# CURRENT AND EMERGING THERAPEUTICS OF ANXIETY AND STRESS DISORDERS

JACK M. GORMAN
JUSTINE M. KENT
JEREMY D. COPLAN

During the 1960s and 1970s the concept of "pharmacologic dissection" became popular as a putative method for differentiating among different categories of psychiatric illness. At the time, it was widely held that anxiety disorders, but not depression, respond to benzodiazepines, whereas depression, but not anxiety disorders, responds to antidepressants. Panic disorder was held to be the one exception, responding only to antidepressants. Alprazolam, selective serotonin reuptake inhibitors (SSRIs), and buspirone had not yet been tested. On the basis of these observations, it was asserted that anxiety and depression are clearly distinct categories of illness.

Thirty years later we find that the situation has changed dramatically. The first inconsistency with the notion of pharmacologic dissection was the clear finding that panic disorder does indeed respond to benzodiazepines. For a while, alprazolam and then clonazepam were regarded by some authorities and clinicians as first-line therapies for panic disorder, replacing tricyclics and monoamine oxidase inhibitors.

An even more potent challenge, however, has come from the evidence not only that anxiety disorders respond to anti-depressants but also that antidepressants work better than benzodiazepines for most of them. As this chapter discusses, antidepressants are now considered the appropriate pharma-cologic intervention for panic disorder, social anxiety disorder, posttraumatic stress disorder (PTSD), and generalized anxiety disorder (GAD). The latter case is particularly interesting. Once considered the sole domain of benzodiazepines, GAD was then shown to be responsive to a drug in an entirely new category, with no relationship whatsoever to the benzodiazepine receptor or  $\gamma$ -aminobutyric acid (GABA)—buspirone. At about the same time evidence

began to accumulate from just a few studies that GAD might also respond to antidepressants. This evidence was largely ignored, and pharmaceutical companies were advised to stay away from GAD, a condition supposedly so placeboresponsive that no drug would ever be shown effective in large clinical trials. To the contrary, venlafaxine is now approved by the Food and Drug Administration (FDA) for the treatment of GAD, and there is also evidence for the efficacy of paroxetine.

At this point, rather than "dissecting" among the anxiety disorders or between anxiety disorders and depression, pharmacologic grounds might lead one to assume that these conditions are variants of each other. This also would probably be an oversimplification. Anxiety and depression are different and we can make distinctions among the anxiety disorders. Nevertheless, the finding that antidepressants are so ubiquitously effective across categories raises interesting questions and challenges. We review here the evidence for responsiveness of four anxiety disorders to medication.

### **PANIC DISORDER**

Panic disorder (PD) has a reported lifetime prevalence of between 1.5% and 3.5% (1,2), is highly comorbid with major depression, and is associated in its own right with significant impairment in psychosocial functioning independent of depressive symptomatology. In the Epidemiologic Catchment Area study, subjective reports of patients with PD indicate that approximately one-third experience poor physical and emotional health, rates comparable with major depression (2).

### **Historical Notes**

Recognized as a distinct disorder that could be distinguished from the general diagnosis of "anxious neurosis," in part through the pharmacologic dissection work of Klein and Fink (3,4) in the 1960s, PD was first categorized as a discrete diagnostic entity in the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III), in 1980. Despite some minor changes in diagnostic criteria in the third edition revised (DSM-III-R) and the fourth edition (DSM-IV), primarily involving the number and frequency of attacks required, the major criteria remain essentially the same. The key triad of symptoms are (a) the occurrence of spontaneous panic attacks; (b) the presence of anticipatory anxiety; and (c) the presence of phobic avoidance, resulting in some degree of functional impairment. The pharmacologic treatment of PD has evolved dramatically since the heterocyclic antidepressants were first established as possessing powerful antipanic properties in the early 1960s (4). Throughout the 1970s and 1980s, the heterocyclic antidepressants continued to be the mainstay of pharmacologic treatment of PD, with the monoamine oxidase inhibitors (MAOIs) used primarily in patients who failed trials of heterocyclic antidepressants. The high potency benzodiazepines were increasingly prescribed as both primary and adjunct treatments throughout this same time period. With the introduction of the SSRIs in the United States in the late 1980s and early 1990s for the treatment of depression, this class of drug began being used in the treatment of PD with promising results. In the late 1990s, several large-scale, controlled trials established the SSRIs to be effective and safe treatments for PD, thus supplanting the heterocyclic antidepressants and benzodiazepines as first-line treatment. Although the serotonin, norepinephrine, and GABA systems remain the traditional targets for the majority of antipanic medications, widely different classes of drugs targeting an array of neurochemical systems are now being explored as potential treatments for PD.

