

# Pharmacotherapy of Social Anxiety Disorder: What Does the Evidence Tell Us?

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The treatment goals for social anxiety disorder (SAD) are to reduce fear, avoidance, physical distress, disability, and comorbidity. This review illustrates some of the primary studies used to evaluate efficacy of treatments for SAD. The selective serotonin reuptake inhibitors (SSRIs) paroxetine, sertraline, fluoxetine, fluvoxamine, and escitalopram and the serotonin-norepinephrine reuptake inhibitor venlafaxine are effective treatments. They have the additional benefit of being able to treat comorbid conditions. For people who do not respond to serotonin reuptake inhibitors, treatment options include benzodiazepines (clonazepam, alprazolam, and bromazepam),  $\alpha_2\delta$  calcium-channel blockers (gabapentin and pregabalin), reversible inhibitors of monoamine oxidase A (moclobemide, although agents in this class are not available in the United States), antiepileptics (levetiracetam), and atypical antipsychotics (olanzapine). The irreversible monoamine oxidase inhibitor phenelzine can be considered an effective third-line therapy. Combination treatments may be beneficial, but more research is needed. Benefits of  $\beta$ -blockers (propranolol and atenolol) are limited to performance anxiety. Botulinum toxin A may be an effective augmentation treatment option for severe axillary hyperhidrosis in patients with SAD. Studies show that patients with SAD who are maintained on paroxetine, sertraline, or clonazepam have a low relapse rate.

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**S**ocial anxiety disorder (SAD), also known as social phobia, has a mean age at onset in the teens<sup>1</sup> and as a consequence impairs educational, social, occupational, and physical functioning.<sup>2</sup> Patients with SAD have an enhanced fear of situations that may cause embarrassment, such as public speaking, attending parties, meetings, and eating in front of others.<sup>2,3</sup> The fear leads to avoidance of these social situations. It is common for the patients to have somatic symptoms (heart palpitations, sweating, tremors, gastrointestinal discomfort, or blushing) before or during social interaction.<sup>4</sup> Patients with SAD have a high rate of comorbidity with other psychiatric disorders, including alcohol and drug abuse.<sup>1</sup> In line with the symptoms of SAD, the goals of treatment are to reduce fear, avoidance, physical distress, disability, and comorbidity. This review describes the main literature on pharmacotherapy of SAD.

## FIRST-LINE TREATMENTS FOR SAD

Serotonin reuptake inhibitors (SRIs) are the favored first-line treatment for SAD. Currently, the U.S. Food and Drug Administration (FDA) has approved paroxetine, sertraline, and venlafaxine for the treatment of SAD. Clinical studies indicate that fluoxetine, fluvoxamine, and escitalopram can also be effective treatments for SAD, though they are not FDA-approved.

### Paroxetine

Immediate-release paroxetine was the first drug approved for the treatment of SAD. The initial major double-blind, placebo-controlled trial of paroxetine showed that paroxetine (20–50 mg/day) produced a significant improvement compared with placebo on the Liebowitz Social Anxiety Scale (LSAS) ( $p < .001$ ).<sup>5</sup> Statistically significant improvement was apparent by 2 weeks and persisted and increased throughout the 12-week study duration.<sup>5</sup> Paroxetine met the treatment goals of reducing phobic avoidance, anticipatory fear, and disability.<sup>5</sup> It also significantly improved social life and work.<sup>5</sup> An analysis of 3 multicenter, double-blind, placebo-controlled studies of paroxetine recommended the paroxetine starting dose to be 20 mg/day, which could be increased as needed.<sup>6</sup>

Controlled-release paroxetine has also been approved for use in SAD. A randomized, double-blind, placebo-controlled, flexible-dose study of controlled-release par-

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oxetine in outpatients with SAD demonstrated that the proportion of patients achieving remission (defined as a 70% decrease in LSAS total score from baseline to study end) was significantly greater in the patients receiving controlled-release paroxetine than in those receiving placebo ( $p < .001$ ).<sup>7</sup> Twice as many controlled-release paroxetine-treated patients as placebo-treated patients achieved functional normality, which was defined as no perceived impairment in work or psychosocial functioning.<sup>7</sup> However, there was only a 24% rate of remission at the end of 12 weeks, a modest response, though significantly greater than what was observed in the placebo group.<sup>7</sup>

