

Social Anxiety Disorder: Designing a Pharmacologic Treatment Strategy

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© Growing appreciation of the prevalence of and morbid sequelae associated with social anxiety disorder has focused increasing interest on the development of effective treatment strategies. A number of pharmacologic interventions, including the monoamine oxidase inhibitors, reversible inhibitors of monoamine oxidase A, β -blockers, benzodiazepines, and selective serotonin reuptake inhibitors, have demonstrated efficacy for the treatment of social anxiety disorder. The choice of initial treatment depends on a variety of factors including comorbidity, prior treatment history, patient preference, and adverse effect profile. This article will examine the effectiveness of various pharmacologic agents for the treatment of social anxiety disorder, discuss considerations for long-term management, and review strategies for optimizing treatment in patients who are partially responsive or unresponsive to initial therapy. (J Clin Psychiatry 1999;60[suppl 9]:20–26)

Growing appreciation of the prevalence of and morbid sequelae associated with social anxiety disorder has focused increasing attention on identifying effective treatment options. The National Comorbidity Survey demonstrated that social anxiety disorder is the third most common lifetime psychiatric disorder (13.3%) after major depression and alcohol dependence.¹ Social anxiety disorder has a significant adverse impact on patients' ability to function in vocational, educational, social, and familial situations and frequently is associated with comorbid disorders such as depression and alcohol or other substance abuse.² The expanding array of pharmacologic and psychosocial treatment strategies for social anxiety disorder has been accompanied by increased understanding of genetic and familial patterns for transmission of the disorder.³ Various models have highlighted the relationship between social anxiety disorder in adulthood and manifestations of anxious temperaments during childhood and have examined potential underlying neurobiological and psychological substrates that may be involved in the development of the disorder.^{4–6}

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A number of pharmacologic agents have been evaluated for the treatment of social anxiety disorder (Table 1). This article will review pharmacologic interventions that have demonstrated efficacy for the treatment of social anxiety disorder, including β -blockers, monoamine oxidase inhibitors (MAOIs), benzodiazepines, and selective serotonin reuptake inhibitors (SSRIs). In addition, use of other potentially effective agents and strategies to optimize treatment for patients who are partially responsive or unresponsive to therapy will be discussed. The choice of initial treatment depends on a number of factors, including comorbidity, prior treatment history, patient preference, and adverse effect profile of the selected agents.

PHARMACOTHERAPY

Because social anxiety disorder is a serious illness associated with significant morbidity, patients should be treated aggressively once the diagnosis is established. Antidepressant therapies are particularly effective for patients who have social anxiety disorder that is comorbid with other mood or affective disorders. The SSRIs now are generally considered first-line pharmacotherapy for patients with social anxiety disorder. Other effective agents may include MAOIs and benzodiazepines.

β -Blockers

β -Blockers decrease autonomic symptoms of arousal, such as tachycardia, tremors, and sweating, and often have been used by performers to decrease anxiety in performance-related situations.⁷ Although an open clinical trial suggested that atenolol (50–100 mg/day) was effective for both generalized and nongeneralized performance-related symptoms,⁸ results from a double-

Table 1. Pharmacotherapy for Social Anxiety Disorder

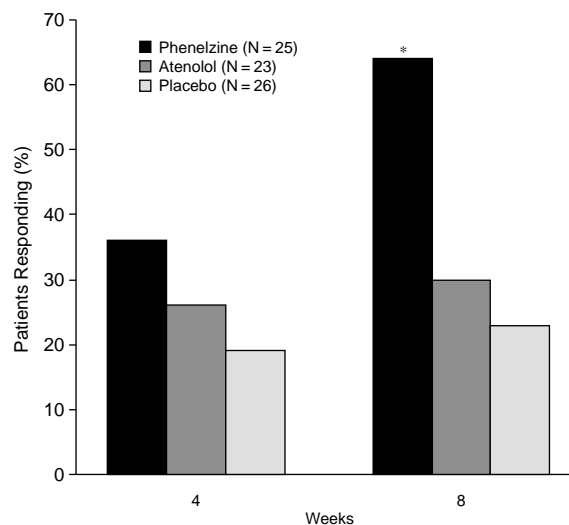
β-Blockers
Monoamine oxidase inhibitors
Benzodiazepines
Selective serotonin reuptake inhibitors
Other agents or combination therapy

blind, placebo-controlled trial demonstrated that atenolol (mean dose = 95 mg/day) was not as effective as phenelzine for the management of social anxiety disorder.⁹ In this study, the response rate to atenolol for patients with nongeneralized social anxiety disorder (40%) was greater than for patients with the generalized subtype (28%), although the number of subjects was inadequate to achieve statistical significance.

