SSRIs and SNRIs: Broad Spectrum of Efficacy Beyond Major Depression

Jack M. Gorman, M.D., and Justine M. Kent, M.D.

Originally studied and introduced for the treatment of depression, the selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) have proven effective for a broad range of psychiatric illnesses, including several anxiety disorders, bulimia, and dysthymia. These drugs have in common important effects on the serotonergic (5-HT) neurotransmission system, which is involved in mediating a substantial number of important functions, including mood, aggression, sexual behavior, and pain. In addition, some of the new antidepressants, like venlafaxine/venlafaxine XR, also have effects on the noradrenergic neurotransmission system, which also appears important in mood and anxiety disorders. These new drugs, because of their specificity for the serotonin and norepinephrine reuptake proteins, lack most of the adverse side effects of tricyclic antidepressants and monoamine oxidase inhibitors. Consequently, in addition to being the usual first-line treatments for major depression, they are also first-line for panic disorder, obsessive-compulsive disorder, social phobia, posttraumatic stress disorder, and bulimia. They may also be the best medication treatments for dysthymia and generalized anxiety disorder. Further advances in psychopharmacology will be driven by discoveries from brain imaging and molecular biological research.

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The selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) have all proven effective in the treatment of major depression. Increasingly, however, these medications are shown to have a broad range of efficacy in seemingly diverse disorders, including all of the anxiety disorders. This development has had both heuristic and clinical implications.

An understanding of the neuroanatomy of the serotonergic neurotransmission system gives insight into the basis for the broad-spectrum efficacy of these second- and third-generation antidepressants. Serotonergic neurons originate in fairly restricted areas in the brain stem raphe region but then project widely throughout the central nervous system. Projections to frontal cortex may mediate mood, to hypothalamus appetite and sleep, and to the amygdala anxiety and fear responses. Serotonin also plays a role in aggression, sexual behavior, and pain. It is no surprise, then, that altering serotonergic neurotransmission with medication affects a wide range of human function.

More recent antidepressants like venlafaxine/venlafaxine XR, nefazodone, and mirtazapine also have actions on the noradrenergic system. In this, they resemble tricyclic antidepressants, many of which have similar dual action on serotonergic and noradrenergic reuptake. Fortunately, however, the newer drugs are almost entirely devoid of the anticholinergic and cardiovascular adverse effects of the tricyclics and thus allow modification of both the serotonergic and noradrenergic systems without producing the toxicity common to the tricyclics. It is now clear that there are important relationships between the 2 neurotransmitter systems.[1] Thus, 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.

One of the challenges in understanding the mechanism of action of antidepressants is the apparent dissociation between the rapid effects they have on neurotransmitter reuptake and the delay in clinical effect. For example, medications like fluoxetine and venlafaxine/venlafaxine XR substantially inhibit serotonin reuptake by the presynaptic neuron after only a few days, but depressed and anxious patients do not realize clinical benefits for several weeks. This implies that reuptake inhibition of serotonin and norepinephrine is probably only the first step of a cascade of neuronal events that ultimately leads to antianxiety and antidepressant effects. 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.[2] 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 undoubtedly explains how antidepressants work at the most fundamental level.

From the Department of Clinical Psychobiology, New York State Psychiatric Institute, and the Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, N.Y.

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Reprint requests to: Jack M. Gorman, M.D., New York State Psychiatric Institute, 722 W. 168th St., New York, NY 10032.