### **Heterocyclic Antidepressants**

Numerous controlled trials have confirmed the efficacy of the heterocyclic antidepressants, since the initial observations of Klein (4), in both the acute and long-term treatment of PD. In general, heterocyclics with greatest serotoninergic reuptake inhibition effect, such as imipramine and clomipramine, appear to be most effective in the treatment of PD (5–7). By far the best studied of this class of antidepressants is imipramine, which due to its well-established efficacy has been generally accepted as the gold standard of PD treatment (8). In the Cross-National Collaborative Panic Study, more than 1,000 patients in 14 countries were randomized into a study comparing imipramine, alprazolam, and placebo (9). At the study's end, imipramine and alprazolam were found to have comparable efficacy, and both were significantly superior to placebo on most outcome measures. A positive dose-response relationship between imipramine levels and clinical improvement has been reported, with plasma levels of 140 mg/mL associated with the greatest improvement in panic symptoms (10). Although several other of the heterocyclic antidepressants have been used in the treatment of PD (amitryptyline, desipramine, nortriptyline, clomipramine), far less controlled data are available supporting their efficacy (11,12). Although effective, side effects often limit the use of this class of medication in the treatment of PD. This is particularly true in the case of clomipramine, which due to its anticholinergic and antihistaminergic effects can be difficult for patients to tolerate (13). The use of the heterocyclic antidepressants is often limited by the presence of comorbid medical conditions such as cardiac disease and glaucoma. Lethality in overdose is another concern given the reported high rates of suicide in this population when depression is comorbid (14–16). Although the SSRIs are often touted as offering a more tolerable side-effect profile than the heterocyclics, the sideeffect burden of imipramine has recently been shown to be comparable to, although different in nature from, that of the SSRIs, with most side effects (with the exception of dry mouth, sweating, and constipation) not persisting beyond the first few weeks of treatment (17).

### **Monoamine Oxidase Inhibitors**

Like the heterocyclic antidepressants, the MAOIs, are clearly established to be effective in the treatment of PD, yet have yielded to newer antidepressants with similar antipanic efficacies but less drug-drug and dietary interactions. Among the MAOIs, phenelzine is the best studied in PD, and its efficacy in the acute treatment of PD is supported by several studies (18-20). Dietary restrictions, lethality in overdose, and drug interaction concerns limit the widespread use of the traditional MAOIs. Stemming from these concerns, the reversible inhibitors of MAOI (RIMAs) were developed and have demonstrably fewer drug-drug and dietary interactions. These include moclobemide and brofaromine, neither of which is currently marketed in the United States, but are used extensively throughout Europe and other parts of the world. The efficacy of moclobemide has been shown in the treatment of PD in placebo-controlled studies (21), and moclobemide has been found to be comparable in efficacy to clomipramine (21) and fluoxetine (22). Moclobemide has also been shown to be as effective as fluoxetine in maintenance treatment of PD (23). Brofaromine was shown to be comparable to fluvoxamine (24) and clomipramine (25) in small randomized, double-blind studies lacking a placebo. In a placebo-controlled study of the efficacy of brofaromine, 30 patients with PD (DSM-III-R definition) were treated for 12 weeks. Although there was no significant reduction in the number of panic attacks for those patients treated with brofaromine, patients demonstrated clinical improvement on several other measures, including agoraphobic avoidance (26).

# **Benzodiazepines**

The high-potency benzodiazepines, another mainstay of treatment for PD, have been shown to be effective, well tolerated, and safe. In the absence of comorbid substance abuse, concerns about abuse potential have proven largely unfounded in this population (27-30). Among the benzodiazepines, alprazolam and clonazepam are labeled for the treatment of panic disorder and have been shown in numerous, controlled trials to be effective treatments (31-36). Clonazepam, with a long half-life of 20 to 50 hours, allows fewer doses per day than the short-acting alprazolam, and may reduce the likelihood of rebound symptoms between doses. The benzodiazepines have repeatedly been shown to offer an early advantage in the treatment of anxiety by providing almost immediate relief of anxiety-related somatic symptoms such as muscle tension and insomnia (27,37,38). However, in the long term, antidepressants may offer the advantage of better targeting and relief of psychic symptoms of anxiety (37), and provide the added benefit of treating associated depressive symptoms. Discontinuing long-term pharmacotherapy with benzodiazepines can be difficult, with as many as a third of patients with PD being unable to discontinue use due to dependence/withdrawal (27). Thus, despite their efficacy and safety, many clinicians remain concerned about the risk of dependence (39).

# Selective Serotonin Reuptake Inhibitors (SSRIs)

Among the antidepressants currently used in the treatment of PD, the SSRIs have become first-line treatments (40,41). Following in the wake of numerous promising open and controlled trials, several large, multicenter, placebo-controlled studies involving hundreds of subjects each have demonstrated the efficacy of the SSRIs in the treatment of PD (Table 66.1) (42-50). Both sertraline and paroxetine are labeled in the United States for the treatment of PD, and citalogram is approved in several European countries for this indication. Although fluvoxamine has not been studied in clinical trials on the scale of the other SSRIs, it has been shown to be efficacious in smaller (<100 subjects), randomized, placebo-controlled studies (25,44). Despite their established efficacy in the treatment of PD, there are certain problems inherent in prescribing the SSRIs in patients with PD. Of primary concern on the initiation of treatment is the commonly observed anxiogenic effect, which, despite being dose-dependent, can nonetheless make the initial several days of treatment a challenge for patients. Initiating treatment with a dose of one-fourth to one-half that of the normal starting dose may greatly reduce the patient's feelings of restlessness and increased anxiety. The delayed onset of anxiolytic action contributes to making the period of SSRI initiation difficult for patients with PD. Other effects such as sexual dysfunction and weight gain with long-term use can make these drugs as problematic as earlier classes for some patients. Overall, though, the side-effect burden associated with SSRI treatment has been shown to be more tolerable for most patients than the heterocyclics and benzodiazepines (51). Because the SSRIs have been associated with a discontinuation syndrome characterized by anxiety, tremor, dizziness, paresthesias, nausea, and other symptoms when abruptly stopped, these medications should be tapered over a few weeks, if possible, to minimize discontinuation symptoms (38).