β-Blockers decrease the perception of anxiety by blunting peripheral autonomic symptoms of arousal. However, these agents are less potent in affecting emotional aspects of the experience. Propranolol (10–80 mg/day) or atenolol (10–50 mg/day) can be used either routinely or on an as-needed basis 1 to 2 hours before a performance situation. A low “test dose” should be tried prior to the day of the performance to determine tolerability before the medication is used in actual situations of concern. Atenolol appears to cause less sedation and other adverse central nervous system effects than does propranolol and can be used once daily for maintenance therapy.

Monoamine Oxidase Inhibitors

Until the advent of SSRIs, MAOIs were considered the mainstay of pharmacotherapy for patients with social anxiety disorder. Initially, open-label trials with phenelzine and tranylcypromine suggested that MAOIs were effective for the treatment of patients with social anxiety disorder.^{10,11} These positive results were confirmed in a double-blind comparison trial evaluating phenelzine (mean dose = 76 mg/day), atenolol (mean dose = 95 mg/day), and placebo in 74 patients with social anxiety disorder.⁹ During the 8-week trial, significantly more patients treated with phenelzine (64%) responded to therapy compared with patients treated with either atenolol (30%) or placebo (23%) (Figure 1). Results for patients with generalized social anxiety disorder were similar to those for the patient sample as a whole, although results for the patients with predominantly performance anxiety (nongeneralized social anxiety disorder) were inconclusive because of the small sample size for this subtype. Another double-blind, placebo-controlled study¹² comparing phenelzine, alprazolam, and cognitive-behavioral group therapy (CBGT) in 65 patients diagnosed with social anxiety disorder also tended to favor phenelzine, although not generally to the level of statistical significance. Of patients treated with phenelzine (mean dose = 55 mg/day), 69% responded to treatment compared with 38% of patients taking alprazo-

Figure 1. Percentage of Patients With Social Anxiety Disorder Who Responded to Phenelzine, Atenolol, or Placebo During 8 Weeks of Treatment^a

^aData from reference 9.

* $p \leq .02$ vs. atenolol or placebo.

lam (mean dose = 4.2 mg/day), 24% of patients treated with CBGT, and 20% of placebo-treated patients.¹² However, the results of this study should be viewed with the caveat that all patients received self-directed exposure treatment and that the sample sizes were relatively small. Thus, at least 3 double-blind, placebo-controlled trials have reported significant benefits in 60% to 91% of patients with social anxiety disorder treated with phenelzine for 8 to 12 weeks.^{9,12,13} Another double-blind, placebo-controlled trial of phenelzine (mean dose = 68 mg/day) and moclobemide (mean dose = 582 mg/day) also demonstrated the effectiveness of both drugs.¹³

Typical doses for phenelzine are 60 to 90 mg/day and for tranylcypromine, 30 to 60 mg/day; some patients may require higher doses to achieve benefits.¹¹ Although MAOIs are considered among the most effective agents for the treatment of mood and anxiety symptoms, their use is limited by the need to adhere to strict dietary restrictions for tyramine-containing foods and to avoid other sympathomimetic agents because of the risk of hypertensive reactions. An array of other side effects, including weight gain, insomnia, and sexual dysfunction, also may decrease patient compliance with therapy.

The safety concerns associated with administering traditional irreversible MAOIs have stimulated interest in reversible inhibitors of monoamine oxidase A (RIMAs), which do not require stringent dietary monitoring and have a much lower risk of hypertensive reactions. Two RIMAs, moclobemide and brofaromine, have demonstrated variable efficacy and generally good tolerability in a number of clinical trials.^{14–16} However, although moclo-

bemide is marketed in Canada and a number of other countries, neither RIMA is available in the United States.