### Sertraline

Sertraline was the second drug to receive an indication for SAD in the United States. An initial double-blind, placebo-controlled study of sertraline (50–200 mg/day) in patients with generalized SAD reported that 53% of sertraline-treated patients compared with 29% of placebo-treated patients responded to treatment by study end (20 weeks), according to the Clinical Global Impressions-Improvement scale (CGI-I) ( $p < .01$ ).<sup>8</sup> Sertraline produced a broad spectrum of effects, significantly improving anticipatory fear, phobic avoidance, and autonomic symptoms compared to placebo ( $p < .01$ ).<sup>8</sup>

In a second study—a double-blind, randomized, 24-week study from Europe—generalized social phobia patients (DSM-IV) receiving sertraline (50–150 mg/day) were significantly more improved than those receiving placebo ( $p < .001$ ) according to the Clinical Global Impressions-Social Phobia scale.<sup>9</sup> In a third study, patients with DSM-IV generalized social phobia were randomized to 12 weeks of double-blind treatment with sertraline (50–200 mg/day) or placebo. According to the primary efficacy variables (LSAS and CGI-I), sertraline produced significantly greater reduction in LSAS total score from baseline compared with placebo ( $p = .001$ ) and a greater proportion of responders on the CGI-I ( $p < .001$ ).<sup>10</sup>

### Fluoxetine

Two negative, placebo-controlled trials of fluoxetine treatment for SAD exist (Kobak et al.<sup>11</sup>; Clark et al.<sup>12</sup>). In addition, a large 2-site trial found efficacy for both fluoxetine and cognitive-behavioral therapy (CBT) over placebo in patients diagnosed with DSM-IV generalized social phobia (Davidson et al.<sup>13</sup>). In that 14-week study,<sup>13</sup> patients were randomized to either fluoxetine or CBT alone, fluoxetine plus CBT, CBT plus placebo, or placebo alone. Though all active treatments were significantly superior to placebo ( $p < .04$ ) as determined using the CGI-I, combined treatment of fluoxetine plus CBT did not yield greater benefit over fluoxetine or CBT alone. CGI-I response rates (score of 1 or 2) were as follows:

fluoxetine (50.9%), CBT (51.7%), CBT plus fluoxetine (54.2%), CBT plus placebo (50.8%), and placebo (31.7%).

### Fluvoxamine

Placebo-controlled trials have shown efficacy for fluvoxamine in SAD.<sup>14,15</sup> In a 12-week, multicenter, double-blind, randomized, placebo-controlled trial, Stein et al.<sup>15</sup> found that fluvoxamine (mean dose = 202 mg/day) had a significantly higher proportion of responders (42.9%) than did placebo (22.7%). Response was defined as a rating of “much improved” or “very much improved” on the CGI-I. In a 12-week, double-blind, placebo-controlled study, van Vliet et al.<sup>14</sup> found statistically significant effects on measures of social anxiety in patients treated with fluvoxamine compared with placebo. However, the level of phobic avoidance between fluvoxamine and placebo failed to reach statistical significance. While the brand form of immediate-release fluvoxamine has been withdrawn from the U.S. market, and the newly developed controlled-release form was never introduced, generic forms of immediate-release fluvoxamine remain available.

### Escitalopram

Recent multicenter studies demonstrate efficacy of escitalopram for SAD. A multicenter, multicountry, randomized, placebo-controlled study compared escitalopram (5, 10, or 20 mg/day), placebo, and paroxetine (20 mg/day) in patients with generalized SAD. Rates of response for all 3 doses of escitalopram and for paroxetine were significantly higher than for placebo at week 12 ( $p < .05$ ).<sup>16</sup> In another multicenter, multicountry, randomized, placebo-controlled study, patients with SAD were randomized to receive escitalopram (10–20 mg/day) or placebo for 12 weeks.<sup>17</sup> By week 12, the efficacy of escitalopram was statistically significant compared with placebo ( $p = .005$ ) as measured by LSAS total score, which indicated significantly more responders to treatment with escitalopram (54%) than with placebo (39%;  $p < .01$ ).