# **Newer Antidepressants**

Among the newer antidepressants, several have demonstrated promise in PD. Venlafaxine, a serotonin-norepinephrine reuptake inhibitor, has shown efficacy (on some measures) in a small, placebo-controlled study (52). Nefazodone, a weak serotonin-norepinephrine reuptake inhibitor with serotonin receptor subtype 2C (5-HT<sub>2C</sub>) antagonist properties, has been shown to reduce anxiety in depressed patients with comorbid PD (53). Mirtazapine enhances both noradrenergic and serotoninergic neurotransmission without reuptake inhibition. Results of an open study involving ten patients suggested that mirtazapine might be effective in the treatment of PD (54). More recently, in a double-blind randomized trial comparing mirtazapine and fluoxetine in the treatment of PD, both drugs showed comparable efficacy on the primary outcome measures and on most secondary outcome measures (55). Adverse events differed between treatments, with weight gain occurring more frequently in those patients receiving mirtazapine, whereas nausea and paresthesias occurred more often in those receiving fluoxetine.

# **Anticonvulsants**

Among the anticonvulsants being used in the treatment of PD are valproate and carbamazepine, and the newest anticonvulsants gabapentin, lamotrigine, pregabalin, and vigabatrin. Valproate has shown promise in several open trials (56-58), and one small placebo-controlled study (59). It may be particularly effective when mood instability is comorbid (60). There is far less support for the use of carbamazepine in the treatment of PD, with uncontrolled studies in patients with PD with EEG abnormalities demonstrating some benefit from carbamazepine treatment (58). However, the only controlled trial of carbamazepine in a small number of PD patients (N = 14) did not report a significant difference for carbamazepine versus placebo in reducing panic attack frequency (61). Gabapentin has shown promise (62) and is recognized as having a benign side-effect profile. Lamotrigine, pregabalin, and vigabatrin are currently under investigation.

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TABLE 66.1. EFFICACY OF THE SSRIS IN THE ACUTE TREATMENT OF PANIC DISORDER BASED ON LARGE-SCALE, PLACEBO-CONTROLLED STUDIES

SSRI	Investigators	Study Design	Dose Range	Outcome
Fluoxetine	Michelson et al., 1998	Multicenter, 10-week study of 243 patients	Fixed dose: 10 or 20 mg/day	20-mg dose was most effective, demonstrating significant change versus placebo on panic attack frequency, CGI improvement scores, Hamilton Anxiety and Depression scores, phobic symptoms, and functional impairment as measured by the Sheehan Disability Scale (family life and social life); the two fluoxetine groups did not differ from placebo in the number of patients who were panic-free at endpoint
	Michelson et al., 2000	Multicenter, 12-week study of 180 patients	Flexible dose: 20–60 mg/day (mean dose = 20 mg)	A significantly greater percentage of patients on fluoxetine were panic-free at endpoint (42%, versus 28% on placebo); significant change versus placebo were found for the CGI Severity, HAM-A, State Anxiety Inventory, and Sheenhan Disability Scale (work and social impairment)
Fluvoxamine	Black et al., 1993	Multicenter, 8-week study of 75 patients randomized to either fluvoxamine, cognitive therapy, or placebo	Flexible dose: up to 300 mg/day (mean dose = 230 mg)	Fluvoxamine was superior to placebo and cognitive therapy at endpoint as measured by the Clinical Anxiety Scale and CGI Severity and Improvement scales; fluvoxamine was superior to placebo as measured by a greater reduction in mean panic attack severity, and number of panic-free patients; fluvoxamine-treated patients demonstrated significant reductions versus placebo on several measures of the Sheehan Disability Scale (work, social/leisure)
Paroxetine	Oehrberg et al., 1995	Multicenter, 12-week study of 120 patients—all received cognitive therapy	Flexible dose: 20–60 mg/day	Number of patients with at least 50% reduction in panic attacks was significantly greater in the paroxetine-treated than placebo group, as was number of patients who had only one or no panic attacks during the final study week. The paroxetine group had significantly greater mean reductions in HAM-A and CGI scores versus placebo
	Ballenger et al., 1998	Multicenter, 10-week study of 278 patients	Fixed dose: 10, 20, or 40 mg/day	40-mg group demonstrated the greatest effects, with significant improvement versus placebo on measures of reduction in number of panic attacks, intensity of attacks, CGI Severity and Improvement scores, phobic fear score, HAM-A score, and MADRS
Sertraline	Pollack et al., 1998	Multicenter, 10-week study of 176 patients	Flexible dose: 50–200 mg	Significant decreases versus placebo at endpoint in number of panic attacks, CGI Improvement and Severity scales, PDSS scores; sertraline also demonstrated superiority on improvement in quality of life scores
	Sheikh et al., 2000	Pooled data from two 12-week studies with a total of 322 patients	Fixed dose: 50, 100, or 200 mg/day	All three doses of sertraline were superior to placebo on frequency of panic attacks, CGI Improvement, and change in panic burden (attack frequency X severity), with no consistent dose-response effect