TREATMENT OF ANXIETY DISORDERS

Panic Disorder

SSRIs are now widely recognized as the first-line medication treatment for panic disorder. There is evidence that all of the marketed SSRIs—fluoxetine, fluvoxamine, sertraline, and paroxetine—as well as a newly available SSRI, citalopram, are effective. Black et al. compared fluvoxamine in doses of 200 to 300 mg daily to placebo and cognitive-behavioral psychotherapy (CBT) in panic disorder patients.[3] In this 8-week trial, fluvoxamine proved superior to both placebo and CBT, with 81% of fluvoxamine-treated patients panic-free by the end of the trial. Although this study has been criticized for methodological problems in the CBT arm, it clearly documents the efficacy of an SSRI. Paroxetine was the first antidepressant to receive Food and Drug Administration (FDA) approval for the specific treatment of panic disorder. In a study by Oehrberg et al.,[4] patients were randomly assigned to receive paroxetine plus cognitive therapy or placebo plus cognitive therapy. Nearly 90% of the paroxetine-treated patients were responders, significantly more than in the placebo arm. In another paroxetine study, Ballenger et al.,[5] tested 3 doses of paroxetine—10, 20, and 40 mg/day—against placebo. The 40-mg/day dose proved significantly more effective than placebo, again with more than 80% of panic disorder patients becoming panic-free. These studies, showing robust antipanic efficacy, have led to the sense that SSRIs may be more effective than tricyclics or benzodiazepines in the treatment of panic disorder. Indeed, 1 meta-analysis found superior efficacy for the SSRIs.[6]

Sertraline was the second antidepressant approved by the FDA for panic disorder. Several multicenter studies formed the basis of that approval.[7] These studies showed that all doses of sertraline were equally effective in treating panic disorder and that sertraline was effective for a range of symptoms that are part of panic disorder, including panic attacks, phobic avoidance, and overall disability. A multicenter study was reported in 1997 in which 2 doses of fluoxetine, 10 and 20 mg/day, were compared to placebo.[8] On most measures, the 20-mg/day dose was superior to placebo, including global improvement, phobic avoidance, and depression. The 10-mg/day dose was superior to placebo for reducing the frequency of panic attacks. It is important to note that an increasing number of studies investigating the efficacy of medications for panic disorder assess improvement across a range of symptom measures and are not restricted to looking only at the effect of the medication on panic attack frequency.

As stated earlier, it is known from preclinical studies that serotonergic neurons project to noradrenergic centers of the brain, including the locus ceruleus. In general, these serotonergic projections are inhibitory to noradrenergic activity. Although SSRIs have no direct effect on noradrenergic release, reuptake, or receptor binding, Coplan et al.[9] investigated whether long-term administration of an SSRI affects noradrenergic activity. Patients with panic disorder were treated with fluoxetine for 12 weeks. The plasma level of the main norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) was measured before treatment and at the end of the trial. MHPG was also measured at baseline in a group of normal controls. At baseline, the patients had significantly higher levels of MHPG than the controls, consistent with previous findings of heightened noradrenergic activity in panic disorder. At 12 weeks, however, there was a significant decrease in MHPG level in the patients, most marked in those who responded to treatment. This suggests that the increase in synaptic serotonin produced by SSRIs and SNRIs may lead to a decrease in noradrenergic activity and therefore a diminution of panic symptoms referable to noradrenergic hyperactivity.

The possibility that both serotonergic and noradrenergic activity are important in the pathophysiology of panic disorder raises the issue of the possible efficacy of SNRIs, which affect both systems. Geracioti[10] reported 4 cases of panic disorder treated with venlafaxine. All 4 patients responded with a minimum of adverse side effects. Interestingly, the doses of venlafaxine were quite low, in the range of 12.5 to 18.75 mg twice daily of the immediate-release formulation. Papp et al.[11] conducted an open-label trial of venlafaxine with 13 panic disorder patients. The patients were started at 25 mg/day of the immediate-release preparation and this was raised by 50 mg weekly to a maximum of 250 mg/day, based on clinical response. Ten patients completed the trial and all 10 were responders with complete elimination of panic attacks by week 10. The mean daily dose of venlafaxine at week 10 was 93.4 mg. This again raises the possibility that venlafaxine may be effective for panic disorder at relatively low doses, although placebo-controlled studies would be necessary to confirm these observations. A multicenter trial is currently underway evaluating the efficacy of nefazodone, which also has affects on both noradrenergic and serotonergic reuptake, for patients with panic disorder.