### Venlafaxine

Numerous studies demonstrate that venlafaxine, an SNRI, can improve symptoms of SAD. One of the first multicenter, randomized, double-blind, placebo-controlled studies of extended-release venlafaxine (75–225 mg/day) in adults with SAD demonstrated that there was a significantly greater percentage of responders in the venlafaxine-treated group (50%) than in the placebo-treated group (34%;  $p < .05$ ) at the 12-week study endpoint.<sup>18</sup>

At lower doses, venlafaxine is a selective serotonin reuptake inhibitor, whereas at higher doses it has been shown to produce substantial occupancy of the norepinephrine transporter in depression.<sup>19</sup> Therefore, a multicenter, randomized, double-blind, placebo-controlled study compared a fixed low dose (75 mg/day) and a flexible higher dose (150–225 mg/day) of extended-release venlafaxine

with placebo in outpatients with generalized SAD.<sup>19</sup> Both doses produced significantly more responders than did placebo based on CGI-I scores ( $p < .001$ ), which indicated no evidence of greater benefit at the higher dose.<sup>19</sup> This finding suggests that the presence of norepinephrine reuptake does not confer a greater level of efficacy of the drug in SAD.<sup>19</sup>

Another multicenter, randomized, double-blind, placebo-controlled study compared flexible doses of extended-release venlafaxine (75–225 mg/day) and paroxetine (20–50 mg/day) and placebo in outpatients with generalized SAD.<sup>20</sup> The response rates based on CGI-I scores were 69% for venlafaxine and 66% for paroxetine, which were significantly better than the rate for placebo (36%;  $p < .001$ ).<sup>20</sup>

### SRI Drugs in Children and Adolescents With SAD

In children and adolescents with SAD, reports indicate that fluvoxamine and extended-release venlafaxine are both more effective than placebo.<sup>21,22</sup> Demonstration of efficacy in both studies is important from the risk-benefit perspective, given recent concerns about emergent suicidality in children and adolescents who are receiving antidepressants. It needs to be kept in mind that untreated social anxiety disorder in young people incurs considerable risks, which are arguably greater than those associated with the treatment.

## ADDITIONAL TREATMENTS FOR SAD

### MAOIs and RIMAs

The irreversible monoamine oxidase inhibitor (MAOI) phenelzine has well-established efficacy in SAD.<sup>23</sup> Phenelzine is equivalent in efficacy to CBT and on some measures may even be superior. However, MAOIs are no longer considered first-line therapy due to the need for MAOI-treated patients to follow a low-tyramine diet to prevent hypertensive crisis, as well as the toxicity concerns, risks, and generally poor tolerability associated with MAOI treatment.<sup>23</sup> Reversible inhibitors of monoamine oxidase A (RIMAs) are less likely to result in hypertensive reactions.<sup>23</sup> However, they are believed to be of weaker efficacy and are not available in the United States.

Some patients with SAD do not respond or only partially respond to SRIs or RIMAs. At this time, it is not clear who will respond to treatment. It is evident from the literature that patients with more severe SAD are less likely to respond to an SSRI or RIMA. Patients with a history of excessive alcohol use or a family history positive for social phobia also tend not to respond well.<sup>24</sup> Also, patients with passive-dependent personality disorder<sup>25</sup> or higher systolic blood pressure and heart rate<sup>26</sup> do not respond as well. These predictors are determined from open-label studies or studies with looser inclusion criteria, since randomized controlled studies typically exclude these types of patients.