(continued)

TABLE 66.1. (continued)

SSRI	Investigators	Study Design	Dose Range	Outcome
Citalopram	Wade et al., 1997	Multicenter, 8-week comparative study with clomipramine and placebo of 475 patients	Fixed dose: citalopram 10 or 15 mg/day, 20 or 30 mg/day, 40 or 60 mg/day; clomipramine 60 or 90 mg/day	Patients treated with citalopram 20/30 or 40/60 mg/day were comparable to clomipramine and superior to placebo as measured by the number of patients panic-free in the final week of treatment, and by mean reduction in HAM-A total and psychic subscale, and the MADRS; only the 40/60-mg/day dose demonstrated superiority to placebo, along with clomipramine, on the HAM-A somatic subscale; on the Physician's Global Improvement Scale and Patient's Global Improvement Scale, the 20/30-mg dose exhibited greater effects; however, both the 20/30- and 40/60-mg/day doses were superior to placebo

CGI, Clinical Global Impression; HAM, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Ashberg Depression Rating Scale; SSRI, selective serotonin reuptake inhibitor.

### **Beta-Blockers**

Although the beta-blockers are more commonly used in the treatment of performance anxiety and as adjunctive treatment in PTSD, a small number of open studies suggest they may be effective in the treatment of PD (63), although they are not considered a first-line treatment.

# **Future Directions**

Several classes of drugs, although initially viewed as promising, have shown limited efficacy in the treatment of PD. These include buspirone, bupropion, ondansetron, and the cholecystokinin (CCK) antagonists (64–67). A number of new classes of drugs are being studied, including the benzo-diazepine partial agonists such as abecarnil and pagaclone, and the corticotropin-releasing hormone (CRH) inhibitors. Experimental agents showing promise in panic-like models in rodents include the group II metabotropic glutamate receptor agonist LY354740 (68) and drugs acting at the neuropeptide receptors, including neuropeptide-Y agonists and neurokinin substance P antagonists (69).

In summary, the expansion of the antipanic armamentarium suggests that, as with many of the psychiatric disorders, there is no single effective treatment of PD. Among the most commonly prescribed classes of drugs for the treatment of PD [benzodiazepines, SSRIs, tricyclic antidepressants (TCAs), and MAOIs], there are probably no major differences in treatment efficacy, with most reported differences in efficacy between classes probably attributable to differences in study design and samples (27). The use of antidepressants, however, and particularly the SSRIs, has supplanted the long-term use of benzodiazepines for this

disorder. Antidepressant use has two main advantages over the benzodiazepines: (a) it provides antidepressant benefits in a population highly susceptible to depressive symptomatology and comorbid major depression (70), and (b) it eliminates the difficulties associated with withdrawal symptoms upon benzodiazepine discontinuation. In the case of comparable efficacy, medication choice is based on factors such as latency to onset of therapeutic action, safety, and the individual side-effect profiles of each medication. In this regard, the SSRIs are currently considered first-line treatment for PD, demonstrating comparable efficacy and superior tolerability to other treatment classes. Combination therapies are frequently used for treatment resistance, and an approach of prescribing a benzodiazepine at the initiation of treatment with an SSRI, and later tapering it, has proved to be popular with clinicians and has recently been demonstrated to be advantageous in the early stages of treatment over an SSRI alone (71).

### **GENERALIZED ANXIETY DISORDER**

The diagnostic criteria for generalized anxiety disorder (GAD) have evolved over the past two decades, undergoing substantial revision to the current definition emphasizing excessive, unrealistic worry as the cardinal feature of this disorder. Defined in 1980 in DSM-III as a disorder of continuous or persistent worry symptoms of at least 1 month's duration, the diagnosis of GAD was reframed in DSM-III-R to require symptoms extended for 6 months or longer, and an emphasis on unrealistic worry was stressed. With DSM-IV, GAD was defined as excessive and persistent

worry, accompanied by three or more physical or psychological symptoms of anxiety, persisting 6 months or longer. Because of the shift in diagnostic criteria and required duration of symptoms over the years, comparison of pharmacologic treatment studies performed prior to the introduction of DSM-III-R is difficult.

