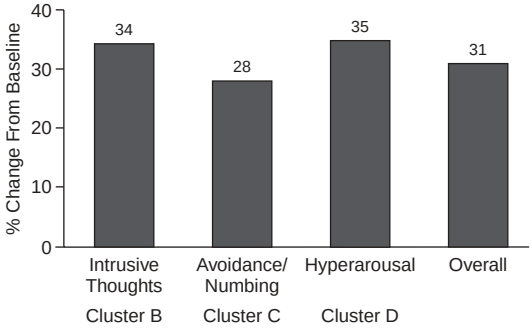
Marshall and colleagues[33] evaluated the effects of paroxetine in a 12-week, open study of 13 noncombat veterans with PTSD. Responders experienced a 43% mean reduction in PTSD symptom scores, and the 3 symptom clusters of intrusion, avoidance/numbing, and arousal were significantly improved by paroxetine treatment. Van der Kolk and associates[34] conducted a controlled trial of fluoxetine in 64 patients (men and women, veterans and nonveterans) with PTSD. Of the 47 patients who com-

Figure 2. Effects of Sertraline vs. Placebo in Posttraumatic Stress Disorder[a]



[a]From Brady et al.,[32] with permission. Signifigant ($p < .001$) mean change in Clinician-Administered PTSD Scale Part 2 (CAPS-2) score from baseline to endpoint estimated from random regression analysis plotted over the 12-week course of treatment. Gray line indicates baseline. Negative change in scores reflects clinical improvement.

Figure 3. Effect of Nefazodone on Overall Posttraumatic Stress Disorder Cluster Symptoms (N = 105)[a]



[a]Adapted from Hidalgo et al.,[38] with permission.

pleted the 5-week study, the fluoxetine-treated patients showed reduced PTSD symptomatology, especially in arousal and numbing symptoms. In a 10-week open trial of fluvoxamine in combat veterans with PTSD, the drug was effective for treating the intrusion, avoidance, and arousal symptom clusters.[35]

Of the drugs with dual noradrenergic and serotonergic reuptake inhibiting properties, venlafaxine was reported by Hamner and Frueh[36] to have a positive effect on a patient with PTSD who had failed to respond to several serotonergic antidepressants. In a study of 6 outpatients with severe, chronic PTSD treated with mirtazapine for 8 weeks, 50% of the sample demonstrated improvement of 50% or more from baseline using a global rating scale.[37] Moreover, improvements were noted on both interviewer- and self-rated scales of PTSD and depression.

Hidalgo and colleagues[38] evaluated nefazodone in 6 open studies involving 105 civilian and veteran outpatients with PTSD; predictors of response included age, sex, and type of trauma. Nefazodone showed a broad spectrum of action on both individual and cluster symptoms of intrusive thoughts, avoidance/numbing, and hyperarousal (Figure 3). Moreover, this pooled analysis included a subset of 21 highly symptomatic, chronically distressed, and disabled Vietnam combat veterans who had been refractory to several previous medications. Twelve weeks of treatment with nefazodone resulted in decreased intrusive recollections, avoidance, and hyperarousal; improved sleep; and improved sexual and social/interpersonal functioning.

POTENTIAL INDICATIONS FOR ANTIDEPRESSANTS

Premenstrual Dysphoric Disorder

PMDD shares characteristics of both depression and anxiety, and several antidepressants are being tested for use in PMDD. The serotonergic agents have been generally reported effective, and fluoxetine has received an indication for use in PMDD in the United Kingdom. Several randomized, placebo-controlled trials have found SSRIs beneficial for PMDD.[39–43] In the largest of these studies, Steiner et al.[41] found both 20 mg/day and 60 mg/day of fluoxetine superior to placebo in reducing tension, irritability, and dysphoria during the late luteal phase of the menstrual cycle. Benefits were seen during the first month of treatment, but there were substantially more dropouts in the 60-mg/day group. Positive results for sertraline (mean daily dose = 80 mg) over placebo were reported in another large multicenter trial that lasted 3 menstrual cycles.[43] Acute phase efficacy for paroxetine was shown in a small randomized, double-blind, placebo-controlled trial,[42] and another small open study[44] reported improvement in symptoms of irritability, depression, mood swings, fatigue, and loss of concentration in women treated with fluvoxamine for 2 menstrual cycles.