Benzodiazepines

High-potency benzodiazepines, such as clonazepam and alprazolam, have demonstrated efficacy in the treatment of panic disorder and also appear to be useful for the management of social anxiety disorder. A number of case reports suggest that alprazolam (1–8 mg/day) and clonazepam (1–3 mg/day) are effective in patients with social anxiety disorder.^{17–20} In a double-blind, placebo-controlled, 10-week trial evaluating 75 patients with social anxiety disorder, Davidson et al.²¹ reported that 78% of clonazepam-treated patients (mean dose = 2.4 mg/day) experienced significant improvement compared with 20% of placebo-treated patients. The response to clonazepam was apparent beginning at week 2. In a double-blind, placebo-controlled trial evaluating alprazolam, phenelzine, and CBGT in 65 patients with social anxiety disorder, 38% of patients treated with alprazolam (mean dose = 4.2 mg/day) responded to therapy. Although there were no significant differences in most measures between groups, alprazolam was associated with a high incidence of relapse within 2 months of discontinuing treatment.¹²

Although not well studied, long-term treatment with benzodiazepines for social anxiety disorder appears effective in clinical practice without the apparent development of therapeutic tolerance or need for dose escalation over time. Overall, the advantages of benzodiazepine therapy include efficacy, rapid onset of effect, feasibility of rapid dose adjustments, and potential for situational or as-needed dosing. The disadvantages of benzodiazepines include side effects, e.g., sedation, ataxia, cognitive impairment, and difficulties with discontinuation because of withdrawal symptomatology. In addition, secondary comorbid alcohol abuse has been reported in 24% to 35% of patients with social anxiety disorder,^{22,23} and these patients may be more likely to abuse benzodiazepines. Many patients with social anxiety disorder also develop comorbid depression that is best treated with an antidepressant and is unlikely to respond to benzodiazepine therapy alone.

In clinical practice, benzodiazepines commonly are combined with antidepressant therapy. The advantage of this combined strategy is that the benzodiazepine provides rapid anxiolysis during the 2- to 4-week period needed for antidepressants to achieve optimal effectiveness. Benzodiazepines also may reduce any increased anxiety that may be associated with initiation of antidepressant therapy. The presence of an antidepressant provides prophylaxis and treatment for comorbid depression in patients with social anxiety disorder. Further, there may be synergistic or additive effects by combining 2 pharmacologic agents with different mechanisms of action. For some patients, the benzodiazepines can be discontinued

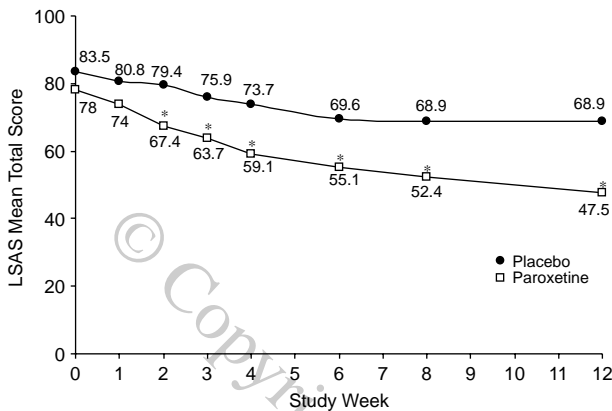
after a few weeks once the antidepressant becomes effective; others benefit from ongoing combined treatment.

Selective Serotonin Reuptake Inhibitors

Increasing clinical experience as well as an expanding body of systematic clinical reports and controlled trials have established the efficacy of SSRIs for the treatment of social anxiety disorder. Citalopram, fluoxetine, paroxetine, and sertraline are reported to be effective for the treatment of social anxiety disorder in a number of open-label evaluations and case reports.^{24–30} Venlafaxine and nefazodone also are potentially useful, based on case reports and open-label study data.^{31,32} Recently, several controlled trials also have demonstrated the effectiveness of SSRIs for social anxiety disorder. Fluvoxamine (150 mg/day) was more effective than placebo in a 12-week controlled trial evaluating 30 patients with social anxiety disorder. Forty-six percent of patients treated with fluvoxamine improved, compared with only 7% of placebo-treated patients.³³ Similar results were obtained in a 12-week, placebo-controlled, double-blind study with fluvoxamine in 92 patients with social anxiety disorder; 43% of fluvoxamine-treated patients versus 23% of those taking placebo were responders at endpoint.³⁴ A small, double-blind, placebo-controlled, crossover study evaluating 12 outpatients diagnosed with social anxiety disorder demonstrated that 50% of patients treated with sertraline (mean dose = 34 mg/day) experienced moderate to marked improvement compared with 9% of patients who received placebo.³⁵