In comparison with panic disorder, PTSD, and obsessive-compulsive disorder (OCD), there are fewer publications devoted to GAD overall, and only a limited number of published controlled clinical medication trials. Several reasons have been proposed for this deficiency, including underrepresentation in clinical settings and a view of GAD as a "mild" disorder (72). In reality, GAD is one of the most commonly diagnosed anxiety disorders, with a lifetime prevalence of 4.1% to 6.6% (73,74), which is often chronic (75), and associated with significant compromise in functioning (76,77). There remains substantial controversy surrounding the validity of GAD as a primary disorder, as opposed to a comorbid condition or a prodromal/residual phase of another disorder (78,79). Findings from epidemiologic studies of GAD suggest that current comorbidity with other disorders is as high as 58% to 65% (73,76), and lifetime comorbidity rates are between 80% and 90% (76,80). Non-comorbid, "pure" GAD lifetime prevalence was found to be only 0.5% in the National Comorbidity Survey (76). Overall, the sum of studies examining quality of life issues support the idea that non-comorbid GAD is relatively rare, but is associated with significant impairment in its own right (81,82).

### **Historical Notes**

Prior to the introduction of the benzodiazepines, the main agents available for the treatment of anxiety were the tricyclic antidepressants (doxepin, imipramine, amitryptyline), antihistamines (diphenhydramine, hydroxyzine), barbiturates (mephobarbital), and the sedative antianxiety agent meprobamate (Milltown). The development of the benzodiazepines in the mid-1950s led to the introduction of chlordiazepoxide (Librium) in 1959, and ushered in an era of benzodiazepine use in the treatment of a wide range of anxiety symptoms related to anxiety and mood disorders, psychosis, and alcohol withdrawal. Greater tolerability and the superior safety profiles of the benzodiazepines resulted in a sharp decline in the use of barbiturates for anxiety disorders (83). The benzodiazepines have remained a common treatment choice for GAD throughout the past two decades. However, concerns about dependence and withdrawal, short-term memory impairment, interactions with alcohol, and psychomotor impairment have resulted in increased interest in alternative medications. The introduction of drugs such as buspirone (1986), SSRIs (from 1980 on), and the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine (1994) have broadened the available treatment armamentarium for GAD significantly.

# **Tricyclic Antidepressants**

Tricyclic antidepressants (TCAs) have been in use in the treatment of GAD for many decades; however, data supporting their efficacy from controlled clinical trials are extremely limited. Imipramine is the only TCA shown to be effective in placebo-controlled trials of GAD patients without comorbid depression (84,85). In comparator trials, imipramine has been shown to have clinical efficacy comparable to the benzodiazepines (84,86,87).

# **Benzodiazepines**

Five benzodiazepines (alprazolam, chlordiazepoxide, clorazepate, diazepam, and lorazepam) are currently labeled as treatments for anxiety (GAD) (88). Clonazepam and alprazolam are labeled specifically for the treatment of PD. There are a limited number of clinical trials demonstrating the efficacy of benzodiazepines in the treatment of GAD in its current (DSM-IV) definition (89,90); however, benzodiazepines have been shown effective in controlled studies using DSM-III criteria for GAD (91).

# **Buspirone**

Buspirone is a serotonin receptor subtype 1A (5-HT<sub>1A</sub>) partial agonist with anxiolytic properties. In a metaanalysis of placebo-controlled comparator trials with benzodiazepines, buspirone showed comparable efficacy to the benzodiazepines in eight trials in 735 patients meeting DSM-III criteria (1 month's duration of illness) for GAD (92). In a metaanalysis of eight placebo-controlled studies in over 500 GAD patients with coexisting depressive symptoms, buspirone demonstrated significant superiority to placebo (93). Prior recent treatment with a benzodiazepine (<1 month) has been shown to predict poor response to subsequent buspirone treatment in GAD (92). This may be due to a combination of factors including the presence of benzodiazepine withdrawal, exacerbation of benzodiazepine discontinuation symptoms by buspirone and its metabolite a-(2-pyridinyl)-piperazine via enhancement of noradrenergic activity (94), and psychological factors such as patient expectations.

### **SSRIs**

The first published study of a medication with significant serotonin reuptake inhibition properties in GAD involved a small, open-label trial of clomipramine (95). The suggestion of efficacy in this study, along with the success of clomipramine in treating other anxiety disorders, raised interest in pharmacologic agents for GAD that target the serotoninergic system. Following several years later, the first comparison trial of an SSRI in the treatment of GAD was published by Rocca and colleagues (89). Treatment efficacy of paroxetine was compared with the tricyclic imipramine and the

benzodiazepine 2'-chlordesmethyldiazepam in 81 subjects with GAD. Of the 63 patients who completed the randomized, 8-week study, 68% of the paroxetine group, 72% of the imipramine group, and 55% of the 2'-chlordesmethyldiazepam group were judged to be responders as measured by a 50% or more decrease in Hamilton Anxiety Rating Scale (HAM-A) scores. The greatest improvement during the first 2 weeks occurred in the group receiving the benzodiazepine, as expected by the early relief of physical anxiety symptoms and insomnia provided by this class of medication. However, from the fourth week forward, the paroxetine and imipramine groups demonstrated superior benefits, particularly in the area of psychic symptoms of anxiety. More recently, the efficacy of paroxetine was demonstrated in a large, fixed-dose study of more than 500 patients with a DSM-IV diagnosis of GAD without major depression (96). Patients were randomized to receive paroxetine 20 mg/ day, paroxetine 40 mg/day, or placebo for 8 weeks. Patients receiving both doses of paroxetine demonstrated significant differences in the primary outcome measure, reduction in HAM-A score, versus placebo, with 68% on 20 mg paroxetine and 81% on 40 mg paroxetine rated as responders based on a Clinical Global Impression (CGI-I) score of 1 or 2, versus 52% on placebo.

