

Anxiety Disorders: A Comprehensive Review of Pharmacotherapies

Ellen J. Hoffman, MD,¹ and Sanjay J. Mathew, MD²

¹Division of Child and Adolescent Psychiatry, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY

²Mood and Anxiety Disorders Program, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY

ABSTRACT

This article reviews the evidence from randomized, placebo-controlled trials and meta-analyses of pharmacological treatments of the following anxiety disorders: generalized anxiety disorder, panic disorder, social anxiety disorder, and post-traumatic stress disorder. There is evidence from multiple randomized, placebo-controlled trials to support the use of selective serotonin reuptake inhibitors as first-line pharmacotherapy in these disorders, and a number of the selective serotonin reuptake inhibitors have received US Food and Drug Administration approval for these indications. Serotonin-norepinephrine reuptake inhibitors are now emerging as first-line treatments for these anxiety disorders alongside the selective serotonin reuptake inhibitors and have been US Food and Drug Administration-approved for some of these indications as well. Benzodiazepines are also effective treatments for anxiety disorders, and although this medication class has the advantage of a rapid onset of action, their use is limited by their potential for abuse and lack of antidepressant properties. In addition to reviewing the clinical trials that have investigated the anxiolytic effects of these commonly used medications, we review the evidence for novel uses of other agents, including anticonvulsants and atypical antipsychotics, in anxiety disorders. *Mt Sinai J Med* 75:248–262, 2008. © 2008 Mount Sinai School of Medicine

Key Words: benzodiazepines, generalized anxiety disorder, panic disorder, post-traumatic stress disorder, pharmacotherapy, selective norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, social anxiety disorder.

The anxiety disorders with the greatest evidence for the efficacy of pharmacotherapy are generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), and obsessive-compulsive disorder, whereas pharmacotherapy evidence for post-traumatic stress disorder (PTSD) is more limited. The therapeutics of obsessive-compulsive disorder are discussed elsewhere in this issue (see Berlin and Hollander), whereas the treatment of specific phobias has been excluded because of space considerations. The medication classes most commonly used for GAD, PD, SAD, and PTSD are selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), whereas other pharmacotherapy approaches include benzodiazepines (BZDs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), anticonvulsants, and atypical antipsychotics.

SSRIs are considered first-line medications for the treatment of GAD, PD, SAD, and PTSD.^{1–4} Although older classes of antidepressant medications—TCAs and MAOIs—have been shown to be effective for anxiety disorders, SSRIs are the most commonly prescribed because of their more favorable side-effect profile. In addition, unlike BZDs, SSRIs have the advantage of treating comorbid depression, whereas long-term administration of SSRIs is not associated with the potential for abuse or physiological dependence. Table 1 shows the non-BZD medications that have been approved by the US Food and Drug Administration (FDA) for the treatment of the anxiety disorders. Table 2 lists the indications and pharmacological properties of commonly used BZDs.

Address Correspondence to:

Sanjay J. Mathew

Department of Psychiatry
Mount Sinai School of Medicine
One Gustave L. Levy Place Box
1217

New York, NY 10019

Email: sanjay.mathew@mssm.edu

Table 1. US Food and Drug Administration–Approved Non-Benzodiazepine Medications for Anxiety Disorders in Adults.

Medication	GAD	PD	PTSD	SAD	Daily Dose Range	Other Approved Psychiatric Indications
SSRIs						
Escitalopram (Lexapro)	✓	–	–	–	10–20 mg	MDD
Fluoxetine (Prozac)	–	✓	–	–	20–60 mg	MDD, OCD, bulimia nervosa, PMDD (Sarafem)
Paroxetine (Paxil)	✓	✓	✓	✓	PD: 10–60 mg SAD: 20–60 mg GAD, PTSD: 20–50 mg	MDD, OCD
Paroxetine CR (Paxil CR)	–	✓	–	✓	PD: 12.5–75 mg SAD: 12.5–37.5 mg	MDD, PMDD
Sertraline (Zoloft)	–	✓	✓	✓	50–200 mg	MDD, OCD, PMDD
SNRIs						
Duloxetine (Cymbalta)	✓	–	–	–	30–120 mg	MDD
Venlafaxine XR (Effexor XR)	✓	✓	–	✓	37.5–225 mg	MDD
Azapirone						
Buspirone (BuSpar)	✓*	–	–	–	15–60 mg	Short-term relief of anxiety symptoms

NOTE: This table includes anxiety disorders, excluding OCD, from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision, and was adapted from Mathew *et al.*¹⁰³

Abbreviations: GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PD, panic disorder; PMDD, premenstrual dysphoric disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

* Approved for anxiety disorders that correspond most closely to GAD as described in the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed., or for anxiety disorders with no individual disorder specified.

GENERALIZED ANXIETY DISORDER

The diagnostic criteria for GAD in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR), include excessive anxiety and worry, difficulty controlling the worry, and symptoms of restlessness, fatigability, poor concentration, irritability, muscle tension, and poor sleep on most days for a period of 6 months.⁵ In clinical trials, the therapeutic response to pharmacotherapy in GAD is assessed with the Hamilton Rating Scale for Anxiety (HAM-A), a 14-question scale in which patients rate the severity of their symptoms, including anxious mood, tension, insomnia, and depressed mood, along with somatic symptoms, such as cardiovascular (palpitations and chest pain), gastrointestinal (nausea or vomiting), and respiratory symptoms (shortness of breath).⁶ The Clinical Global Impression Improvement (CGI-I) and Clinical Global Impression Severity (CGI-S) scales are clinician-rated scales that are also used in assessing the response in GAD as well as other psychiatric disorders.⁷