A number of trials have demonstrated the efficacy of paroxetine for the treatment of patients with generalized social anxiety disorder. Data from 2 large, multicenter, flexible-dose studies (1 in the United States, 1 in Europe) demonstrated a significant advantage for treatment with paroxetine compared with placebo based on measures of social anxiety. In paroxetine-treated patients who completed the studies, 69% and 66% responded to acute treatment at the end of 12 weeks compared with 29% and 32% of patients who received placebo^{36,37} (also SmithKline Beecham Pharmaceuticals, data on file, study PAR-502, March 1998). In the intent-to-treat analysis, 55.0% of patients treated with paroxetine were rated as much or very much improved after 12 weeks compared with 23.9% of patients treated with placebo (odds ratio = 3.88; 95% confidence interval [CI] = 2.81–5.36).³⁷ Improvement, as measured by reduction from baseline in the Liebowitz Social Anxiety Scale (LSAS), was more than twice as large in paroxetine-treated patients (39.1% improvement) as in placebo-treated patients (17.4% improvement) (Figure 2).^{36,37} Another randomized, double-blind, fixed-dose comparison of paroxetine, 20 mg/day, 40 mg/day, 60 mg/day, or placebo in the treatment of generalized social anxiety disorder demonstrated significant benefit for patients treated with paroxetine at all 3 doses compared with placebo.

Figure 2. Mean Total Score on the Liebowitz Social Anxiety Scale (LSAS) for Paroxetine-Treated and Placebo-Treated Patients^a



^aReproduced from reference 37, with permission.
* $p < .001$ vs. placebo.

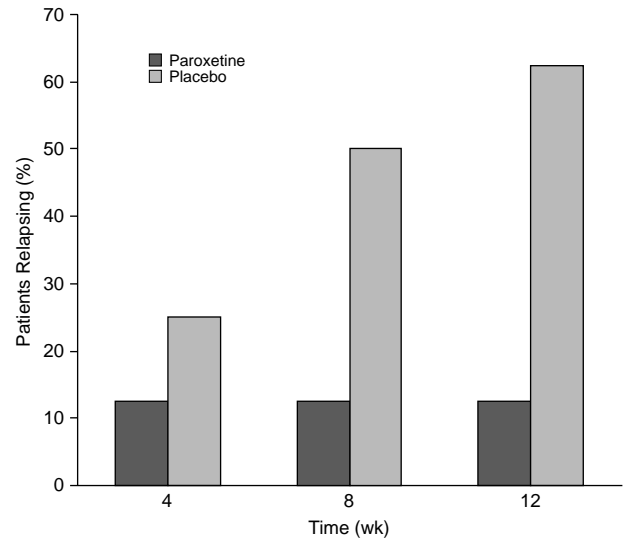
bo. There were no significant differences in efficacy between the 3 doses of paroxetine.³⁸ In an 11-week, forced-escalation study of paroxetine (mean dose = 40 mg/day) that evaluated 36 patients with generalized social anxiety disorder, Stein et al.³⁹ noted that 77% of paroxetine-treated patients were rated as responders. Subsequently, 16 of the responders were randomly assigned in a double-blind fashion to 12 weeks of therapy with either same-dose paroxetine or tapered discontinuation and placebo substitution. Twelve weeks after randomization, 87.5% of the paroxetine-treated patients remained well, compared with only 37.5% of patients who switched to placebo, suggesting the persistence of benefits with continued treatment over time and the high rate of relapse with early treatment discontinuation (Figure 3).

These data suggest that the SSRIs are effective for the treatment of patients with social anxiety disorder. In addition, SSRIs are particularly useful for patients with comorbid depression or other anxiety disorders. Beneficial therapeutic response, lack of dietary restrictions, and low incidence of adverse effects make the SSRIs the pharmacologic treatment of choice for patients with social anxiety disorder.

Other Medications

A variety of other pharmacologic strategies have been employed for the treatment of social anxiety disorder⁴⁰ (Table 2). Gabapentin, a nonbenzodiazepine gamma aminobutyric acid (GABA) analogue, was shown to be effective for social anxiety disorder during a 14-week, double-blind, placebo-controlled study (N = 69) in a dosage range of 600 to 3600 mg/day.⁴¹ Buspirone also has been evaluated for the treatment of social anxiety disorder. Although 2 open-label studies suggested the potential efficacy of buspirone for the treatment of social anxiety disorder, par-

Figure 3. Percentage of Responders to Paroxetine Who Relapsed Within 12 Weeks After Randomization to Continued Paroxetine or Placebo^a



^aReproduced from reference 39, with permission.