Generalized Anxiety Disorder

Two obstacles have impeded research into the psychopharmacology of generalized anxiety disorder (GAD). First, it was widely assumed by psychiatrists and other physicians that only benzodiazepines and buspirone are effective. Antidepressants were thought, if anything, to have the potential to worsen GAD. Second, GAD was felt to be an illness that rarely presents to psychiatrists as opposed to primary care physicians. Accumulating a sufficiently large number of GAD patients for a clinical trial of a new medication seemed nearly impossible.

Both assumptions are almost certainly incorrect. It is interesting to remember that none of the benzodiazepines or even buspirone were actually tested for efficacy with patients meeting current criteria for generalized anxiety disorder. Trials for these medications anteceded our present nomenclature. Although benzodiazepines and buspirone

are clearly effective for GAD, there has always been the suspicion, based in part on some research, that tricyclic antidepressants are also effective.

Studies with sufficient sample size to make meaningful comparisons are beginning to be reported that involve antidepressant use for GAD. Although more work is clearly needed, there is once again the suggestion that antidepressants may indeed be effective and, most surprisingly, may be superior on many counts to benzodiazepines.

For example, in a recently reported study, Rocca et al.[12] compared imipramine, paroxetine, and a standard benzodiazepine in the treatment of GAD. Interestingly, decreases in the Hamilton Rating Scale for Anxiety score were observed for all 3 medications at 2 weeks, but at 4 and 6 weeks, the antidepressants had actually produced greater decreases in the anxiety score than the benzodiazepine. The conclusion from this study, which admittedly did not have a placebo control, was that antidepressants may prove superior to benzodiazepines in the treatment of generalized anxiety if patients and their doctors wait long enough to appreciate the full response. Venlafaxine was also reported to be useful for the treatment of GAD in 8 of 11 patients treated openly for 8 weeks.[13]

The extended-release (XR) preparation of venlafaxine has also been found useful in GAD. Venlafaxine XR 225 mg/day was significantly more effective than placebo, as measured on the Hamilton Rating Scale for Anxiety and the Clinical Global Impressions-Severity in an 8-week randomized, placebo-controlled study in 377 patients who met criteria for GAD, but not major depression.[14] Entsuah et al.[15] found 75 mg/day and 150 mg/day of venlafaxine XR to be significantly better than placebo or buspirone on the Hospital Anxiety and Depression scale, a patient-rated scale.

Although it is obvious that the number of GAD studies remains small, clinicians should consider using antidepressants like paroxetine and extended-release venlafaxine. Both drugs avoid the well-known discontinuation problems inherent in benzodiazepine use and may even offer superior efficacy in the long run.

Obsessive-Compulsive Disorder

A long history of literature implicates serotonergic abnormalities in obsessive-compulsive disorder (OCD). The hypothesis that some kind of inadequacy in the serotonergic neurotransmitter system is involved in OCD rests on platelet, CSF 5-hydroxyindoleacetic acid (5-HIAA), and neuroendocrine challenge studies. More recently, brain imaging studies have implicated abnormal activity in the frontal cortex and parts of the basal ganglia. Of great interest is the recent finding of a possible relationship between OCD and streptococcal infection in children.[16] Ultimately, this may mean that, for some patients, treatments like antibiotics and plasmapheresis might be effective.

For now, however, the effective pharmacologic treatments for OCD are all antidepressants that inhibit serotonin reuptake. One tricyclic, clomipramine, and 4 SSRIs—fluvoxamine, fluoxetine, paroxetine, and sertraline—are approved by the FDA for the treatment of OCD. A number of studies substantiate the efficacy of clomipramine in OCD[17] and some believe that it is more effective than the SSRIs. However, head-to-head comparisons of SSRIs to clomipramine generally show the former to be equally effective and much better tolerated.[18,19] Hence, an SSRI is almost invariably the first-line treatment for OCD.