SSRIs and SNRIs

Multiple double-blind, placebo-controlled randomized clinical trials (RCTs), using large multicenter

sample sizes, have demonstrated the efficacy of several SSRIs in GAD (reviewed by Mathew and Hoffman¹). Paroxetine and escitalopram are the SSRIs that are approved by the FDA for the treatment of GAD. Two 8-week RCTs found that paroxetine, in fixed (20 or 40 mg/day) or flexible (20–50 mg/day) doses, led to significant reductions in HAM-A versus placebo (8 and 9, respectively). (Please note that in this review, when we state that study results are “significant,” we are referring to statistical significance: $P < 0.05$.) Both studies found that a significant percentage of patients treated with paroxetine (62%–68%) received CGI-I scores indicating that they were “much improved” or “very much improved” after 2 months in comparison with approximately 47% of patients in the placebo group.^{8,9} Also, a significant number of patients (approximately one-third) who were treated with paroxetine attained remission (defined as HAM-A ≤ 7) by the end of these studies.^{8,9} Escitalopram (10–20 mg/day) was similarly found to be effective in GAD in a flexibly dosed 8-week RCT, leading to significant reductions in HAM-A scores beginning in the first week of treatment as well as significant CGI-I response rates versus placebo (58% versus 38%) by study end.¹⁰ Davidson *et al.*¹¹ investigated the long-term efficacy of escitalopram in GAD in a 6-month open-label extension study for completers of three 8-week, double-blind, controlled

Table 2. Characteristics of Commonly Used Benzodiazepines.

Generic Name (Brand Name)	FDA-Approved Psychiatric Indications	Routes of Administration	Oral Dose Equivalency (mg)	Approved Oral Dose Range (mg)	Rate of Onset After Oral Dose	Elimination Half-Life (Hours)	Strengths (mg) and Available Preparations
Alprazolam (Xanax)	GAD,* PD; short-term relief of anxiety symptoms; anxiety associated with depression Alprazolam XR (Xanax XR): PD	PO	0.5	0.75–4 Alprazolam XR: 3–6 (suggested), 1–10 (used in clinical trials)	Intermediate	6–20	0.25, 0.5, 1, 2 Alprazolam Intensol (concentrated solution): 1 mg/mL Alprazolam XR: 0.5, 1, 2, 3 Niravam (alprazolam orally disintegrating): 0.25, 0.5, 1, 2
Chlordiazepoxide (Librium)	Anxiety disorders;† short-term relief of anxiety symptoms; ETOH withdrawal; preoperative anxiety	PO	10.0	15–100	Intermediate	30–100	5, 10, 25
Clonazepam (Klonopin)	PD	PO	0.25	0.5–4	Intermediate	18–40	0.5, 1, 2 Klonopin wafers: 0.125, 0.25, 0.5, 1, 2
Clozapemate (Tranxene)	Anxiety disorders;† short-term relief of anxiety symptoms; ETOH withdrawal	PO	7.5	15–60 Tranxene SD: 11.25–45	Rapid	30–100	Tranxene T-tab: 3.75, 7.5, 15 Tranxene SD: 11.25, 22.5
Diazepam (Valium)	Anxiety disorders;† short-term relief of anxiety symptoms; ETOH withdrawal	PO, PR, IM, IV	5.0	4–40	Rapid	30–100	2, 5, 10 Solution: 5 mg/5 mL Intensol: 5 mg/mL Diastat (diazepam rectal): 2.5 gel AcuDial gel: 10, 20 IM, IV 2 mg/mL IM, IV
Lorazepam (Ativan)	Anxiety disorders;† short-term relief of anxiety symptoms; anxiety associated with depression	PO, IM, IV	1.0	1–10	Intermediate	10–20	0.5, 1, 2 Concentrated: 2 mg/mL IM, IV
Oxazepam (Serax)	Anxiety disorders;† short-term relief of anxiety symptoms; anxiety associated with depression; anxiety in older patients; ETOH withdrawal	PO	15.0	30–120	Intermediate-slow	8–12	10, 15, 30
Temazepam (Restoril)	Insomnia, short-term	PO	30.0	7.5–30	Intermediate	8–20	7.5, 15, 30
Triazolam (Halcion)	Insomnia, short-term	PO	0.25	0.125–0.5	Intermediate	2–5	0.125, 0.25

NOTE: This table was adapted from Mathew *et al.*,¹⁰³ Rosenbaum *et al.*,¹²⁹ and Goddard *et al.*¹³⁰

Abbreviations: ETOH, ethanol; FDA, US Food and Drug Administration; GAD, generalized anxiety disorder; IM, intramuscular; IV, intravenous; PO, per os; PD, panic disorder; PR, per rectum; SD, single dose.

* Approved for anxiety disorders that correspond most closely to GAD as described in the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed.

† No individual disorder is specified.

escitalopram trials and showed ongoing improvement in HAM-A and quality-of-life scores in the open-label phase, in which the last visit of the lead-in trial was defined as baseline, such that 76% of patients in the extension trial were responders and 49% were remitters.

Relapse prevention studies demonstrated that in comparison with patients who continued to receive escitalopram or paroxetine for 6 months, the risk of relapse was approximately 4 to 5 times greater in the placebo groups.^{12,13} There are also studies demonstrating the efficacy of sertraline in GAD,^{14,15} although it has not been approved by the FDA for this indication. With respect to other SSRIs (citalopram, fluoxetine, and fluvoxamine), although there is evidence that these medications treat anxiety symptoms in depressed patients, to our knowledge, there are no published RCTs of these medications for GAD.