Table 2. Other Potentially Effective Agents for the Treatment of Social Anxiety Disorder

Medication	Recommended Dose
Gabapentin	600–3600 mg/d
Venlafaxine	75–300 mg/d
Nefazodone	300–500 mg/d
Buspirone	45–60 mg/d (adjunctively)
Bupropion	300–450 mg/d
Clonidine	0.1 mg twice daily
Pramipexole	0.125 mg 3 times daily
Ondansetron	0.25 mg twice daily

ticularly at higher doses,^{42,43} a double-blind, placebo-controlled study of buspirone compared with cognitive-behavioral therapy failed to demonstrate significant efficacy, although the doses of buspirone in this study were low (32 mg/day).⁴⁴ Van Ameringen et al.⁴⁵ reported that buspirone may augment the effects of SSRIs. In an open-label trial evaluating 10 patients with social anxiety disorder who only had a partial response to SSRI therapy, addition of buspirone (mean dose = 45 mg/day) led to a 70% response rate.

The use of tricyclic antidepressants (TCAs) also has been examined in the treatment of social anxiety disorder. Initially, open-label trials with imipramine and clomipramine in a heterogeneous group of patients with phobic conditions suggested the potential efficacy of TCAs for social anxiety disorder.^{46,47} However, a double-blind, placebo-controlled trial (N = 41) with imipramine (mean dose = 149 mg/day) demonstrated that imipramine had no greater efficacy than placebo in the treatment of patients with social anxiety disorder.⁴⁸ Thus, the TCAs generally are not useful for the treatment of this condition.

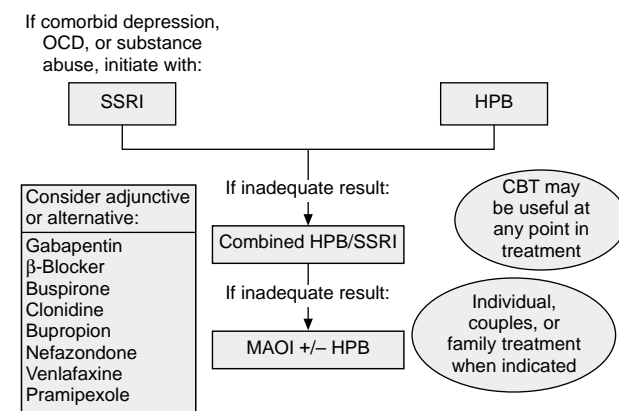
Case reports and open-label trials have reported potential benefits of other pharmacologic agents for the treatment of social anxiety disorder, including bupropion (300 mg/day),⁴⁹ clonidine (0.1 mg/day),⁵⁰ and pramipexole (0.125 mg 3 times daily) (M.H.P., unpublished data, 1998). In addition, a multicenter, double-blind, randomized, placebo-controlled trial of the 5-HT₃ antagonist ondansetron in 275 patients with social anxiety disorder suggested some potential benefit for this agent as well.⁵¹ However, the true utility of these agents in the management of social anxiety disorder remains to be determined in systematic study and practice.

OPTIMIZING PHARMACOTHERAPY FOR SOCIAL ANXIETY DISORDER

A number of general principles may be useful in developing effective treatment strategies for patients with social anxiety disorder. In clinical practice, selection of appropriate pharmacotherapy usually involves consideration of relevant comorbid conditions. SSRIs, as broad-spectrum agents, can be used for the management of patients with social anxiety disorder that occurs comorbidly with panic disorder, depression, posttraumatic stress disorder, and obsessive-compulsive disorder. The MAOIs also are effective for a broad array of anxiety and depressive disorders. However, an unfavorable side effect profile and the requirement for careful dietary monitoring typically relegate MAOIs to use as second-line agents. In patients who require rapid onset of effect, use of benzodiazepines and combined benzodiazepine-antidepressant therapy should be considered. However, comorbid alcohol abuse is a relative contraindication for the use of benzodiazepines and also complicates MAOI therapy because of the potential for adverse drug interactions.