As with most anxious patients, starting doses of antidepressants are often lower for OCD than for depression. For example, initial doses of 25 mg/day for clomipramine or 10 mg/day for fluoxetine are not uncommon. Fluvoxamine is usually begun at about 50 mg/day. On the other hand, many clinicians find that OCD patients ultimately require fairly high doses of antidepressants. Hence, daily doses of 50 mg of paroxetine, 200 mg of sertraline, 80 mg of fluoxetine, or 300 mg of fluvoxamine may be needed to achieve optimal response. One of the interesting aspects of using antidepressants for anxiety disorders is the great variety of doses used for different conditions. These may differ from what is needed for depressed patients. For example, 20 mg/day of paroxetine is often sufficient for depression while 40 mg/day of paroxetine appears to be required for panic disorder. Similarly, while 20 mg/day of fluoxetine is generally effective for depression, 80 mg/day of fluoxetine may be required for OCD. Only when we have a fuller understanding of the mechanism of action of antidepressants and of the actual neurotransmitter and receptor abnormalities in various psychiatric illnesses will we be able to approach this issue.

If medication treatment is successful for OCD, it generally must be continued indefinitely.[20] At present, there is no evidence that there is ever a point beyond which medication can be safely discontinued without a high risk of relapse of OCD.

Even with aggressive medication therapy, however, many patients with OCD have significant residual symptoms or are only partial responders. Many medications have been cited as potentiating the response of the antidepressants for OCD, including buspirone, lithium, and fenfluramine. None of them, however, have proven to be robustly effective. The addition of an antipsychotic medication, like pimozide, to antidepressants for patients with concomitant tics or for patients whose obsessions border on delusional thinking may be effective. Many clinicians believe that combination medication and cognitive-behavioral treatment is superior to either modality alone, although empirical evidence for this is lacking. The ultimate treatment for refractory OCD is psychosurgery. While this is extreme, recent experience suggests that it may alleviate symptoms that otherwise render the OCD patient's life miserable without imposing significant cognitive compromise.

Social Phobia

Many medications—with many false starts—have been studied in the treatment of social phobia. One impediment to progress in this area has been the mistaken idea that social phobia is not a serious illness. Indeed, specific forms of

social phobia, like the fear of public speaking, appear to be so common in the general population that it is arguable whether they represent a psychiatric abnormality or a variant of normal human behavior. On the other hand, there is no question that the generalized form of social phobia, in which the patient is fearful of multiple performance and social situations, is a serious disorder with high rates of disability, concomitant mood disorder, and substance abuse. Fortunately, evidence now exists that medication and cognitive-behavioral psychotherapy are effective interventions.

β-Adrenergic blocking drugs originally seemed likely to be helpful for social phobia for 2 reasons. First, many of the symptoms reported by patients with social phobia during episodes of intense anxiety—heart pounding, flushing, sweating, and trembling—appear referable to the autonomic nervous system. By inhibiting the action of epinephrine in the peripheral nervous system and target organs, it was hoped that β-blockers could prevent these symptoms and lead to secondary reduction in phobic avoidance. Second, there is substantial literature and anecdotal experience attesting to the benefits of β-blockers for performance anxiety situations such as public speaking and musical performance.

In fact, although it does appear that β-blockers administered acutely before a feared performance situation may be beneficial, they do not have efficacy better than placebo in the treatment of generalized social phobia. Until recently, 2 medication options had been shown useful for social phobia, each with attendant problems—clonazepam and phenelzine.