### Benzodiazepines

If a patient is resistant to SRIs, benzodiazepines are a credible treatment option for which reasonably compelling efficacy data exist. A double-blind, placebo-controlled study evaluated clonazepam (0.25–3.0 mg/day) in patients with SAD.<sup>27</sup> At study end (week 10), clonazepam was significantly more effective than placebo, with response rates of 78% for clonazepam and 20% for placebo according to CGI-I response rates ( $p < .0001$ ).<sup>27</sup> However, significantly more clonazepam-treated patients than placebo-treated patients reported anorgasmia (23% vs. 3%;  $p = .001$ ), unsteadiness (29% vs. 0%;  $p = .001$ ), dizziness (29% vs. 0%;  $p = .01$ ), and blurred vision concentration (12% vs. 0%;  $p = .03$ ).<sup>27</sup> Physicians are generally aware that SSRIs and other antidepressants cause sexual side effects, but overlook the fact that clonazepam, and perhaps other benzodiazepines, can also cause sexual side effects.

Versiani et al.<sup>28</sup> conducted a double-blind, 12-week study of SAD patients randomized to either bromazepam or placebo. At weeks 8 and 12, bromazepam demonstrated statistically significant superior efficacy to placebo. The response rate for bromazepam was 83% compared with 20% for placebo, suggesting the drug may be an alternative for SAD treatment.<sup>28</sup> Alprazolam has also been studied for the treatment of SAD. Gelernter et al.<sup>29</sup> studied alprazolam in patients with SAD. Only 38% of patients on alprazolam treatment were considered responders at 12 weeks.

Overall, the potential benefits of benzodiazepines in SAD are that they have a rapid onset, they are well tolerated, the dose can be adjusted rapidly, and they can be used as needed,<sup>30</sup> which is particularly valuable for treating performance anxiety. However, there are potential drawbacks of using benzodiazepines to treat SAD, including sedation, discontinuation difficulties, potential for abuse,<sup>31</sup> and minimal efficacy for comorbid depression.<sup>23</sup>

### $\alpha_2\delta$ Calcium-Channel Blockers

The  $\alpha_2\delta$  calcium-channel blockers gabapentin and pregabalin are also options for treatment-resistant SAD. Gabapentin (900–3600 mg/day) was evaluated in a randomized, double-blind, placebo-controlled, flexible-dose study of outpatients ( $N = 82$ ) with SAD.<sup>32</sup> Gabapentin did significantly better than placebo on all main measures, namely, LSAS, Brief Social Phobia Scale (BSPS), Social Phobia Inventory, and Marks-Mathews' Fear Questionnaire scores ( $p = .002$  to  $.008$ ).<sup>32</sup> Pregabalin, at high doses, is also effective for SAD. A multicenter, placebo-controlled, double-blind study of pregabalin 600 mg/day, pregabalin 150 mg/day, and placebo reported a CGI-I response rate of 43% ( $p = .03$  vs. placebo), 21%, and 22%, respectively.<sup>33</sup> The LSAS response rate was low (28%, 14%, and 13%, respectively), and there was no signifi-

cant improvement for either dose of pregabalin compared with placebo.<sup>33</sup> Even though the 600-mg/day dosage demonstrated efficacy, 42% of the patients treated with this dosage reported sleepiness, 40% reported dizziness, 21% each reported abnormal thinking and headaches, and 19% reported tiredness, and this dosage was associated with a mean weight gain of 1.7 kg.<sup>33</sup> The full impact of these side effects is difficult to assess at the present time.

### Other Treatments

Based on small trials, there appear to be a variety of other drugs that may have efficacy for SAD. Positive findings have been shown with the atypical antipsychotic olanzapine and the antiepileptic drug levetiracetam.<sup>34,35</sup> For example, a recent placebo-controlled pilot study of levetiracetam (up to 3000 mg/day) in patients with SAD showed that levetiracetam-treated patients had a higher response rate than placebo-treated patients according to the BSPS; while between-group difference was statistically significant, the effect size in this small sample was moderate. The rate of response was low, but the response to levetiracetam was greater than the response to placebo. Therefore, levetiracetam is marginally effective at this dose.