### Venlafaxine

Venlafaxine is an inhibitor of SNRI. Venlafaxine has recently been demonstrated in humans, using peripheral measures, to have primarily 5-HT reuptake inhibition properties at low doses (75 mg/day), with increasing norepinephrine (NE) reuptake inhibition properties at higher doses (375 mg/day) (97). Shown to be effective in the treatment of anxiety symptoms associated with major depression (98,99), the extended release (XR) form of venlafaxine has been shown to be effective in the treatment of GAD (DSM-IV criteria) in several placebo-controlled studies (100,101). In a placebo-controlled multicenter comparator trial, 405 patients with GAD were randomized to receive venlafaxine XR (75 or 150 mg/day), buspirone (30 mg/day), or placebo for 8 weeks. For the 365 patients for whom efficacy measures were obtained, there was no significant difference between groups in improvement on the primary outcome measure, the HAM-A. However, both doses of venlafaxine were shown to be superior to placebo in improving HAM-A psychic anxiety and anxious mood scores at the endpoint (week 8), and venlafaxine demonstrated superiority to placebo and buspirone on the CGI-S at the same time point. More robust efficacy findings for venlafaxine were reported in a recent large, multicenter trial, involving 377 outpatients with GAD without comorbid depression (101). Patients were randomly assigned to receive either placebo or venlafaxine XR at one of three doses (75, 150, or 225 mg/day) for 8 weeks. Of the 349 patients included in the efficacy analysis, those receiving 225 mg/day demonstrated significant improvement across seven of the eight outcome measures, and the 225-mg/day group was the only group to show significant improvement in scores on both of the CGI subscales (severity, global improvement) versus placebo.

# Other Agents (Trazodone, Nefazodone, Anticonvulsants, Partial GABA Agonists)

In a randomized, placebo-controlled comparator trial of trazodone, diazepam, and imipramine in the treatment of 230 patients with GAD, trazodone was found to be superior to placebo yet somewhat less effective than diazepam and imipramine at the study's endpoint (84). The antidepressant nefazodone, which antagonizes the 5-HT<sub>2C</sub> receptor and inhibits the reuptake of both serotonin and NE, has shown promise in the treatment of GAD in an open trial (102). Anticonvulsants such as valproate and carbamazepine have been used in the treatment of GAD; however, evidence of their efficacy is primarily anecdotal, as there are no controlled clinical trials for either of these medications in the treatment of GAD (103). Other agents such as the partial GABA agonist abecarnil have not demonstrated significant efficacy versus placebo in GAD (101).

In summary, although the benzodiazepines have been the mainstay of pharmacotherapy for GAD since their introduction, significant concerns regarding their long-term use in GAD have fueled the search for other effective treatments. Given the chronic nature of GAD, medications such as buspirone, and the antidepressants venlafaxine and paroxetine, which have fewer effects on cognitive and psychomotor function, now represent first-line therapies for GAD.

### **SOCIAL PHOBIA**

Social phobia (SP) (or social anxiety disorder) is reported to be the most common anxiety disorder with a 1-year prevalence of 7% to 8% and a lifetime prevalence of 13% to 14% in patients aged 15 to 54 years. Social anxiety disorder can be classified into two subtypes—discrete and generalized. Level of disability with SP can be high, and 70% to 80% of patients have comorbid psychiatric disorders, particularly depression and substance abuse (104). Given the high degree of burden of illness in SP, its treatment has become a major priority.

### **Historical Notes**

Liebowitz et al. (105) noted that SP, like atypical depression (106), had a specific responsivity to the MAOIs, whereas TCAs, although effective for PD and "typical" major depression, were not effective for SP (107). The efficacy of the MAOIs, which block reuptake of dopamine in addition to NE and serotonin, prompted speculation about a poten-

tial "dopaminergic" component to the neurobiology of SP. Several open clinical studies have attempted to utilize the "dopamine component" concept in phamacotherapy with some success, e.g., seligiline (108) and pergolide (109). However, as data accumulated, other systems were also implicated, and the pharmacologic dissection approach seemed less applicable (see above). Positive results with the highpotency benzodiazepine clonazepam (110) suggested a GABAergic component. However, the suitability of benzodiazepines for long-term treatment of a chronic condition such as social anxiety disorder has been questioned. In addition, the benzodiazepines are ineffective against comorbid depression.