Along with SSRIs, SNRIs are emerging as first-line medications in treating anxiety disorders. Both venlafaxine XR and recently duloxetine (in 2007) have gained FDA approval for the treatment of GAD. There are short- and long-term RCTs of venlafaxine XR in GAD. Two 6-month RCTs of fixed (37.5, 75, and 150 mg/day) or flexible (75–225 mg/day) doses of venlafaxine XR found significant reductions in HAM-A by study end in the medication groups versus the placebo groups.^{16,17} Allgulander *et al.*¹⁶ showed that venlafaxine XR at 75 or 150 mg/day sustained significant HAM-A response rates ($\geq 50\%$ reduction in the total score) from week 2 onward. Gelenberg *et al.*¹⁷ reported that venlafaxine XR (75–225 mg/day) led to significant HAM-A response rates ($\geq 40\%$ reduction in the total score) beginning at week 1. In the short-term treatment of GAD, Rickels *et al.*¹⁸ conducted an 8-week RCT of venlafaxine XR (75, 150, or 225 mg/day) and concluded that only the group receiving the 225 mg/day dose saw a significant reduction in total HAM-A scores by study end. In another 8-week, placebo-controlled RCT, Davidson *et al.*¹⁹ compared venlafaxine XR (75 or 150 mg/day) and the azapirone buspirone (30 mg/day, dosed as 10 mg three times a day) and found that CGI-I response rates, but not HAM-A response rates, were significantly greater only in the 75 mg/day venlafaxine XR and buspirone groups in comparison with the placebo group by study end. However, both venlafaxine XR doses were significantly better than buspirone and placebo on the Hospital Anxiety and Depression Anxiety subscale, which is patient-rated, by week 3.¹⁹ A relatively small, 8-week RCT with 46 patients with GAD described significant response (defined as $\geq 50\%$ reduction in HAM-A; 92%) and remission (63%) rates in the

venlafaxine XR (75–150 mg/day) group versus the placebo group.²⁰ Another 8-week RCT, however, found no significant differences in HAM-A or CGI-I scores between placebo and venlafaxine XR (75 or 150 mg/day) or diazepam (15 mg/day); a secondary analysis that omitted study centers in which there was no difference between diazepam and placebo showed significant HAM-A and CGI-I reductions in both venlafaxine XR groups versus placebo.²¹

Duloxetine was found to be effective in GAD in two 10-week, multicenter RCTs.^{22,23} Rynn *et al.*²² found that duloxetine (60–120 mg/day, progressively titrated) led to a significant decrease in HAM-A, although no significant differences in remission rates were observed. In addition, there were significant increases in the heart rate, blood pressure, and some liver measures in the duloxetine group in comparison with placebo, but the magnitude of the changes was not thought to be clinically relevant.²² In a placebo-controlled, head-to-head RCT comparing duloxetine (60–120 mg/day) and venlafaxine XR (75–225 mg/day), there was a significant decrease in total HAM-A scores in both active treatment groups beginning at weeks 1 and 2, respectively.²³ However, Hartford *et al.*²³ noted that in comparison with placebo, the percentage of patients achieving remission was greater in the venlafaxine XR group ($P \geq 0.05$) but not in the duloxetine group.

Additional head-to-head studies of SSRIs and SNRIs in GAD are limited by the absence of placebo controls. One 6-month study showed that both escitalopram (10–20 mg/day) and paroxetine (20–50 mg/day) led to similar HAM-A and quality-of-life improvements, although escitalopram was better tolerated than paroxetine.²⁴ A 2-month head-to-head study found that sertraline (25–100 mg/day) and paroxetine (10–40 mg/day) led to similar response (61%–68%) and remission (40%–46%) rates.²⁵ In a small, 8-week, open-label study, both venlafaxine XR (37.5–225 mg/day) and paroxetine (10–40 mg/day) led to significant HAM-A and CGI-S reductions over time.²⁶ Of note, paroxetine led to significantly more weight gain than venlafaxine XR, whereas venlafaxine XR resulted in significant increases in the mean change of systolic and diastolic blood pressure from the baseline to the endpoint in comparison with paroxetine.²⁶

BZDs and Buspirone

Multiple RCTs have demonstrated the short- and long-term efficacy of BZDs in anxiety disorders, including GAD, PD, and SAD (reviewed by Mathew and Hoffman,¹ Katon,² and Davidson³). BZDs are effective in the acute treatment of GAD and have

a rapid onset of action.^{27,28} However, long-term use of BZDs in GAD is problematic because few patients achieve and sustain remission with BZD monotherapy (reviewed by Gorman²⁹). Advantages of BZDs over SSRIs and SNRIs include their ability to be used on an “as-needed” basis for anxiety and their rapid onset of action, which leads to their frequent use in clinical practice as adjunctive medications for stabilization during initiation of an SSRI or SNRI. In addition, longer acting BZDs, such as clonazepam or alprazolam XR, may be used to decrease breakthrough anxiety (reviewed by Katon²). Studies have also shown that BZDs preferentially affect the somatic symptoms in GAD,^{27,28} whereas SSRIs have been found to have a greater effect on the psychic symptoms.^{8,9,25} However, the disadvantages of BZDs are the risks of abuse and physiological dependence with long-term use,³⁰ as well as their lack of antidepressant effects, which is important given that depression and GAD are often comorbid.²⁹

Buspirone is an azapirone, a serotonin 1A (5-hydroxytryptamine receptor 1A) agonist, approved by the FDA for treating “anxiety disorders,” a broad diagnosis corresponding most closely to GAD in the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. (DSM-III). A retrospective meta-analysis of pooled data from 8 placebo-controlled studies found that buspirone resulted in a significant improvement in HAM-A for GAD.³¹ Advantages of buspirone include its overall tolerability and lack of addictive potential (reviewed by Mathew and Hoffman¹), although an important limitation is evidence of decreased efficacy in patients with recent prior BZD use.³² Also, RCTs have shown that buspirone is not effective in PD^{33–35} or SAD.³⁶

Anticonvulsants

There is emerging evidence from RCTs for pregabalin in GAD (reviewed by Mula *et al.*³⁷). Although its exact mechanism of action is unknown, pregabalin binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, which reduces neurotransmitter release. Pregabalin has been approved by the FDA as an adjunctive treatment for partial seizures as well as diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia; in 2006, it was approved by the European Commission for treating GAD, but at this time, it is not approved by the FDA for this indication.