### Combination Treatment

Combining an SSRI with a benzodiazepine can produce beneficial effects for patients who are partial responders or nonresponders to either type of agent. One randomized, double-blind, placebo-controlled study evaluated the efficacy of paroxetine with clonazepam in patients with generalized SAD.<sup>31</sup> All patients were treated with flexible-dose, open-label paroxetine (20–40 mg/day).<sup>31</sup> In addition, patients were randomly assigned to receive clonazepam (1–2 mg/day) or placebo for 10 weeks.<sup>31</sup> According to the CGI-I score, the response rate was 79% for patients taking paroxetine and clonazepam compared to 43% for those taking paroxetine and placebo, suggesting that the 2 drugs, with different mechanisms of action, may complement each other to produce a better outcome than paroxetine alone.<sup>31</sup> However, significant differences were not found on all measures.

### SAD and Hyperhidrosis

As many as 25% to 33% of patients with SAD have hyperhidrosis.<sup>36</sup> Hyperhidrosis can cause substantial distress for people with SAD, yet there is little research on its treatment.<sup>36</sup> A newly researched treatment option for patients with SAD and severe axillary hyperhidrosis is botulinum toxin A. In a double-blind trial, all subjects received 8 weeks of paroxetine, as well as a one-time bilateral intra-axillary intradermal injection of either botulinum toxin or saline.<sup>37</sup> On the Hyperhidrosis Disorder Severity Scale, the response rate for botulinum toxin

was 65% compared with 10% for placebo at 8 weeks ( $p < .01$ ).<sup>37</sup> Botulinum toxin may therefore be an effective treatment of axillary hyperhidrosis when given with a drug such as paroxetine in patients with SAD.<sup>37</sup>

### COMORBIDITY

Patients with SAD have a high rate of comorbid disorders.<sup>1</sup> Simple phobia and agoraphobia are the most common comorbid disorders with SAD.<sup>1</sup> Alcohol abuse and major depression also have a high rate of comorbidity with SAD.<sup>1</sup> In patients who develop SAD before they are 15 years old, 70% develop major depression and 40% develop alcoholism.<sup>38</sup> Therefore, early-onset SAD has major significance for these comorbidities.<sup>38</sup>

Treatment of comorbid anxiety and depression is often challenging, but unfortunately very few data are available as to the efficacy of usual treatment.<sup>39</sup> In an open-label trial of patients with generalized SAD and comorbid major depression,<sup>39</sup> escitalopram (10–20 mg/day) treatment was associated with overall intent-to-treat response rates of 75% for major depression and 45% for SAD at 24-week follow-up, suggesting limited benefit for the drug. It is possible that at a higher dose, escitalopram would have produced a greater effect on social anxiety.<sup>39</sup>

Results of a small double-blind, placebo-controlled pilot study showed that paroxetine (20–60 mg/day) is an effective treatment for patients with SAD and comorbid alcohol abuse.<sup>40</sup> According to the CGI-I rating, 67% of paroxetine-treated patients compared with 22% of placebo-treated patients showed a decrease in SAD symptoms, while alcohol intake decreased in 50% of the paroxetine-treated patients compared with 11% of the placebo-treated patients.<sup>40</sup>

### RELAPSE PREVENTION

SAD is a chronic condition, and relapse prevention is a concern. There have been several studies evaluating relapse.

#### Paroxetine

The efficacy of paroxetine maintenance treatment in preventing relapse was assessed in a study with an open-label, 12-week treatment phase followed by a randomized, double-blind, placebo-controlled maintenance 24-week treatment phase.<sup>41</sup> Significantly fewer patients who were maintained on paroxetine relapsed (14%) compared with patients who were maintained on placebo treatment (39%) ( $p < .001$ ).<sup>41</sup> A significantly greater proportion of patients in the paroxetine group were considered “much improved” or “very much improved” on the CGI-I at the end of the study compared with the placebo group (78% vs. 51%;  $p < .001$ ).<sup>41</sup> Various assessment scales, includ-

ing the LSAS, revealed significantly greater improvement with paroxetine.<sup>41</sup>