In a controlled trial, Davidson et al. showed that the benzodiazepine clonazepam was more effective than placebo for social phobia.[21] In that study, 78% of the patients were rated as responders to the active drug. However, concerns have been raised that people with social phobia may have great difficulty discontinuing benzodiazepines and that, given the high rate of alcohol use in social phobia, they may be relatively contraindicated. Liebowitz et al.[22] showed that the monoamine oxidase inhibitor (MAOI) phenelzine is quite effective for social phobia and this became a frequently prescribed medication. The well-known and protean adverse side effects of MAOIs, however, limit the enthusiasm of most psychiatrists for using them widely. Interestingly, though tricyclic antidepressants seem effective for other anxiety disorders like panic and OCD, they appear to be ineffective for social phobia.

A number of open and controlled trials attest to the efficacy of SSRIs for social phobia, and although no drug yet has official FDA approval for this condition, they are now seen as the logical first-line medication therapy. For example, a controlled trial by van Vliet et al. reported that 47% of social phobic patients responded to fluvoxamine compared with 8% to placebo.[23] Katzelnick et al.[24] implemented a placebo-controlled, crossover trial of sertraline for social phobia and found that 42% of patients taking the active drug were rated as moderately to markedly improved compared with 17% taking placebo. Several open-label trials of fluoxetine have also reported successful treatment of social phobia.[25] In perhaps the largest medication study for social phobia yet conducted, 187 patients were randomly assigned to receive either paroxetine or placebo. As reported by Stein,[26] 69% of the patients taking paroxetine responded compared with only 29% taking placebo. Taken together, the results indicate that, given the relative safety of SSRIs and the relatively large database now available, they should be considered the first-line treatment for social phobia.

Venlafaxine has also been reported to treat social phobia successfully, primarily in patients who had failed to respond or were unable to tolerate an SSRI. Kelsey[27] reported that 8 of 9 patients with social phobia had a marked response to venlafaxine.

Posttraumatic Stress Disorder

Clinical trials evaluating treatments for posttraumatic stress disorder (PTSD) are in a relatively nascent stage. Anecdotal and open-label studies have reported efficacy for many medications, including anticonvulsants, benzodiazepines, clonazepam, and antidepressants. There have been very few controlled trials. At this moment, SSRIs have probably been the most extensively studied, with positive reports from open-treatment studies available in the literature for fluoxetine,[28] sertraline,[29] and fluvoxamine.[30] Van der Kolk et al.[31] conducted a controlled trial of fluoxetine with 64 veterans and nonveterans with PTSD. Of the 47 patients who completed the 5-week study, those in the fluoxetine group had significantly reduced PTSD symptoms compared with the placebo group. Unfortunately, the trial was terminated after just 5 weeks, which may not be sufficient to document the full potential of an SSRI like fluoxetine to ameliorate PTSD symptoms. Nevertheless, this is probably the most convincing and methodologically sound clinical trial yet conducted for PTSD patients and suggests that SSRIs may be important first-line therapies. At present, multicenter clinical trials in PTSD are underway for nefazodone and sertraline.

Dysthymia

Although traditionally dysthymia has been considered a neurotic illness amenable only to psychotherapy, a number of trials have now documented that antidepressants are effective. When only tricyclics and MAOIs were available, it was sometimes difficult to justify the use of medication given the substantial side effect burden. Given the safety and tolerability of SSRIs and SNRIs, however, the risk-to-benefit ratio has clearly shifted so that the clinician must now ask if there is any justification for *not* prescribing an antidepressant to a patient with dysthymia. Far from a benign illness, it is now well recognized that patients with dysthymia suffer substantially from chronic illness that is frequently complicated by major depression.

A complete review of all of the antidepressant studies for dysthymia is beyond the scope of this article. Neverthe-

Table 1. Antidepressant Treatment of Dysthymia (Hellerstein et al.)*

35 patients with dysthymia and without major depressive disorder
8 wk fluoxetine vs placebo
Response in 10/16 (62.5%) fluoxetine patients vs 3/16 (18.8%) placebo patients
Fluoxetine > placebo at 8 wk on HAM-D and CGI

*Data from reference 32. Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression.