RCTs have demonstrated the efficacy of pregabalin in GAD after 4 and 6 weeks, although long-term studies are still needed. A recent dose-response analysis by Bech³⁸ pooled data from 4 short-term, fixed-dose RCTs of pregabalin in GAD^{39–42} and concluded that pregabalin in the range of 200 to

450 mg/day resulted in HAM-A effect sizes (ESs) > 0.40 with a “plateau-like response curve.” However, a lower dose of pregabalin (150 mg/day) led to an ES < 0.40, and at a higher dose (600 mg/day), ESs were similar to those found for 200 to 450 mg/day pregabalin.³⁸ One potential advantage of pregabalin is that it appears to have a relatively rapid onset of action. In a 6-week RCT, all 3 pregabalin doses tested (200 mg/day divided into 2 doses a day, 400 mg/day divided into 2 doses a day, and 450 mg/day divided into 3 doses a day) resulted in significant HAM-A reductions in comparison with placebo beginning at week 1.⁴¹ Another 6-week RCT in GAD, which compared pregabalin doses of 400 or 600 mg/day divided into 2 doses a day and a venlafaxine dose of 75 mg/day divided into 2 doses a day, reported significant improvements in HAM-A scores versus placebo beginning at week 1 in both pregabalin groups and at week 2 in the venlafaxine group.⁴³

Additionally, in 4-week RCTs, pregabalin appears to demonstrate efficacy comparable to that of BZDs in reducing HAM-A,^{39,40,42} while apparently resulting in less withdrawal. During discontinuation, Pande *et al.*⁴⁰ reported no significant difference in Physician Withdrawal Checklist scores for pregabalin versus placebo, unlike lorazepam; other studies reported some significant increases in Physician Withdrawal Checklist scores for pregabalin versus placebo, although these changes were not considered clinically significant and appeared to be dose-related.^{39,41,42} The most commonly reported side effects of pregabalin include somnolence and dizziness and weight gain in patients taking higher doses.

Evidence for the anticonvulsant tiagabine (Gabatril), a gamma-aminobutyric acid reuptake inhibitor, in GAD is very limited (reviewed by Mathew and Hoffman¹).

Atypical Antipsychotics

There are a few RCTs that have investigated the role of atypical antipsychotics in anxiety disorders, as these medications have been considered adjunctive treatments in these disorders because of their broad neurochemical effects on postsynaptic 5-hydroxytryptamine 2 receptors and the modulation of 5-hydroxytryptamine receptor 1A (reviewed by Mathew and Hoffman¹). Two very small RCTs investigated olanzapine and risperidone as adjunctive agents in patients with GAD who did not respond to another medication, either fluoxetine in the olanzapine study⁴⁴ or another medication (an SSRI, SNRI, BZD, or other anxiolytic or antidepressant) in the risperidone study.⁴⁵ Although olanzapine

augmentation resulted in a significant number of HAM-A responders after 6 weeks⁴⁴ and adjunctive risperidone led to significant HAM-A reductions after 5 weeks,⁴⁵ there were no significant findings for other outcome measures. In addition, olanzapine resulted in sedation and significant weight gain (11.0 lb on average),⁴⁴ and side effects of risperidone included somnolence, dizziness, and blurred vision.⁴⁵

GAD Meta-Analysis

In a meta-analysis of RCTs of antidepressants, including imipramine, venlafaxine, and paroxetine, in adults with GAD alone, Kapczinski *et al.*⁴⁶ reported that antidepressants were more effective than placebo and that dropout rates were not different among the antidepressants. The number needed to treat for these antidepressants as a group in GAD was calculated to be between 5 and 6.⁴⁶

PANIC DISORDER

DSM-IV-TR criteria for PD include recurrent panic attacks (periods of intense fear that peak within 10 minutes and are associated with symptoms such as palpitations, sweating, shortness of breath, chest pain, and lightheadedness) as well as persistent worry about the attacks or fear of having more attacks, which may result in a change in behavior (reviewed by Katon²). PD may occur with or without agoraphobia, which is described in DSM-IV-TR as anxiety about and avoidance of being in situations where escape may be difficult.⁵ Clinical trials assessing the efficacy of pharmacotherapy in PD examine outcome measures such as panic attack frequency, the percentage of patients who are free of attacks, and the change in the total number of attacks. The Panic Disorder Severity Scale (PDSS), which measures the severity of PD symptoms, including panic attack frequency, distress during attacks, anticipatory anxiety, agoraphobia, avoidance of bodily sensations, and impairment of work and social functioning, is also used in some studies.⁴⁷ Of note, PD is one of the anxiety disorders that tends to have higher placebo responsivity.⁴⁸

SSRIs and SNRIs

Both SSRIs [paroxetine, controlled-release paroxetine (paroxetine CR), sertraline, and fluoxetine] and the SNRI venlafaxine XR have been approved by the FDA to treat PD. The SSRIs are recommended as first-line medications in PD on the basis of their safety and overall tolerability, although SSRIs, TCAs, and

BZDs have been shown to be equally effective in the treatment of PD and associated anxiety symptoms (reviewed by Heuer *et al.*⁴⁹). If a patient with PD does not respond to treatment with an SSRI, a trial with another SSRI should be attempted, and if that fails, switching to a medication in a different class, such as venlafaxine XR (SNRI) or a TCA or BZD, is recommended.⁴⁹ There is also evidence for initial augmentation of SSRIs with BZDs early in the treatment of PD (see the subsection on BZDs) due to the rapid onset of action of BZDs. SSRIs should be initiated at low doses with slow titration to minimize side effects, which may include nausea, anxiety, tremors, jitteriness, sexual dysfunction, and insomnia, as patients with PD may be sensitive to side effects.^{2,49}

RCTs have provided evidence for the efficacy of many SSRIs in PD. In 12- and 36-week RCTs using the TCA clomipramine as an active comparator, paroxetine was found to be effective in PD.^{50,51} Also, paroxetine (40 mg/day) resulted in significant reductions in the total number of panic attacks by week 4 of a 10-week RCT.⁵² A pooled analysis of three 10-week RCTs showed that paroxetine CR led to a significantly greater percentage of panic-free patients versus placebo (63% versus 53%) in the 2 weeks prior to the study endpoint.⁵³ RCTs have also investigated sertraline in PD.^{54–56} One multicenter, 10-week RCT of sertraline (50–200 mg/day) found that sertraline led to significant reductions in the frequency of panic attacks and in PDSS scores by the study endpoint,⁵⁴ whereas another 10-week RCT reported a significant decrease in the number of panic attacks per week in the observed case analysis by week 3, and a significant percentage of patients were panic-free by the study endpoint in the sertraline group.⁵⁵ A 28-week discontinuation RCT showed that significantly fewer patients who continued on sertraline after 1 year of open-label treatment experienced an exacerbation of PD symptoms in comparison with those switched to placebo.⁵⁶