### Sertraline

Relapse prevention was also assessed with sertraline. Patients with generalized SAD who responded to 20 weeks of double-blind treatment with either sertraline (50–200 mg/day) or placebo were eligible to enter the second phase of the study.<sup>42</sup> In the second phase, patients who responded to sertraline were randomly and blindly assigned to maintain sertraline or were tapered off sertraline and switched to placebo for 24 weeks. Patients who responded to placebo remained on placebo.<sup>42</sup> At study endpoint, 4% of the patients maintained on sertraline treatment compared with 36% of the patients switched to placebo relapsed ( $p = .01$ ).<sup>42</sup> An interesting aspect of this study was the inclusion of a double-blind expression in placebo responders who ultimately were shown to relapse almost at the same rate (27%) as those who were switched from sertraline to placebo. This finding suggests that placebo response is less likely to endure as well as response associated with an SSRI.

### Escitalopram

To assess the prevention of relapse with escitalopram, a 24-week, randomized, double-blind, placebo-controlled study was conducted in patients with DSM-IV–defined generalized SAD who responded to 12-week open-label treatment with escitalopram.<sup>43</sup> Those responding to the 12-week open-label treatment of escitalopram (10–20 mg/day) with a CGI-I score of 1 or 2 were randomized to 24 weeks of double-blind treatment with escitalopram (10 or 20 mg/day) or placebo. With relapse defined as LSAS total score  $\geq 10$  or withdrawal due to lack of efficacy, there was a significant advantage for escitalopram compared with placebo for relapse and time to relapse ( $p < .001$ ). The risk of relapse was 2.8 times higher for placebo-treated patients than for escitalopram-treated patients ( $p < .001$ ), resulting in significantly fewer escitalopram-treated patients relapsing (22% vs. 50%), at both doses.<sup>43</sup>

### Clonazepam

Discontinuation of clonazepam is also associated with relapse. Patients with SAD were treated with open-label clonazepam for 6 months.<sup>44</sup> All patients who responded to treatment were randomly assigned to maintain clonazepam treatment or were switched to placebo via a slow fixed-dose taper with replacement for 5 months.<sup>44</sup> In the maintenance group, none of the patients relapsed, whereas in the placebo-switch group 20% of the patients relapsed<sup>44</sup>; symptoms, in general, worsened in the placebo group. The authors concluded that maintenance therapy with clonazepam conferred protection against relapse and that it was also possible to taper the drug slowly with minimal withdrawal difficulty.<sup>44</sup>

## PERFORMANCE ANXIETY

There is evidence that propranolol can help with performance anxiety, e.g., in students who take the Scholastic Aptitude Test (SAT); an improvement in score was noted among anxious subjects after being given a single 40-mg dose of propranolol 1 hour before retaking the SAT.<sup>45</sup>

In addition, 4 double-blind, placebo-controlled studies have evaluated propranolol (10–120 mg) in treating performance-specific anxiety. Ophthalmic surgeons with tremor and anxiety,<sup>46</sup> medical students under mild stress,<sup>47</sup> patients with dental phobia,<sup>48</sup> and patients with surgery anxiety<sup>49</sup> have been studied. The studies reported that, compared with placebo, propranolol significantly reduced surgical tremor and anxiety in surgeons ( $p < .01$ ),<sup>46</sup> improved test scores in medical students ( $p < .05$ ),<sup>47</sup> reduced anxiety and pain in dental patients ( $p < .05$ ),<sup>48</sup> and reduced anxiety in day surgery patients.<sup>49</sup> These findings suggest a limited place for  $\beta$ -blockers such as propranolol in various situations where either performance or other anxiety is elevated. Their role in rigorously diagnosed SAD of non-generalized type is still not established.

## DISCUSSION

In some patients with SAD, pharmacotherapy is very effective, while in other patients, there is a more modest effect. There is no evidence that higher doses of paroxetine or extended-release venlafaxine produce better results than lower doses. It is recommended to achieve at least the minimum therapeutic dose (e.g., sertraline 150 mg, extended-release paroxetine 25 mg) by 4 to 6 weeks, assuming adequate tolerability, and then increase if necessary. It may take months before the full efficacy becomes apparent, partly perhaps because of the diverse clinical pattern of SAD coupled with the need to unlearn deeply entrenched maladaptive behaviors.