# RIMAs (Reversible Inhibitor of Monoamine Oxidase A)

Although phenelzine demonstrated efficacy, the need for dietary restrictions severely limited its use. Moclobemide is a RIMA with a much lower propensity to induce hypertensive crises and has a more favorable side-effect profile. Moclobemide had been reported to have efficacy in early studies in the treatment of social phobia (111). However, conflicting results have subsequently been reported in placebo-controlled trials. Some studies have shown moclobemide to be more effective than placebo, whereas two recent, large, randomized placebo-controlled trials conducted in the United States have reported less robust results (112,113). Brofaromine, another drug in the RIMA class, may still hold promise. The safety and efficacy of brofaromine were examined in a multicenter trial of 102 outpatients with SP (114). Brofaromine produced a significantly greater change from baseline in Liebowitz Social Anxiety Scale (LSAS) scores compared with placebo.

#### **SSRIs**

Based on clinical evidence, SSRIs are the first-line treatment in social anxiety disorder (115). The most extensive database for the treatment of social anxiety disorder exists for the SSRI paroxetine. Several large, multicenter, placebo-controlled trials have been completed on three different continents (116–119). In all cited studies, a significantly greater proportion of patients responded to paroxetine treatment compared with placebo. Paroxetine is currently the only SSRI licensed for use in this condition in the United States. The SSRIs are particularly attractive agents due to their favorable tolerance and safety profile, although typical SSRI side effects may nevertheless be problematic.

Despite promising open studies with fluvoxamine, fluoxetine, and citalopram (120,121) only fluvoxamine has been tested under double-blind, randomized, placebo-controlled trial conditions (122). Like paroxetine, fluvoxamine yielded efficacy data superior to placebo. A report on a multicenter sertraline trial was pending at the time of this writing.

As is the case with PD, buspirone does not appear effective for SP as monotherapy in placebo-controlled double-blind studies (123). It may, however, have a role in augmentation of the SSRIs.

# Serotonin/Norepinephrine Reuptake Inhibitors

One open label study (124) aimed to evaluate the clinical response to venlafaxine in SP in 12 patients who were nonresponders to SSRIs, and to assess how the response could be influenced by Axis II comorbidity with avoidant personality disorder (APD). The duration of the study was 15 weeks using an open flexible-dosing regimen in individuals with or without concomitant APD. Venlafaxine improved SP and/or APD symptomatology, as demonstrated by decreasing LSAS total scores. Similar favorable open-labeled results have been reported for nefazodone (125,126). Placebo-controlled studies are warranted.

### **Anticonvulsants**

A randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate the efficacy and safety of gabapentin in relieving the symptoms of social phobia. A significant reduction in the symptoms of social phobia was observed among patients on gabapentin compared with those on placebo as evaluated by clinician- and patient-rated scales (127). Adverse events were consistent with the known side-effect profile of gabapentin. The efficacy of other novel anticonvulsants remains to be investigated, although encouraging results have been reported for the gabapentin-like compound, pregabalin (128).

### **POSTTRAUMATIC STRESS DISORDER**

Despite the high prevalence, chronicity, and associated comorbidity of PTSD in the community, relatively few placebo-controlled studies have evaluated the efficacy of pharmacotherapy for this disorder. The symptom overlap between PTSD and other pharmacotherapy-responsive disorders has suggested that pharmacotherapy might be effective. Nevertheless, in those placebo-controlled trials investigating the pharmacotherapy of PTSD that have been carried out, statistically significant efficacy for the treatment being studied has traditionally been inconsistent. One of the key methodologic limitations has been the fact that most studies have been conducted with war veterans, who are likely to constitute a more treatment-refractory population.

### **SSRIs**

More recently, a total of 187 civilian outpatients with DSM-III-R PTSD (73% were women, and 61.5% experienced

physical or sexual assault) were treated with the SSRI sertraline in a placebo-controlled design (129). Sertraline effectively diminished symptoms of PTSD of moderate to marked severity in comparison to placebo. Using a conservative last-observation-carried-forward analysis, treatment with sertraline resulted in a responder rate of 53% at the study's endpoint compared with 32% for placebo (p =.008). Sertraline is the first medication approved by the FDA for the treatment of PTSD. Similar positive results have been reported for the SSRI fluoxetine in civilian populations (130,131). In a study by van der Kolk et al. (132), fluoxetine was found to be most effective in the nonveteran versus veteran portion of his study sample. Although published placebo-controlled data for paroxetine are not available, Marshall et al. (133) have argued that this particular SSRI may have specific advantages because of its relatively low activating properties. Direct comparative studies are lacking.

### **Combat Veteran PTSD**

Among combat veterans, PTSD is a highly prevalent and often chronic disorder, persisting in as many as 15% of Vietnam veterans for at least 20 years (134). Treatment response in veterans with combat-related PTSD has been disappointing. Although anxiolytics, anticonvulsants, antipsychotics, and antidepressants, including SSRIs, have been tried, none has been consistently associated with improvement in all primary symptom domains (i.e., intrusive recollections, avoidance/numbing, and hyperarousal). In an open study using nefazodone, at mean daily doses of 430 mg (range, 200 to 600 mg/day), 19 treatment-refractory PTSD patients demonstrated benefit after 12 weeks (134). Double-blind placebo controlled studies would be of interest.