Table 2. Antidepressant Treatment of Dysthymia (Thase et al.)*

416 patients with early-onset dysthymia, without concurrent major depressive disorder
12 wk sertraline vs imipramine vs placebo
Both active treatments superior to placebo on HAM-D and MADRS
By CGI criteria, positive response in 59% sertraline, 64% imipramine, 44% placebo
More imipramine than sertraline patients discontinued treatment for adverse events

*Data from reference 33. Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Table 3. Antidepressant Treatment of Bulimia (Goldstein et al.)*

483 patients with bulimia
16 wk fluoxetine vs placebo
Fluoxetine > placebo in vomiting and binge-eating reduction

*Data from reference 34.

Table 4. Treatment of Bulimia (Walsh et al.)*

120 women with bulimia
Supportive, dynamic vs cognitive behavioral therapy
2-stage medication treatment: desipramine, fluoxetine
CBT > supportive therapy
Medication and therapy > placebo and therapy
CBT and medication > medication alone

*Data from reference 35. Abbreviation: CBT = cognitive-behavioral therapy.

less, 2 of the best studies are depicted in Tables 1 and 2. In an 8-week study, Hellerstein et al.[32] randomly assigned 35 patients with dysthymia but no major depression to receive either fluoxetine or placebo. Ten (62.5%) of 16 patients taking fluoxetine were rated as responders compared to only 3 (18.8%) of 16 taking placebo. Further, fluoxetine-treated patients experienced significantly greater decreases on the Hamilton Rating Scale for Depression (HAM-D) and more improvement on the Clinical Global Impressions (CGI) scale than the placebo-treated patients. In a large trial, Thase et al.[33] randomly assigned 416 patients with dysthymia to a 12-week comparison of sertraline, imipramine, and placebo. Both active drugs produced superior outcomes on the HAM-D. By CGI criteria, a positive response was seen in 59% of patients taking sertraline, 64% taking imipramine, and 44% taking placebo, but more patients taking imipramine discontinued the trial because of an adverse event than did those taking sertraline. Most clinicians now believe that a trial using an SSRI or SNRI for patients with dysthymia is warranted.

Bulimia

Although bulimia is generally not considered as severe an illness as anorexia nervosa, it is interesting that only the former appears to be an antidepressant-responsive syndrome. To date, clinical trials attempting to show antidepressant efficacy in anorexia have been disappointing, even though this condition seems to involve aberrant brain mechanisms as clearly as any psychiatric illness. On the other hand, there is now considerable evidence that SSRIs are effective for bulimia.

We will not attempt to review the entire clinical trial literature for bulimia but rather highlight 2 representative studies that are described in Tables 3 and 4. In one study, Goldstein et al.[34] randomly assigned 483 patients with bulimia to 16 weeks of fluoxetine versus placebo. The fluoxetine group had greater decreases in self-induced vomiting and binge-eating than the placebo group. In a second study, Walsh et al.[35] entered 120 women with bulimia into a placebo-controlled study with 3 objectives: (1) to compare a supportive, psychodynamically oriented psychotherapy to a specific CBT, (2) to assess the benefit of a 2-stage medication therapy in which patients received fluoxetine if initial treatment with desipramine was either ineffective or not tolerated, and (3) to determine if medication plus psychotherapy would be superior to medication alone. Three results were evident: (1) CBT was superior to supportive psychotherapy, (2) medication plus therapy proved superior to placebo plus therapy, and (3) CBT plus medication was superior to medication alone.

Fluoxetine now has FDA approval for the treatment of bulimia. The Walsh et al. study suggests that the combination of a specific CBT for bulimia plus SSRI is probably the most powerful treatment. Once again, a new generation antidepressant is proven to be a first-line medication for a disorder other than depression.