Investigators have also reported on intermittent dosing strategies for PMDD. Young et al.,[45] who were the first to examine the use of an SSRI given only during the luteal phase, found that sertraline given intermittently was significantly more effective than placebo in reducing both behavioral and physical symptoms as assessed by the Calendar of Premenstrual Experience.

A few studies have reported on long-term treatment of PMDD. A group of responders to fluoxetine were openly followed for up to 2 years, and 21 of 60 continued to do well.[46] Elks[47] treated 11 women with fluoxetine and found continued moderate-to-marked relief over 3 to 20 months.

Dual-action antidepressants have also been used successfully in patients with PMDD. Freeman and colleagues[48] followed 33 women who had responded to nefazodone during an 8-week open trial for up to 1 year. Of this group, 19 completed 1 to 3 additional months, 6 completed 4 to 6 additional months, and 8 completed 6 to 12 additional months of treatment. The mean nefazodone

dose was 327 mg/day, and significant improvement, which occurred by the end of the first cycle of treatment, was maintained for the entire course of treatment.

Borderline Personality Disorder

Because of their serotonergic-enhancing properties, the SSRIs have proved efficacious in reducing some of the impulsive, aggressive, and self-destructive behaviors that accompany borderline personality disorder. Several open studies of fluoxetine[49–51] have reported positive therapeutic effects in patients with borderline personality disorder who experience depression, obsessive-compulsive symptoms, and self-injurious or suicidal behavior. In a placebo-controlled, double-blind study, my colleagues and I[52] found a clinical and statistically significant decrease in anger in 13 fluoxetine-treated patients. The reduction in anger was independent of changes in depression. An open trial of sertraline in 8 patients with borderline personality disorder showed significant changes in baseline scores of both irritability and overt aggression on the Overt Aggression Scale by the end of 4 weeks, and improvement continued to occur through week 8.

Among the non-SSRIs, the combined-action antidepressant venlafaxine was studied in a 12-week trial in 44 patients with borderline personality disorder. Markovitz and Wagner[53] reported that venlafaxine was effective as an initial intervention for treating this disorder and may benefit individuals in whom fluoxetine and sertraline have been ineffective.

Eating Disorders and Obesity

Because of the frequent overlap in symptoms of depressive, obsessive-compulsive, and eating disorders, the use of SSRIs in the treatment of eating disorders is of paramount interest. However, there continues to be considerable uncertainty regarding the role of medication in the therapy of eating disorders (anorexia nervosa, bulimia nervosa, and binge-eating disorder) and obesity.[54] The American Psychiatric Association Practice Guideline for Eating Disorders[55] recommends a multidisciplinary approach to treatment, that is, primary interventions of family and individual psychotherapies that incorporate a major cognitive-behavioral component, with pharmacotherapy as an adjunct.

Most clinical trials of SSRIs in patients with anorexia nervosa have been disappointing; moreover, most trials have focused on adults, and anorexia nervosa and bulimia nervosa typically have an onset in adolescence. A double-blind, placebo-controlled trial in 31 hospitalized anorexic women suggested that the impact of fluoxetine—provided within the context of a behaviorally oriented program—was disappointing.[54]

On the other hand, there is increasing evidence that SSRIs are effective in treating patients who have bulimia nervosa, and fluoxetine has received FDA approval for use in this disorder. In a randomized, placebo-controlled trial in 120 bulimic women, the patients who received fluoxetine in combination with psychological treatment experienced greater improvement in the behavioral symptoms of binge eating and vomiting than patients who received placebo and psychological treatment.[56] Additionally, medication plus cognitive-behavioral therapy (CBT)—as compared with supportive psychotherapy—was superior to medication alone. A large multicenter, double-blind, randomized, 16-week trial in 483 men and women found that fluoxetine treatment resulted in significantly greater reductions than placebo in weekly vomiting and binge-eating episodes; improvement was also seen in other outcome measures such as rating scale scores.[57] To determine the efficacy of fluvoxamine in preventing relapse of bulimia nervosa, a double-blind, placebo-controlled, 12-week study was done in 72 successfully treated bulimic patients.[58] Despite a high dropout rate in the fluvoxamine-treated group, both intent-to-treat and completer analyses showed that fluvoxamine had a significant effect in reducing a return to bulimic behavior.