The efficacy of the antidepressant drug bupropion in the treatment of male combat veterans with chronic PTSD was investigated in an open-label study of 6 weeks' duration (135). Improvement was seen in hyperarousal symptoms but was less significant than the change in depressive symptoms. Mirtazapine, a novel drug with both noradrenergic and serotoninergic properties, may be effective in individuals who demonstrate intolerance to side effects of, or a limited response to, SSRIs. Three of six severely refractory PTSD patients treated with mirtazapine were assessed as responders in a pilot study (136). Case reports have suggested benefit for refractory patients treated with venlafaxine (137) and risperidone (138). Raskind et al. (139) reported that the  $\alpha_1$ -adrenergic antagonist prazosin ameliorated combat nightmares in a small sample of veterans with PTSD.

#### **Monoamine Oxidase Inhibitors**

Traditional MAOIs have shown efficacy in the treatment of PTSD, but their use is limited by serious drug and food interactions. Moclobemide, a RIMA, is relatively free of these limitations and is therefore potentially useful in the treatment of PTSD. Moclobemide was highly effective in an open-labeled design (140). However, in a double-blind, randomized, placebo-controlled, multicenter study, brofaromine, also a RIMA, failed to surpass efficacy levels seen with placebo. Thus, the role for RIMAs remains unclear at this time.

### **Anticonvulsants**

Despite a long-recognized role for anticonvulsants in the treatment of PTSD (141), few placebo-controlled studies have been reported. An open study of divalproex reported favorable results (142). In a placebo-controlled study, patients treated with lamotrigine showed improvement on reexperiencing and avoidance/numbing symptoms compared to placebo-treated patients (143). The authors concluded that lamotrigine may be effective as a primary psychopharmacologic treatment in both combat and civilian PTSD and could also be considered as an adjunct to antidepressant therapy used in the treatment of PTSD. Further large-sample, double-blind, placebo-controlled trials are warranted.

# **Summary and Future Directions**

Current management of PTSD is well summarized by Davidson et al. (144). Clearly, there are many challenges associated with the treatment of PTSD. Different patients with PTSD may not respond to pharmacotherapy in the same manner, and it is unclear whether this is related to gender, trauma type, or other factors. Antidepressants, particularly the SSRIs, are currently the form of pharmacotherapy for patients with PTSD with greatest support in the literature. Psychosocial techniques, such as cognitive-behavioral therapy or stress inoculation training, are effective and may be considered as adjunctive therapy with medication. Larger placebo-controlled studies for many different classes of medications would be desirable in moving the field forward. In addition, carefully conducted polypharmacy in which drug interactions are well understood may well be necessary for more difficult cases.

In a review by Shalev and colleagues (145), a synthesis of findings in PTSD studies is provided. Most studies explored a single treatment modality (e.g., pharmacologic, behavioral). The cumulated evidence from these studies suggests that several treatment protocols reduce PTSD symptoms and improve the patient's quality of life. The magnitude of the results, however, was often limited, and remission was rarely achieved. Given the shortcoming of unidimensional treatment of PTSD, it was suggested by the authors that combining biological, psychological, and psychosocial treatment yields the best results.

A host of novel compounds show promise for the treatment of PTSD (146). Such classes of compounds include corticotropin-releasing factor antagonists, neuropeptide-Y

enhancers, antiadrenergic compounds, drugs that down-regulate glucocorticoid receptors, more specific serotoninergic agents, agents that normalize opioid function, substance P antagonists, N-methyl-D-aspartate facilitators, glutamatergic antagonists, and antikindling/antisensitization anticonvulsants.

#### CONCLUSION

Antidepressants are the logical first choice for most patients with anxiety disorders, based on their efficacy and tolerability. Although maintaining a role, the use of benzodiazepines for first-line or long-term therapy is now less likely. Does this mean that anxiety disorders are a variant of depression? Certainly, anxiety disorders and depression are highly comorbid. Untreated, the majority of patients with anxiety disorders eventually develop depression, whereas a large fraction of depressed patients suffer from clinically significant comorbid anxiety, if not an overt syndromal anxiety disorder.

Pharmacologic dissection is clearly perilous, leaving us prone to inferences based on limited knowledge. Most of the antidepressants that successfully treat anxiety disorders manipulate the reuptake of serotonin, norepinephrine, or both. Altering the brain circuits through these modulatory neurotransmitters in turn has wide-ranging effects on many other systems in the brain. The release of CRH from extrahypothalamic sites like the amygdala is only one such system. Hence, there may be a common denominator among anxiety disorders and between anxiety disorders and depression at one or more points in these complex circuits.

The observation, then, that antidepressants work for the four anxiety disorders discussed in this chapter warrants, in our opinion, only the following inference: it is highly likely that some substrate of the serotonin and norepinephrine systems is malfunctioning in several anxiety disorders and depression. This could be the locus of a common genetic or environmental vulnerability to both categories of illness. Although it will not likely tell us that anxiety and depression are fundamentally the same thing, the search for such common substrates and vulnerabilities, suggested but not guaranteed by the psychopharmacologic findings, is likely to be very illuminating.

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