CONCLUSION

We have reviewed the efficacy of SSRIs and SNRIs in 7 disorders other than major depression: panic disorder, GAD, OCD, social phobia, posttraumatic stress disorder, dysthymia, and bulimia. In each case there is now widespread consensus, mainly based on randomized, placebo-controlled, double-blind trials, that SSRIs and SNRIs are not only useful but are indeed the medication treatments of first choice. This is undoubtedly due in part to the fact that serotonin is involved in the regulation of diverse functions. Hence, it is no surprise that drugs that affect the serotonin system are not only effective for disorders of mood (major depression and dysthymia) but also disorders of fear responses (panic disorder), social interaction (social phobia), and appetitive behavior (bulimia). Evidence also exists that some of these conditions, including depression, panic dis-

order, and obsessive-compulsive disorder, also involve abnormalities of the noradrenergic system. We have pointed to the fact that serotonergic neurons have important effects on the noradrenergic system as one way of explaining the efficacy of the SSRIs. In addition, the SNRIs like venlafaxine/venlafaxine XR, which directly affect both serotonergic and noradrenergic systems, have been shown to be effective in the anxiety disorders in addition to depression.

Ultimately, our ability to design optimal medications for psychiatric illness will depend on 2 advances in neuroscience and psychiatric research. First, we must understand the fundamental pathophysiology of mood and anxiety disorders. Second, we must understand the effect of current antidepressant medications on neuronal second messengers, transcription factors, and gene expression. At our current pace, there is reason for optimism on both fronts. In the meantime, it is fortunate that the new generation of antidepressants has a broad spectrum of clinical efficacy that permits us to treat patients with a wide variety of illnesses with medications that are relatively simple to administer, safe, and well tolerated.

Drug names: buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil), clonazepam (Klonopin), desipramine (Norpramin and others), fenfluramine (Pondimin), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), pimozide (Orap), sertraline (Zoloft), venlafaxine (Effexor).