There is also evidence from RCTs for fluoxetine,⁵⁷ fluvoxamine,^{58–60} escitalopram,⁶¹ and citalopram^{62,63} in PD. In a 12-week RCT of fluoxetine (20 mg/day, increased to a maximum of 60 mg/day after 6 weeks in patients who did not respond sufficiently), Michelson *et al.*⁵⁷ reported a significant reduction in PDSS scores and a significant increase in the proportion of patients who were free of panic attacks after both 6 and 12 weeks of treatment, although there were variable results in an older fluoxetine trial in which lower doses were used.⁶⁴ Stahl *et al.*⁶¹ compared escitalopram (10–20 mg/day) and citalopram (20–40 mg/day) in a 10-week, placebo-controlled trial and reported that escitalopram, but

not citalopram, led to a significant decrease in panic attack frequency by the study endpoint, although the proportion of patients who were panic-free was significant only at the trend level for the escitalopram group ($P = 0.051$). Both escitalopram and citalopram groups demonstrated significant improvements on CGI-I after 10 weeks.⁶¹ In a 12-week, head-to-head study of sertraline and paroxetine, which lacked a placebo arm, both medications demonstrated efficacy in PD, although there were numerically fewer dropouts due to adverse events and significantly less weight gain in the sertraline group.⁶⁵

Venlafaxine XR (75 or 150 mg/day) and paroxetine (40 mg/day) were compared in a 12-week, placebo-controlled, double-blind trial, which found no significant differences in efficacy between the venlafaxine XR and paroxetine groups; both groups saw a significant percentage of panic-free patients by study end.⁶⁶ In another multicenter trial, venlafaxine XR (75–225 mg/day) resulted in a significant reduction in the frequency of full-symptom panic attacks in comparison with placebo after 10 weeks, and although venlafaxine XR did not result in a significantly greater number of patients who were free of panic attacks by the study endpoint, there was a significant percentage of CGI-I responders and remitters in the venlafaxine XR group.⁶⁷ Of note, there was a significant increase in heart rate in the venlafaxine XR group (change from the baseline in the supine pulse rate = 2.18 beats per minute).⁶⁷ Venlafaxine XR was also shown to be effective in preventing relapse in PD.⁶⁸

BZDs

Although there is evidence from earlier studies supporting the use of BZD monotherapy in PD, more recent studies have examined and provided evidence for the common clinical usage of BZDs in combination with SSRIs in the acute treatment of PD.^{69,70} Goddard *et al.*⁶⁹ reported that there were significantly more responders after 1 week in patients receiving sertraline plus clonazepam versus sertraline plus placebo, although there were no group differences in response during weeks 4 to 12 (clonazepam was tapered and discontinued after 3 weeks). Pollack *et al.*⁷⁰ reported a similar finding of an early benefit of combination treatment (paroxetine plus clonazepam) versus paroxetine monotherapy generally in the first 5 weeks. However, by the conclusion of the 12-week study, there was no significant difference in outcome between the monotherapy or combination groups or a group treated with combination therapy for 4 weeks

followed by clonazepam taper, with a significant improvement on PDSS in all groups.

PD Meta-Analyses

Meta-analyses determined moderate ESs (~0.4–0.55) and tolerability of SSRIs comparable to those of TCAs and BZDs in PD.^{71,72} Studies have also investigated the efficacy of pharmacotherapy versus psychotherapy in PD. Mitte⁷¹ reported that cognitive-behavioral and behavioral therapies were at least as effective as pharmacotherapy, and pharmacotherapy was superior to placebo. In a Cochrane Collaboration meta-analysis of 23 randomized studies comparing psychotherapy and antidepressants in PD, Furukawa *et al.*⁷³ found that in the first few months of treatment, the combination of psychotherapy and pharmacotherapy was more effective than either antidepressant treatment or psychotherapy alone, and this trend persisted as long as the medication was continued. They concluded that either combination therapy or psychotherapy alone may be used as first-line treatment in PD.⁷³

SOCIAL ANXIETY DISORDER

In DSM-IV-TR, generalized SAD, on which we concentrate in this article, is characterized by a persistent fear of social situations, such that exposure to these situations leads to anxiety and avoidance of these situations, which interfere with the person's functioning (reviewed by Schneier⁷⁴). Nongeneralized or "performance-type" SAD involves fear of public speaking or performance situations only.⁷⁴ Most RCTs use the Liebowitz Social Anxiety Scale (LSAS), which assesses a patient's level of fear and avoidance of 24 distinct social situations, such as attending a party, meeting strangers, or being the center of attention, in order to study the efficacy of pharmacotherapy in treating generalized SAD.⁷⁵

SSRIs and SNRIs

SSRIs and SNRIs are considered first-line medications for generalized SAD.⁷⁴ Paroxetine, paroxetine CR, sertraline, and venlafaxine XR are FDA-approved for treating SAD. These medications are often started at half of the usual effective dose, and the dose is increased after the first week of treatment.⁷⁴ Although their dose-response curve is relatively flat, doses of these medications are typically increased as tolerated in patients who do not respond after 4 weeks, as some patients benefit from increased doses.⁷⁴ Although many patients improve within the

first few weeks of treatment, it has been suggested that initial SSRI trials should last 12 weeks, as at least 25% of those who do not respond after 8 weeks may respond during the subsequent 4 weeks at the same medication dose; to decrease the risk of relapse, maintenance pharmacotherapy for those patients who respond after 12 weeks is recommended.⁷⁴