Effective dose levels should be targeted for initial treatment, e.g., paroxetine, 20 mg/day; phenelzine, 60 mg/day, but clinical experience suggests that doses may be increased for partial responders or for patients who do not respond to initial therapy. Therapeutic effects may appear within the first 2 to 4 weeks of antidepressant treatment and within the first week or two of therapy with benzodiazepines. Full therapeutic benefits may require weeks or months of continued therapy as patients test the anxiolytic effects of treatment by exposing themselves to fearful situations over time. It appears that most patients with social anxiety disorder maintain benefits for years during continued therapy. However, relapse rates are high following drug discontinuation. For instance, 74% of patients who responded to clonazepam, 90% of moclobemide responders, and 62% of patients who responded to paroxetine experienced relapse when pharmacotherapy was discontinued.^{13,21,39} Conversely, the study conducted by Stein et al.³⁹ demonstrated that therapeutic benefits were maintained in patients with social anxiety disorder

Figure 4. Algorithm for the Treatment of Social Anxiety Disorder^a



^aAbbreviations: CBT = cognitive-behavioral therapy, HPB = high-potency benzodiazepine, MAOI = monoamine oxidase inhibitor, OCD = obsessive-compulsive disorder, SSRI = selective serotonin reuptake inhibitor.

who received uninterrupted maintenance therapy with paroxetine.

Cognitive-behavioral therapies have potent benefits for the treatment of patients with social anxiety disorder.⁵² Although the strategy of combining pharmacotherapy and cognitive-behavioral therapy has not been subjected to large-scale systematic study, combination therapy may provide synergistic or additive benefits. In the study conducted by Gelernter et al.,¹² all patients received self-exposure therapy in addition to phenelzine, alprazolam, behavioral therapy, or placebo. Subsequently, patients who discontinued phenelzine had a lower-than-expected rate of relapse. This lower rate may have been associated with the additional self-exposure behavioral therapy conducted in conjunction with the medication. It is reasonable to combine behavioral therapy in the form of self-exposure instructions with pharmacotherapy for all patients with social anxiety disorder. Formal cognitive-behavioral therapy should be considered for patients who remain symptomatic despite these interventions.

It also is important to consider psychosocial issues when evaluating and treating patients with social anxiety disorder. For some patients, difficulties with confidence, self-esteem, and interpersonal relationships may diminish as the social anxiety symptoms are controlled. For others, however, difficulties with anxiety, often dating back to childhood, may have had significant effects on personality and relationships. These patients may benefit from psychotherapeutic exploration and treatment.

In the absence of definitive data addressing the issue of the optimal duration of therapy for patients with social anxiety disorder, it is reasonable to maintain pharmacotherapy for at least 1 year once patients experience robust clinical response before considering treatment discontinuation.

Similar to other mood and anxiety disorders, ongoing pharmacotherapy may be necessary for patients to maintain benefits. Patients with social anxiety disorder who experience poor or partial response to initial pharmacotherapy may benefit from cognitive-behavioral therapy as well as a variety of pharmacologic alternative or augmentation strategies. These strategies include combined SSRI and benzodiazepine therapy, MAOIs alone or in combination with benzodiazepines, and other novel interventions, such as gabapentin, buspirone, clonidine, bupropion, nefazodone, venlafaxine, and pramipexole (Figure 4).

CONCLUSION

The past 15 years have seen a steady growth in both research and clinical practice devoted to developing treatment strategies for the management of social anxiety disorder. A number of pharmacologic and cognitive-behavioral therapies have demonstrated a clear benefit for the treatment of social anxiety disorder. In clinical practice, the SSRIs are considered first-line pharmacotherapy for the management of social anxiety disorder because of their broad spectrum of efficacy in commonly comorbid disorders, e.g., major depression, panic disorder, obsessive-compulsive disorder, and greater tolerability compared with other medications. The benzodiazepines and MAOIs also are clearly effective for the treatment of social anxiety disorder. In addition, a number of other pharmacologic strategies have shown potential promise for the treatment of this distressing and often disabling condition.

Drug names: alprazolam (Xanax), atenolol (Tenormin), bupropion (Wellbutrin), buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil), clonazepam (Klonopin), clonidine (Catapres), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), imipramine (Tofranil and others), nefazodone (Serzone), ondansetron (Zofran), paroxetine (Paxil), phenelzine (Nardil), pramipexole (Mirapex), propranolol (Inderal and others), sertraline (Zoloft), tranylcypromine (Parnate), venlafaxine (Effexor).

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