REFERENCES

1. Aston-Jones G, Akaoka H, Charlety P, et al. Serotonin selectively attenuates glutamate-evoked activation of noradrenergic locus coeruleus neurons. J Neurosci 1991;11:760–769
2. Hyman SE, Nestler ES. Initiation and adaptation: a paradigm for understanding psychotropic drug action. Am J Psychiatry 1996;153:151–162
3. Black DW, Wesner R, Bowers W, et al. A comparison of fluvoxamine, cognitive therapy, and placebo in the treatment of panic disorder. Arch Gen Psychiatry 1993;50:44–50
4. Oehrberg S, Christiansen 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
5. 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
6. Boyer W. Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attacks: a meta-analysis. Int Clin Psychopharmacol 1995;10:45–49
7. Wolkow R, Apter J, Clayton A, et al. Double-blind flexible dose study of sertraline and placebo in patients with panic disorder. Presented at the 20th Annual Meeting of the Collegium Internationale Neuropsychopharmacologicum; June 23–27, 1996; Melbourne, Australia
8. Lydiard RB, Pollack MH, Judge R, et al. Fluoxetine in panic disorder: a placebo-controlled study. Presented at the 10th Congress of the European College of Neuropsychopharmacology; September 1997; Venice, Italy
9. 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
10. Geracioti TD Jr. Venlafaxine treatment of panic disorder: a case series. J Clin Psychiatry 1995;56:408–410
11. Papp LA, Sinha S, Coplan JD, et al. Low dose venlafaxine treatment in panic disorder. Psychopharmacol Bull 1998;134:207–209
12. Rocca P, Fonzo V, Scotta M, et al. Paroxetine efficacy in the treatment of generalized anxiety disorder. Acta Psychiatr Scand 1997;95:440–450
13. Johnson MR, Emmanuel N, Crawford M, et al. Treatment of generalized anxiety disorder with venlafaxine: a series of 11 cases [letter]. J Clin Psychopharmacol 1998;18:418–419
14. Aguiar LM, Haskins T, Rudolph RL, et al. Double-blind placebo-controlled study of once-daily venlafaxine extended release in outpatients with GAD. In: New Research Program and Abstracts of the Annual Meeting of the American Psychiatric Association; June 3, 1998; Toronto, Canada. NR643:241
15. Entsuah R, Derivan AT, Haskins T, et al. Double-blind placebo-controlled study of once daily venlafaxine extended release and buspirone. In: New Research Program and Abstracts of the Annual Meeting of the American Psychiatric Association; June 3, 1998; Toronto, Canada. NR644:241
16. Murphy TK, Goodman WK, Fudge MW, et al. B lymphocyte antigen D8/17: a peripheral marker for childhood-onset obsessive-compulsive disorder and Tourette's syndrome? Am J Psychiatry 1997;154:402–407
17. Clomipramine Collaborative Study Group. Clomipramine in the treatment of patients with obsessive-compulsive disorder. Arch Gen Psychiatry 1991;48:730–738
18. Pigott TA, Pato MT, Bernstein SE, et al. Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder: behavioral and biological results. Arch Gen Psychiatry 1990;47:926–932
19. Zohar J, Judge R. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. OCD Paroxetine Study Investigators. Br J Psychiatry 1996;169:468-474
20. Pato MT, Zohar-Kadouch R, Zohar J, et al. Return of symptoms after discontinuation of clomipramine in patients with obsessive compulsive disorder. Am J Psychiatry 1988;145:1521–1525
21. Davidson JR, Potts N, Richichi E, et al. Treatment of social phobia with clonazepam and placebo. J Clin Psychopharmacol 1993;13:423–428
22. Liebowitz MR, Schneier F, Campeas R, et al. Phenelzine vs atenolol in social phobia: a placebo controlled comparison. Arch Gen Psychiatry 1992;39:290–300
23. van Vliet IM, den Boer JA, Westenberg HGM. Psychopharmacological treatment of social phobia: a double-blind placebo controlled study with fluvoxamine. Psychopharmacology (Berl) 1994;115:128–134
24. 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
25. Schneier FR, Chin SJ, Hollander E, et al. Fluoxetine for the treatment of social phobia. J Clin Psychopharmacol 1992;12:62–64
26. Stein M. An update on social phobia. Presented at the U.S. Psychiatric and Mental Health Congress; November 1997; Orlando, Fla
27. Kelsey JE. Venlafaxine in social phobia. Psychopharmacol Bull 1995;31:767–771
28. Nagy LM, Morgan CA, Southwick SM, et al. Open prospective trial of fluoxetine for posttraumatic stress disorder. J Clin Psychopharmacol 1993;13:107–113
29. Kline NA, Bow BM, Brown SA, et al. Sertraline efficacy in depressed combat veterans with post-traumatic stress disorder [letter]. Am J Psychiatry 1994;151:621
30. 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
31. van der Kolk BA, Dreyfuss D, Michaels M, et al. Fluoxetine in posttraumatic stress disorder. J Clin Psychiatry 1994;55:517–522
32. Hellerstein DJ, Yanowitch P, Rosenthal J, et al. A randomized double-blind study of fluoxetine versus placebo in the treatment of dysthymia. Am J Psychiatry 1993;150:1169–1175
33. Thase ME, Fava M, Halbreich U, et al. A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. Arch Gen Psychiatry 1996;53:777–784
34. Goldstein DJ, Wilson MG, Thompson VL, et al. Long-term fluoxetine treatment of bulimia nervosa. Br J Psychiatry 1995;166:660–666
35. Walsh BT, Wilson GT, Loeb KL, et al. Medication and psychotherapy in the treatment of bulimia nervosa. Am J Psychiatry 1997;154:523–531

DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated for these specified uses: citalopram, fluoxetine, fluvoxamine, nefazodone, venlafaxine for treatment of panic disorder; paroxetine, venlafaxine for treatment of generalized anxiety disorder; clonazepam, fluoxetine, fluvoxamine, paroxetine, phenelzine, sertraline for treatment of schizophrenia; clonazepam, fluoxetine, fluvoxamine, nefazodone, sertraline for treatment of posttraumatic stress disorder.