Further advances in the pharmacotherapy of SAD are to be hoped for, including the development of novel drug classes and exploration of a role for D-cycloserine in conjunction with psychotherapy. We also need to know whether the use of psychotherapy as an augmentation strategy has any merit, as proposed elsewhere.<sup>12</sup>

## SUMMARY

To summarize, there are many drugs with established efficacy for SAD (Table 1). The SSRIs fluvoxamine (immediate and extended release), paroxetine (immediate and extended release), sertraline, fluoxetine, and escitalopram and the SNRI extended-release venlafaxine have proven efficacy. They are considered the first-line therapies for SAD. There is no evidence, however, that a dual-acting SNRI is better than a single-acting SSRI for SAD. There are many choices for second-line therapeutics. The ben-

**Table 1. Drugs With Established Efficacy for Social Anxiety Disorder (SAD)**

| Drug Class/Drug   |
|---|
| <b>First-Line Treatments (SRIs)</b>   |
| SSRIs   |
| Paroxetine immediate release <sup>a</sup> and controlled release <sup>a</sup> |
| Sertraline <sup>a</sup>   |
| Fluoxetine  |
| Fluvoxamine immediate release and controlled release                          |
| Escitalopram  |
| SNRI  |
| Venlafaxine extended release <sup>a</sup>                                     |
| <b>Second-Line Treatments</b>   |
| RIMA  |
| Moclobemide   |
| Benzodiazepines   |
| Clonazepam  |
| Alprazolam  |
| Bromazepam  |
| $\alpha_2\delta$ Calcium-channel blockers                                     |
| Gabapentin  |
| Pregabalin  |
| Atypical antipsychotic  |
| Olanzapine  |
| Antiepileptic drugs   |
| Tiagabine   |
| Levetiracetam   |
| Combination treatments  |
| SSRI + benzodiazepine   |
| <b>Third-Line Treatments</b>  |
| MAOI  |
| Phenelzine  |
| <b>Performance Anxiety</b>  |
| $\beta$ -Blockers   |
| Propranolol   |
| Atenolol  |

<sup>a</sup>Approved by the U.S. Food and Drug Administration for the treatment of SAD.

Abbreviations: MAOI = monoamine oxidase inhibitor, RIMA = reversible inhibitor of monoamine oxidase A, SNRI = serotonin-norepinephrine reuptake inhibitor, SRI = serotonin reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

zodiazepines clonazepam and bromazepam are good choices for second-line therapy, while the  $\alpha_2\delta$  calcium-channel blockers gabapentin and pregabalin may possibly provide benefit. The RIMAs, including moclobemide, have been used successfully to treat SAD. Atypical antipsychotics may be helpful for SAD, but they will probably always be a second-line treatment because SRIs are safer. An effective third-line therapy is the MAOI phenelzine. Combination treatments may be beneficial, but more research is needed.  $\beta$ -Blockers are effective for performance anxiety, although it is difficult to map the symptom picture of subjects in the early studies cited with today's DSM-IV criteria, thus making it hard to tell whether they indeed had SAD. A study by Liebowitz and colleagues,<sup>50</sup> for example, found a good effect for the MAOI phenelzine, but only a marginal effect for atenolol, and that only in the performance subtype. More research is needed to establish additional treatments for performance anxiety.

*Drug names:* alprazolam (Xanax, Niravam, and others), atenolol (Tonormin and others), clonazepam (Klonopin and others), escitalopram (Lexapro), fluoxetine (Prozac and others), gabapentin (Neurontin and others), levetiracetam (Keppra), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), pregabalin (Lyrica), propranolol (Innopran, Inderal, and others), sertraline (Zoloft), tiagabine (Gabitril), venlafaxine (Effexor).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, alprazolam, atenolol, clonazepam, escitalopram, fluoxetine, gabapentin, levetiracetam, olanzapine, phenelzine, pregabalin, propranolol, and tiagabine are not approved by the U.S. Food and Drug Administration for the treatment of social anxiety disorder.

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