Binge-eating disorder is characterized by repeated episodes of excessive food consumption that is similar to bulimia nervosa, but lacks the compensatory measures of vomiting, laxative abuse, fasting, or excessive exercise. Clinical trials of SSRIs as treatment for patients with binge-eating disorder are sparse. A multicenter, 52-week, double-blind, placebo-controlled trial of fluoxetine in obese subjects divided the population into binge (N = 22) and nonbinge (N = 23) eaters.[59] All subjects received behavioral therapy, and half the subjects received fluoxetine. Subjects treated with fluoxetine plus behavioral therapy lost significantly more weight than placebo plus behavioral therapy, but there was no significant difference between binge and nonbinge eaters.

Health risks associated with obesity are well known. Although dieting and exercise are effective in producing short-term weight loss, long-term maintenance of weight loss is difficult. Some of the initial trials of SSRIs—in which one of the side effects was weight loss—coupled with the role of serotonin in appetite regulation led to trials of SSRIs as a pharmacologic treatment for obesity. A short-term, 8-week, double-blind, placebo-controlled trial of fluoxetine in 120 nondepressed obese subjects showed a significantly greater weight loss among fluoxetine-treated patients than placebo.[60] However, in a long-term, 52-week, placebo-controlled fluoxetine trial in 458 obese outpatients, the maximum mean weight loss occurred at week 20; at 52 weeks there was no treatment difference.[61] Similarly, in a 54-week trial (N = 53) of sertraline combined with relapse prevention training after treatment with a very low-calorie diet, the sertraline-treated subjects reported significantly greater reductions in hunger, and they lost more weight than placebo at 6 weeks.[62] Again, however, the differences in weight change between sertraline-

treated and placebo groups were not statistically significant at the end of 54 weeks.

Smoking Cessation

The prevalence of smoking is especially high in psychiatric patients; over 50% of all psychiatric patients and over 80% of patients with substance abuse disorders are current smokers.[63] Of those individuals who try to quit smoking each year, less than 5% are successful in unaided attempts because of dependence on nicotine.[64] Bupropion SR (sustained release) is the only non-nicotine medication approved by the FDA as an aid to smoking cessation. Initially developed as an antidepressant, bupropion is believed to work on the dopaminergic and/or noradrenergic neurotransmitters that are involved in perpetuating nicotine dependence. Jorenby and colleagues[65] conducted a double-blind, placebo-controlled study in 893 subjects for comparison of bupropion SR (N = 244), a nicotine patch (N = 245), bupropion plus a nicotine patch (N = 245), and placebo (N = 160) as treatment for smoking cessation. Bupropion SR alone or in combination with a nicotine patch resulted in significantly higher long-term rates of smoking cessation than the nicotine patch alone or placebo. Abstinence rates were also higher with combination therapy than with bupropion alone, but the difference was not statistically significant.

In one arm of a smoking cessation study, Dalack and colleagues[66] examined the utility of fluoxetine in a randomized, double-blind study in 39 nondepressed smokers who had a history of major depression. Self-rated scales were compared at baseline and after 3 weeks of medication treatment prior to the attempt to quit. Although there was substantial improvement from baseline in several subscale scores for the fluoxetine-treated group, a comparison of the change in scores for the placebo and fluoxetine groups failed to show a statistically significant difference. In another study, 253 adult smokers with no clinically significant depression were randomly selected on a double-blind basis to receive fluoxetine or placebo in combination with CBT for 10 weeks.[67] Logistic regression analyses showed that 1 and 3 months after the quit date, fluoxetine increased the likelihood of abstinence, compared with placebo, among smokers with minor depression but not among those with little or no depression.