There are multiple RCTs supporting the efficacy of these medications in SAD. Paroxetine and paroxetine CR were shown to be effective in flexibly dosed, 12-week, multicenter RCTs of SAD.^{76–78} Paroxetine (20–50 mg/day) led to significant reductions in LSAS by week 2⁷⁶ and week 4⁷⁷ in 2 studies. In a 12-week, fixed-dose RCT of paroxetine (20, 40, and 60 mg/day), only the 20 mg/day dose resulted in significant LSAS reductions by study end, although the number of CGI-I responders was significant for the 40-mg group.⁷⁹ In the study by Lepola *et al.*,⁷⁸ there was a significant reduction in LSAS by week 6 in the paroxetine CR group, and significantly more patients in this group achieved remission on CGI-I. RCTs have also demonstrated the efficacy of sertraline (50–200 mg/day) in SAD after 12⁸⁰ and 20 weeks.⁸¹ In a multinational RCT, escitalopram (10–20 mg) led to significant reductions in LSAS after 12 weeks.⁸² There is also evidence from 10- to 12-week RCTs for fluvoxamine^{83,84} and fluvoxamine CR^{85,86} in SAD, although a 12-week extension of a 12-week RCT showed continued but nonsignificant LSAS improvement in the fluvoxamine CR group versus placebo.⁸⁷ Also of note, there are 2 negative RCTs of fluoxetine in SAD.^{88,89} However, Davidson *et al.*⁹⁰ compared fluoxetine (titrated to 40–60 mg/day), group comprehensive cognitive-behavioral therapy (CCBT), fluoxetine plus CCBT, and CCBT plus placebo versus placebo alone in a 14-week RCT and found significantly greater response versus placebo in all treatment groups by study end, with no differences between the active treatments. In another RCT comparing pharmacotherapy and psychotherapy in SAD, Blomhoff *et al.*⁹¹ investigated sertraline monotherapy, exposure therapy, and combination treatment versus placebo or general medical care and found a greater percentage of responders in the sertraline group versus the non-sertraline group. Although only combination treatment resulted in significant response versus placebo beginning at week 12, both combination treatment and sertraline monotherapy resulted in significant response versus placebo by the end of the 24-week study.⁹¹ There is also evidence from longer term relapse-prevention studies for paroxetine,⁹² sertraline,⁹³ and escitalopram⁹⁴ in SAD.

Two 12-week, multicenter RCTs in SAD demonstrated that venlafaxine XR (75–225 mg/day) resulted in significant LSAS reductions beginning at week

4⁹⁵ or week 6.⁹⁶ Of note, both studies reported small but significant increases in the supine systolic (~0.6–2.3 mm Hg) and diastolic (~0.25–2.6 mm Hg) blood pressure, supine pulse rate (~1.3–4.9 beats per minute), and cholesterol levels (~0.3 mmol/L) in the venlafaxine XR groups.^{95,96} There is also evidence for the efficacy of venlafaxine XR in a longer term (6-month), multicenter RCT.⁹⁷ Both fixed low-dose venlafaxine XR (75 mg/day) and flexible higher doses (150–225 mg/day) resulted in significant decreases in LSAS versus placebo beginning at week 4 and significant remission rates on LSAS by study end.⁹⁷

In 2 head-to-head RCTs comparing venlafaxine XR (75–225 mg/day) and paroxetine (20–50 mg/day) in SAD, there were no significant differences in efficacy between the 2 active treatment groups after 12 weeks, as both resulted in significant decreases in LSAS and significant response rates versus placebo.^{98,99} Another head-to-head, 24-week, placebo-controlled study found that escitalopram (5 and 20 mg/day) and paroxetine (20 mg/day) led to significant LSAS reductions versus placebo after 12 weeks, and in the observed case sample, all 3 escitalopram groups (5, 10, and 20 mg/day) and the paroxetine group (20 mg/day) experienced significant LSAS reductions by study end.¹⁰⁰ Although escitalopram (20 mg/day) resulted in significantly greater reductions than paroxetine (20 mg/day) in LSAS from week 16 onward,¹⁰⁰ these doses are not necessarily equivalent.

BZDs

There is evidence to support the use of BZDs in SAD in patients resistant to or unable to tolerate SSRIs (reviewed by Davidson³ and Schneier⁷⁴). However, Seedat and Stein¹⁰¹ conducted a small, 10-week RCT of open-label paroxetine given in combination with clonazepam or placebo in SAD, and no significant differences between the 2 groups were found early or later in treatment. In addition, BZDs may be used “as needed” in performance-type or nongeneralized SAD, for which they are taken about 30 minutes prior to a performance (reviewed by Schneier⁷⁴).

Anticonvulsants

One multicenter, 10-week RCT of pregabalin in SAD reported that pregabalin at 600 mg/day, but not at 150 mg/day, demonstrated efficacy in reducing LSAS scores.¹⁰² Although pregabalin at 600 mg/day resulted in a significant percentage of responders on CGI-I, the LSAS response percentage was not significant.¹⁰² Gabapentin, which is approved by the

FDA for partial seizures, neuropathic pain, and postherpetic neuralgia, has been used “off-label” in anxiety disorders, although RCT data have shown only a modest benefit (reviewed by Mathew *et al.*¹⁰³). In an RCT for SAD, gabapentin led to significant reductions in LSAS after 14 weeks, but the LSAS response rate was only 32% and not significant versus placebo.¹⁰⁴

Nongeneralized SAD or “Performance Anxiety”

Beta-blockers may be taken approximately 1 hour before a performance to help performance-type SAD (reviewed by Schneier⁷⁴). For example, propranolol may be used at an initial dose of 10 mg, with a target dose of 10 to 40 mg, and used on an as-needed basis, although side effects include hypotension and bradycardia.⁷⁴

