SSRIs and SNRIs: Broad Spectrum of Efficacy Beyond Major Depression

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Originally studied and introduced for the treatment of depression, 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. 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.

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.
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. 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 Oehberg et al., 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, Bfllenger et al. 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. Geraci and other2 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 effects on both noradrenergic and serotonergic reuptake, for patients with panic disorder.

Generalized Anxiety Disorder

Two obstacles have impeded research into the pharmacology 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, Roca et al. 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.

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. Entsuah et al. 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. 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 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. 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. 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 vari-
ant 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 in-
terventions.

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 auto-
nomic nervous system. By inhibiting the action of epi-
nephrine in the peripheral nervous system and target or-
gans, it was hoped that β-blockers could prevent these
symptoms and lead to secondary, reduction in phobic
avoidance. Second, there is substantial literature and anec-
dotal 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 admin-
istered 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 re-
cently, 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 pla-
cebo for social phobia. In that study, 78% of the patients
were rated as responders to the active drug. However, con-
cerns 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 be-
came 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
appear 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 effi-
cacy 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 ex-
ample, 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 imple-
mplemented 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 im-
proved compared with 17% taking placebo. Several open-
label trials of fluoxetine have also reported successful
treatment of social phobia.25 In perhaps the largest medica-
tion 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 pla-
cebo. 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 pho-
bia successfully, primarily in patients who had failed to re-
spond or were unable to tolerate an SSRI. Kelsey27 re-
ported that 8 of 9 patients with social phobia had a marked
treatment for social phobia.

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, benzodi-
azepines, 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 fluvox-
amine.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. Unfortu-
nately, 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. Nev-
ertheless, this is probably the most convincing and meth-
odologically sound clinical trial yet conducted for PTSD
patients and suggests that SSRIs may be important first-
time 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 be-
nign 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-

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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
aData 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
aData 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.

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 serotonin 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).

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