Alcoholism

Substantial progress has been made in determining the role of pharmacotherapy in alcoholism, specifically in the areas of withdrawal reaction, decreasing consumption, relapse prevention, and comorbid psychiatric illnesses.[68] Numerous pharmacologic agents and dosage regimens have been investigated for the treatment of the alcohol withdrawal syndrome. There is wide variability in treatment response (i.e., effect size) for all medications, and compliance seems to be essential for successful treatment. Antidepressants have shown efficacy in the treatment of alcoholism with comorbid depression, and SSRIs seem to have more beneficial short-term than long-term effects.

Fluoxetine demonstrates efficacy in major depression and suggested efficacy in comorbid alcoholism. In a 12-week, double-blind, parallel-group trial, 51 patients with diagnoses of comorbid major depression and alcohol dependence were randomly selected to receive fluoxetine or placebo.[69] The improvement in depressive symptoms during the trial was significantly greater in the fluoxetine-treated patients than placebo. Moreover, total alcohol consumption during the trial was significantly lower in the fluoxetine group than in the placebo group. In another study, 36 recently abstinent, depressed alcoholics were randomly selected to receive either sertraline or placebo in a 6-week, double-blind trial.[70] There were significant differences between the sertraline and placebo groups on the HAM-D at weeks 3 and 6 and on the BDI at week 3. Patients receiving sertraline had significantly lower mean posttreatment HAM-D and BDI scores than placebo. Additionally, significantly more sertraline-treated patients obtained a CGI rating of "very much improved." Positive effects of SSRIs in nondepressed alcoholic patients have not been demonstrated.

Chronic Fatigue Syndrome

Chronic fatigue syndrome is a medical condition with criteria of a 6-month history of worsening fatigue and the presence of 4 of 8 symptoms that include memory and sleep impairment as well as lymph node, joint, and muscular pain. Gruber and associates[71] include chronic fatigue syndrome in a group of interfacing treatment-resistant depressive disorders that appear to benefit from antidepressant medications from several different chemical families. Goodnick and Jorge[72] reported improvement of symptoms—particularly pain and insomnia—in 3 patients with chronic fatigue syndrome who were treated with nefazodone. In an open evaluation, 10 patients with chronic fatigue syndrome were treated with nefazodone and appropriate behavioral and sleep-wake–cycle strategies.[73] Eight of 10 patients reported improvement in the key symptom of fatigue; 4 patients reported moderate-to-marked relief. Additionally, moderate-to-marked improvement was seen in sleep disturbance (7 patients) and mood (8 patients).

CONCLUSION

Although one should be cautious about assuming that drugs that work in patients with major depression are also effective in depressive or anxious subtypes, many open and controlled studies show that antidepressants are proving to be useful in a variety of psychiatric disorders. Antidepressants affect many systems in the brain in numerous key areas; thus, they may have positive effects in disorders both related to and comorbid with depression. As evidence

mounts for the efficacy of the second- and third-generation antidepressants across a broad spectrum of psychiatric disorders, their use is likely to continue to increase.

Drug names: bupropion (Zyban), buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined, to the best of his knowledge, the following agents mentioned in this article are not approved by the U.S. Food and Drug Administration for treatment of the following disorders: mirtazapine, paroxetine, and nefazodone for generalized anxiety disorder; nefazodone for obsessive-compulsive disorder; fluoxetine, fluvoxamine, nefazodone, sertraline, paroxetine, and venlafaxine for social phobia; fluoxetine, fluvoxamine, nefazodone, and venlafaxine for panic disorder; fluoxetine, fluvoxamine, nefazodone, paroxetine, and venlafaxine for posttraumatic stress disorder; fluoxetine, nefazodone, paroxetine, and sertraline for premenstrual dysphoric disorder; fluoxetine and venlafaxine for borderline personality disorder; fluvoxamine for bulimia; fluoxetine for binge-eating disorder; fluoxetine for smoking cessation; fluoxetine and sertraline for alcoholism; and nefazodone for chronic fatigue syndrome.