SAD Meta-Analyses

There are a number of meta-analyses of RCTs supporting the use of SSRIs in SAD.^{105,106} In a meta-analysis comparing SSRIs and non-SSRIs in SAD, no significant differences between medications or medication classes, including SSRIs, an MAOI, BZD, and gabapentin, were found, although the use of SSRIs as first-line treatments in SAD was supported on the basis of their tolerability, their ability to treat comorbid conditions, and the stability of the ES (LSAS ES for the SSRIs was 0.65).¹⁰⁷ The Cochrane Collaboration reviewed 37 RCTs of SSRIs, MAOIs, and other medications (including BZDs, buspirone, and gabapentin) in SAD and concluded that patients who received any medication were less likely than those given placebo to be nonresponders.¹⁰⁸ SSRIs were found to reduce symptom severity on LSAS, whereas MAOIs did not. The authors suggested that there may be a publication bias, suggesting that there might be more variation in medication responses in SAD than in the trials included in the analysis. However, maintenance trials demonstrated decreased relapse risk of medication versus placebo.¹⁰⁸

Another meta-analysis compared psychological interventions, including cognitive restructuring and exposure, with pharmacological treatments in SAD, including SSRIs, BZDs, and MAOIs, in RCTs and non-RCTs.¹⁰⁹ On self-report measures, SSRIs and BZDs were found to be equally effective, with the largest mean ES compared to psychological and other pharmacological treatments (ES for SSRIs = 1.697, BZDs = 2.095), and their confidence intervals overlapped. A trend favored BZDs overall, which outperformed MAOIs and the psychological treatments, although SSRIs did not; on observer-rated

measures, which included data from only a small number of trials, all of the treatments, including BZDs, SSRIs, MAOIs, and exposure with cognitive restructuring, were similarly effective and superior to placebo or wait-list control.¹⁰⁹

POST-TRAUMATIC STRESS DISORDER

PTSD, which may occur after exposure to a traumatic event, is defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV), by 3 symptom clusters—re-experiencing the event, emotional numbing/avoidance of stimuli associated with the trauma, and hyperarousal—that persist for more than 1 month and lead to functional impairment.⁵ The “gold standard” in assessing PTSD symptoms is the Clinician-Administered PTSD Scale (CAPS), which is a structured interview that has been shown to be both reliable and valid.¹¹⁰ CAPS is used in many RCTs to determine the efficacy of pharmacotherapy in PTSD.

As Mathew *et al.*¹⁰³ observed, a major limitation in the PTSD psychopharmacology literature is the lack of long-term studies (see the Cochrane Review of PTSD⁴ discussed later). Because of limitations in the pharmacotherapy data for PTSD, guidelines from the National Institute for Health and Clinical Excellence (www.nice.org.uk), an independent source, have suggested that pharmacotherapy should not be used as a routine first-line PTSD treatment for adults, in preference to trauma-focused psychological therapy, on account of stronger evidence for exposure-based psychotherapies (reviewed by Mathew *et al.*¹⁰³).

SSRIs and SNRIs

Two SSRIs (paroxetine and sertraline) have received FDA approval for PTSD, although in short-term trials ESs have been modest, and only paroxetine has been shown to be superior to placebo in all 3 PTSD symptom clusters.^{111,112} A 6-month RCT of flexibly dosed venlafaxine XR (37.5–300 mg/day) in PTSD reported improvements in re-experiencing and avoidance/numbing but not in hyperarousal symptoms; remission rates (CAPS score \leq 20) in the venlafaxine XR group were almost 51% and 37.5% of those in the placebo group.¹¹³ Although there was overall efficacy versus placebo, the CAPS ES was small (about 0.3).¹¹³ Davidson *et al.*¹¹⁴ conducted a 12-week, multicenter RCT with placebo and sertraline control arms and reported efficacy of venlafaxine XR in PTSD, although the ES versus placebo was 0.266. Both of these studies used higher maximum daily venlafaxine XR doses than the FDA-approved doses

for other indications, including major depression and other anxiety disorders.

Anticonvulsants

There have been very limited studies and few RCTs of anticonvulsants in PTSD, and none is FDA-approved for this indication. With respect to RCTs, there was a multicenter, adequately sized RCT of tiagabine in PTSD, which was negative, finding no efficacy of tiagabine versus placebo.¹¹⁵ There was 1 very small, preliminary 12-week RCT of lamotrigine, which is FDA-approved for maintenance therapy in bipolar disorder, in 15 patients who met DSM-IV-TR criteria for a primary diagnosis of PTSD, which suggested some benefit.¹¹⁶ There was 1 relatively small (n = 38) 12-week RCT of topiramate, which is approved by the FDA for migraine prophylaxis and seizures, in non-combat-related PTSD, which found no significant difference in CAPS scores between topiramate and placebo groups by study end.¹¹⁷ There are only open-label and retrospective studies of other anticonvulsants in PTSD (reviewed by Mula *et al.*³⁷).

Antipsychotics

There is some preliminary evidence for adjunctive risperidone in combat-related PTSD (reviewed by Gao *et al.*¹¹⁸). In 1 RCT in male patients with chronic, combat-related PTSD, adjunctive risperidone, added to a stable psychotropic regimen in most patients, led to significant CAPS improvement after 16 weeks, although treatment included an initial 5 weeks at a VA residential psychosocial program.¹¹⁹ Another study in combat veterans with chronic PTSD and psychotic symptoms reported that adjunctive risperidone led to significant improvement in psychotic symptoms but not CAPS scores versus placebo after 5 weeks.¹²⁰ Padala *et al.*¹²¹ conducted a small, 12-week pilot RCT of risperidone monotherapy in women who had PTSD due to sexual assault and domestic abuse, and they found that risperidone led to a decrease in PTSD symptoms. There are more inconsistent findings for olanzapine in PTSD, as there was 1 small negative RCT of olanzapine monotherapy,¹²² although another small RCT of olanzapine augmentation of SSRIs found significant CAPS score reductions versus placebo after 8 weeks but no significant difference in the percentage of CGI-I responders, and patients in the olanzapine group gained approximately 13 lb on average.¹²³

Alpha-1 Adrenergic Antagonists

As sleep disturbance occurs in up to 70% of patients with PTSD and norepinephrine is involved in stress-related arousal, the alpha-1-adrenergic antagonist

prazosin, an FDA-approved antihypertensive and treatment for benign prostatic hypertrophy, has been investigated specifically to target nightmares in PTSD (reviewed by Dierks *et al.*¹²⁴). There is preliminary evidence from relatively small RCTs and open-label trials and a retrospective chart review, which have their limitations, for prazosin treatment of PTSD-related nightmares, although further RCTs are indicated (reviewed by Dierks *et al.*¹²⁴).