REFERENCES

1. Coplan JD, Papp LA, Pine D, et al. Clinical improvement with fluoxetine therapy and noradrenergic function in patients with panic disorder. Arch Gen Psychiatry 1997;54:643–648
2. Davidson JRT, DuPont RL, Hedges D, et al. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. J Clin Psychiatry 1999;60:528–535
3. Rocca P, Fonzo V, Scotta M, et al. Paroxetine efficacy in the treatment of generalized anxiety disorder. Acta Psychiatr Scand 1997;95:444–450
4. Goodnick PJ, Puig A, DeVane CL, et al. Mirtazapine in major depression with comorbid generalized anxiety disorder. J Clin Psychiatry 1999;60: 446–448
5. Hedges DW, Reimherr FW, Strong RE, et al. An open trial of nefazodone in adult patients with generalized anxiety disorder. Psychopharmacol Bull 1996;32:671–676
6. Hollander E, Kwon JH, Stein DJ, et al. Obsessive-compulsive and spectrum disorders: overview and quality of life issues. J Clin Psychiatry 1996; 57(suppl 8):3–6
7. Gorman JM, Kent JM. SSRIs and SNRIs: broad spectrum of efficacy beyond major depression. J Clin Psychiatry 1999;60(suppl 4):33–38
8. Mundo E, Bianchi L, Bellodi L. Efficacy of fluvoxamine, paroxetine, and citalopram in the treatment of obsessive-compulsive disorder: a single-blind study. J Clin Psychopharmacol 1997;17:267–271
9. Flament MF, Bisserbe J-C. Pharmacologic treatment of obsessive-compulsive disorder: comparative studies. J Clin Psychiatry 1997;58 (suppl 12):18–22
10. Nelson EC. An open-label study of nefazodone in the treatment of depression with and without comorbid obsessive compulsive disorder. Ann Clin Psychiatry 1994;6:249–253
11. Stein MB, Walker JR, Forde DR. Setting diagnostic thresholds for social phobia: considerations from a community survey of social anxiety. Am J Psychiatry 1994;151:408–412
12. Stein MB, Liebowitz MR, Lydiard RB, et al. Paroxetine treatment of generalized social phobia (social anxiety disorder): a randomized controlled trial. JAMA 1998;280:708–713
13. Stein MB, Fyer AJ, Davidson JR, et al. Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind, placebo-controlled study. Am J Psychiatry 1999;156:756–760
14. van Vliet IM, den Boer JA, Westenberg HG. Psychopharmacological treatment of social phobia: a double blind placebo controlled study with fluvoxamine. Psychopharmacology (Berl) 1994;115:128–134
15. Katzelnick DJ, Kobak KA, Greist JH, et al. Sertraline for social phobia: a double-blind, placebo-controlled crossover study. Am J Psychiatry 1995; 152:1368–1371
16. Altamura AC, Pioli R, Vitto M, et al. Venlafaxine in social phobia: a study in selective serotonin reuptake inhibitor non-responders. Int Clin Psychopharmacol 1999;14:239–245
17. Kelsey JE. Venlafaxine in social phobia. Psychopharmacol Bull 1995;31: 767–771
18. Worthington JJ III, Zucker BG, Fones CS, et al. Nefazodone for social phobia: a clinical case series. Depress Anxiety 1998;8:131–133
19. Van Ameringen M, Mancini C, Oakman JM. Nefazodone in social phobia. J Clin Psychiatry 1999;60:96–100
20. Oehrberg S, Cristiansen PE, Behnke K, et al. Paroxetine in the treatment of panic disorder: a randomised, double-blind, placebo-controlled study. Br J Psychiatry 1995;167:374–379
21. Ballenger JC, Wheadon DE, Steiner M, et al. Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. Am J Psychiatry 1998;155:36–42
22. Pohl RB, Wolkow RM, Clary CM. Sertraline in the treatment of panic disorder: a double-blind multicenter trial. Am J Psychiatry 1998;155: 1189–1195
23. Gorman JM, Liebowitz MR, Fyer AJ, et al. An open trial of fluoxetine in the treatment of panic attacks. J Clin Psychopharmacol 1987;7:329–332
24. den Boer JA, Westenberg HG. Serotonin function in panic disorder: a double-blind placebo controlled study with fluvoxamine and ritanserin. Psychopharmacology (Berl) 1990;102:85–94
25. Sheehan DV. Current concepts in the treatment of panic disorder. J Clin Psychiatry 1999;60(suppl 18):16–21
26. Papp LA, Sinha SS, Martinez JM, et al. Low-dose venlafaxine treatment in panic disorder. Psychopharmacol Bull 1998;34:207–209
27. DeMartinis NA, Schweizer E, Rickels K. An open-label trial of nefazodone in high comorbidity panic disorder. J Clin Psychiatry 1996;57:245–248
28. Berigan TR, Casas A, Harazin J. Nefazodone and the treatment of panic [letter]. J Clin Psychiatry 1998;59:256–257
29. Davidson JRT, Connor KM. Management of posttraumatic stress disorder: diagnostic and therapeutic issues. J Clin Psychiatry 1999;60(suppl 18): 33–38
30. Kline NA, Dow BM, Brown SA, et al. Sertraline efficacy in depressed combat veterans with posttraumatic stress disorder [letter]. Am J Psychiatry 1994;151:621
31. Rothbaum BO, Ninan PT, Thomas L. Sertraline in the treatment of rape victims with posttraumatic stress disorder. J Trauma Stress 1996;9: 865–871
32. Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. JAMA 2000;183:1837–1844
33. Marshall RD, Schneier FR, Fallon BA, et al. An open trial of paroxetine in patients with noncombat-related, chronic posttraumatic stress disorder. J Clin Psychopharmacol 1998;18:10–18
34. van der Kolk BA, Dreyfuss D, Michaels M, et al. Fluoxetine in posttraumatic stress disorder. J Clin Psychiatry 1994;55:517–522
35. Marmar CR, Schoenfeld F, Weiss DS, et al. Open trial of fluvoxamine treatment for combat-related posttraumatic stress disorder. J Clin Psychiatry 1996;57(suppl 8):66–70
36. Hamner MB, Frueh BC. Response to venlafaxine in a previously antidepressant treatment-resistant combat veteran with post-traumatic stress disorder. Int Clin Psychopharmacol 1998;13:233–234
37. Connor KM, Davidson JR, Weisler RH, et al. A pilot study of mirtazapine in post-traumatic stress disorder. Int Clin Psychopharmacol 1999;14:29–31
38. Hidalgo R, Hertzberg MA, Mellman T, et al. Nefazodone in post-traumatic stress disorder: results from six open-label trials. Int Clin Psychopharmacol 1999;14:61–68
39. Wood SH, Mortola JF, Chan YF, et al. Treatment of premenstrual syndrome with fluoxetine: a double-blind, placebo-controlled, crossover study. Obstet Gynecol 1992;80:339–344
40. Menkes DB, Taghavi E, Mason PA, et al. Fluoxetine treatment of severe premenstrual syndrome. BMJ 1992;305:346–347
41. Steiner M, Steinberg S, Stewart D, et al. Fluoxetine in the treatment of premenstrual dysphoria. Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study. N Engl J Med 1995;332:1529–1534
42. Eriksson E, Hedberg MA, Andersch B, et al. The serotonin reuptake inhibitor paroxetine is superior to the noradrenaline reuptake inhibitor maprotiline in the treatment of premenstrual syndrome. Neuropsychopharmacology 1995;12:167–176
43. Yonkers KA, Halbreich U, Freeman E, et al. Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment: a randomized controlled trial. Sertraline Premenstrual Dysphoric Collaborative Study Group. JAMA 1997;278:983–988