PTS Meta-Analysis

The Cochrane Collaboration also conducted a meta-analysis of 35 short-term (≤ 14 weeks) RCTs of pharmacotherapy of PTSD, finding that pharmacotherapy demonstrated efficacy in all PTSD symptom domains compared to placebo and in treating comorbid depressive symptoms and improving quality of life.⁴ In the groups receiving medication, symptom severity and CGI-I response were significantly better in 17 and 13 trials, respectively.⁴ Although there were limited direct-comparison trials of medications, SSRI trials contributed the most to overall ES and treatment response in the meta-analysis, and this led the authors to support the recommendation of SSRIs as first-line medications in PTSD.⁴ There is also evidence for the efficacy of SSRIs in relapse prevention in 3 studies, which were reviewed by Stein *et al.*,⁴ who reported that these results are consistent with recommendations for 6 to 12 months of medication treatment for acute PTSD and 12 months or more of interventions for chronic PTSD in order to prevent relapse. Notably, Stein *et al.* observed that war veterans are more resistant to medication treatment than other patients with PTSD, and there are few studies that directly compare psychotherapy and psychopharmacology in PTSD.

TCAs and MAOIs

TCAs are effective treatments for GAD and have a long history in treating anxiety, although few studies have investigated them in DSM-IV–defined GAD.¹ In an 8-week RCT of patients with DSM-III GAD by Rickels *et al.*²⁷ comparing imipramine, diazepam, and trazodone, diazepam resulted in the greatest improvement during the first 2 weeks, after which imipramine was significantly more effective in reducing total HAM-A scores (reviewed by Baldwin and Polkinghorn¹²⁵); all 3 treatment groups were found to be effective in reducing anxiety symptoms by study end (reviewed by Lydiard and Monnier¹²⁶). However, the use of TCAs is limited by their overall poorer tolerability in comparison with the newer SSRIs and SNRIs.

There is evidence from short- and long-term studies for the TCA clomipramine in PD.^{50,51} One randomized, placebo-controlled trial compared patients with PD who received imipramine alone, cognitive-behavioral therapy (CBT) alone, CBT plus imipramine, or CBT plus placebo for an acute phase (3 months), and responders were followed for a maintenance phase (6 months) and another 6 months after they discontinued treatment.¹²⁷ In both the acute and maintenance phases, imipramine and CBT were each statistically superior to placebo on the PDSS.¹²⁷ In the acute phase, CBT plus imipramine was not superior to CBT plus placebo, but in the maintenance phase, the combined treatment led to significantly lower PDSS scores, but not PDSS or CGI-I response rates, in comparison with CBT plus placebo; after treatment discontinuation, CBT appeared to have a more lasting effect, with greater response rates in the CBT alone and CBT plus placebo groups versus placebo at 6-month follow-up.¹²⁷ Of note, there are no RCTs supporting TCAs in generalized SAD.

Although there is evidence for the efficacy of MAOIs in PD, SAD, and PTSD,¹²⁸ their use in these disorders is limited because of their poorer tolerability and risks of toxicity, as patients taking MAOIs are required to follow a low-tyramine diet to prevent hypertensive crisis.³

CONCLUSION

Evidence from multiple RCTs supports the use of SSRIs as first-line pharmacotherapy in the treatment of anxiety disorders, including GAD, PD, SAD, and PTSD. SNRIs, namely, venlafaxine XR and duloxetine, are now FDA-approved for the treatment of GAD, and venlafaxine XR is also approved by the FDA to treat PD and SAD, so SNRIs are emerging as first-line medications in anxiety disorders as well. Although older antidepressant agents, such as TCAs, also are efficacious in treating anxiety disorders, their use in clinical practice is limited by their less favorable side-effect profile in comparison with SSRIs; however, meta-analyses have demonstrated similar dropout rates for these 2 medication groups. The use of MAOIs is also limited by the need for patients to maintain a low-tyramine diet to prevent hypertensive crisis. BZDs are likewise very effective in treating anxiety disorders, and there are studies supporting their use as adjunctive agents in the short-term management of these disorders, given their rapid onset of action and ability to be used on an as-needed basis, whereas their long-term use is limited by the potential for abuse and dependence as well as

their lack of antidepressant effects, as depression is often comorbid with the anxiety disorders. Pregabalin, an adjunctive anticonvulsant that is FDA-approved for treating postherpetic neuralgia, diabetic peripheral neuropathy, and fibromyalgia, is being increasingly studied in GAD, as there is preliminary evidence of efficacy, although long-term studies are needed. Buspirone remains an alternative treatment with no abuse liability in GAD, although it has not been found to be effective in PD or SAD. More recent studies are investigating the potential use of atypical antipsychotics in anxiety disorders because of their broad effects on the serotonin system, although further studies are needed. In PTSD, meta-analytic evidence supports the use of SSRIs as first-line pharmacotherapy, although National Institute for Health and Clinical Excellence guidelines have suggested that there is greater evidence to support trauma-focused psychotherapy over pharmacotherapy in PTSD. Newer agents, such as the alpha-1-antagonists, are being studied for their potential to treat nightmares in PTSD because of their noradrenergic effects. Meta-analyses continue to support the efficacy of both psychotherapy and pharmacotherapy in treating anxiety disorders. Although further studies of effectiveness data for the various anxiolytics are indicated, a recent STAR*D study found that patients with "anxious depression" were less likely to remit and more likely to develop side effects in response to pharmacotherapy, suggesting that comorbid anxiety contributes to poorer overall outcomes in real-world settings.¹³¹

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Dr. Mathew has been named as an inventor on a use-patent of ketamine for the treatment of depression. If ketamine were shown to be effective in the treatment of depression and received approval from the Food and Drug Administration (FDA) for this indication, Dr. Mathew could benefit financially.

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