44. Freeman EW, Rickels K, Sondheimer SJ. Fluvoxamine for premenstrual dysphoric disorder: a pilot study. J Clin Psychiatry 1996;57(suppl 8):56–60
45. Young SA, Hurt PH, Benedek DM, et al. Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: a randomized, double-blind, placebo-controlled crossover trial. J Clin Psychiatry 1998; 59:76–80
46. Pearlstein TB, Stone AB. Long-term fluoxetine treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1994;55:332–335
47. Elks ML. Open trial of fluoxetine therapy for premenstrual syndrome. South Med J 1993;86:503–507
48. Freeman EW, Rickels K, Sondheimer SJ, et al. Nefazodone in the treatment of premenstrual syndrome: a preliminary study. J Clin Psychopharmacol 1994;14:180–186
49. Norden MJ. Fluoxetine in borderline personality disorder. Prog Neuropsychopharmacol Biol Psychiatry 1989;13:885–893
50. Cornelius JR, Soloff PH, Perel JM, et al. Fluoxetine trial in borderline personality disorder. Psychopharmacol Bull 1990;26:151–154
51. Markovitz PJ, Calabrese JR, Schulz SC, et al. Fluoxetine in the treatment of borderline and schizotypal personality disorders. Am J Psychiatry 1991; 148:1064–1067
52. Salzman C, Wolfson AN, Schatzberg A, et al. Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. J Clin Psychopharmacol 1995;15:23–29
53. Markovitz PJ, Wagner SC. Venlafaxine in the treatment of borderline personality disorder. Psychopharmacol Bull 1995;31:773–777
54. Mayer LES, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. J Clin Psychiatry 1998;59(suppl 15):28–34
55. American Psychiatric Association. Practice Guideline for Eating Disorders. Am J Psychiatry 1993;150:212–228
56. Walsh BT, Wilson GT, Loeb KL, et al. Medication and psychotherapy in the treatment of bulimia nervosa. Am J Psychiatry 1997;154:523–531
57. Goldstein DJ, Wilson MG, Thompson VL, et al. Long-term fluoxetine treatment of bulimia nervosa. Fluoxetine Bulimia Nervosa Research Group. Br J Psychiatry 1995;166:660–666
58. Fichter MM, Kruger R, Rief W, et al. Fluvoxamine in prevention of relapse in bulimia nervosa: effects on eating-specific psychopathology. J Clin Psychopharmacol 1996;16:9–18
59. Marcus MD, Wing RR, Ewing L, et al. A double-blind, placebo-controlled trial of fluoxetine plus behavior modification in the treatment of obese binge-eaters and non–binge-eaters. Am J Psychiatry 1990;147:876–881
60. Levine LR, Rosenblatt S, Bosomworth J. Use of a serotonin re-uptake inhibitor, fluoxetine, in the treatment of obesity. Int J Obes 1987;11:185–190
61. Goldstein DJ, Rampey AH Jr, Enas GG, et al. Fluoxetine: a randomized clinical trial in the treatment of obesity. Int J Obes Relat Metab Disord 1994;18:129–135
62. Wadden TA, Bartlett SJ, Foster GD, et al. Sertraline and relapse prevention training following treatment by very-low-calorie diet: a controlled clinical trial. Obes Res 1995;3:549–557
63. Goldstein MG. Bupropion sustained release and smoking cessation. J Clin Psychiatry 1998;59(suppl 4):66–72
64. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
65. Jorenby DE, Leischow S, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 1999;340:685–691
66. Dalack GW, Glassman AH, Rivelli S, et al. Mood, major depression, and fluoxetine response in cigarette smokers. Am J Psychiatry 1995;152: 398–403
67. Hitsman B, Pingitore R, Spring B, et al. Antidepressant pharmacotherapy helps some cigarette smokers more than others. J Consult Clin Psychol 1999;67:547–554
68. Schaffer A, Naranjo CA. Recommended drug treatment strategies for the alcoholic patient. Drugs 1998;56:571–585
69. Cornelius JR, Salloum IM, Ehler JG, et al. Fluoxetine in depressed alcoholics: a double-blind, placebo-controlled trial. Arch Gen Psychiatry 1997;54: 700–705
70. Roy A. Placebo-controlled study of sertraline in depressed recently abstinent alcoholics. Biol Psychiatry 1998;44:633–637
71. Gruber AJ, Hudson JI, Pope JG Jr. The management of treatment-resistant depression in disorders on the interface of psychiatry and medicine: fibromyalgia, chronic fatigue syndrome, migraine, irritable bowel syndrome, atypical facial pain, and premenstrual dysphoric disorder. Psychiatr Clin North Am 1996;19:351–369
72. Goodnick PJ, Jorge CM. Treatment of chronic fatigue syndrome with nefazodone. Am J Psychiatry 1999;156:797–798
73. Hickie I. Nefazodone for patients with chronic fatigue syndrome. Aust N Z J Psychiatry 1999;33:278–280