

Treatment of Social Phobia With Antidepressants

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This article reviews evidence for the utility of antidepressant medications in the treatment of social phobia. Monoamine oxidase inhibitors (MAOIs) were the first antidepressants shown to be effective for social phobia, but dietary restrictions and a relatively high rate of adverse effects often relegate MAOIs to use after other treatments have been found ineffective. Reversible inhibitors of monoamine oxidase (RIMAs) hold promise as safer alternatives to MAOIs, but RIMAs may be less effective and are currently unavailable in the United States. Selective serotonin reuptake inhibitors (SSRIs), of which paroxetine has been the best studied in social phobia to date, have recently emerged as a first-line treatment for the generalized subtype of social phobia. The SSRIs are well tolerated and consistently have been shown to be efficacious in controlled trials.

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Early evidence that antidepressants might have utility in the treatment of social phobia emerged in the 1970s when studies found efficacy for monoamine oxidase inhibitors (MAOIs) in patient samples that included both patients with agoraphobia and those with social phobia.¹ In the early 1980s, the MAOI phenelzine was also reported to be particularly effective in patients with atypical depression for reducing interpersonal sensitivity, a feature common to social phobia.² During the 15 years that followed, a variety of small clinical trials of antidepressants further established the efficacy of MAOIs for social phobia, suggested the lack of efficacy for tricyclic antidepressants, and found selective serotonin reuptake inhibitors (SSRIs) efficacious. The turn of the millennium has seen the publication of several large multicenter studies confirming the utility of SSRIs and investigating reversible inhibitors of monoamine oxidase (RIMAs), as well as the first acceptance of social phobia as a drug indication by the U.S. Food and Drug Administration (FDA).

For the treatment of social phobia, antidepressants have advantages similar to those previously reported for antide-

pressant treatment of other anxiety disorders, such as panic disorder and obsessive-compulsive disorder. In particular, the high rate of comorbidity of anxiety disorders with depression³ makes treatment with antidepressants an efficient choice in patients with marked comorbid depression. It should be noted, however, that most controlled trials of antidepressants for social phobia have excluded patients with comorbid major depression or scores above a specified cutoff on depression rating scales. These studies have demonstrated the efficacy of antidepressants for social phobia independent of comorbid depressive symptoms.

Additionally, for SSRIs in particular, high levels of patient acceptance and low liability of abuse in comparison with the benzodiazepines are significant advantages, the latter especially for patients with substance abuse, which is also frequently comorbid with social phobia.³ Finally, some patients unwilling or unable to tolerate the anxiety-provoking aspects of cognitive-behavioral therapy (CBT) may become able to do so after an antidepressant medication has partially controlled their symptoms.

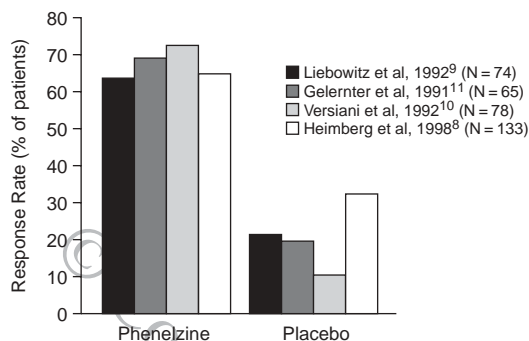
This review will focus on placebo-controlled trials of antidepressant medications. In considering this literature, it is important to take into account the generalizability of the findings. Most treatment trials in patients with social phobia that have reported diagnosis by subtype have predominantly recruited individuals with a generalized subtype—those who fear most social situations—and some trials have specifically limited enrollment to this subtype. It seems likely, therefore, that most of the findings from the literature are relevant to individuals with the generalized subtype of social phobia, but not necessarily relevant to those with nongeneralized forms, such as public-speaking anxiety only. Studies of the generalized subtype reflect the population that is most likely to experience impairment and seek treatment for social phobia.⁴ However, even patients

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Figure 1. Response Rates in Placebo-Controlled Studies of Phenzelzine for Social Phobia



presenting with fears of public speaking as a chief complaint often turn out to have more generalized fears on further investigation.

Most of the existing trials are studies of only 8 to 12 weeks' duration, with just a few studies looking at longer-term treatment. This is an important limitation of the literature because social phobia is often a chronic, lifelong condition.⁵ Data about persistence of effects after discontinuation of antidepressants are also rather limited, and evidence establishing guidelines for optimal duration of treatment is virtually nonexistent.

The clinical trials in individuals with social phobia have used a variety of different outcome measures, which must be considered when comparing findings across studies. Many have used a categorical measure of response, such as the Clinical Global Impressions scale (CGI), which categorizes patients on a 7-point scale beginning with 1 = very much improved, 2 = much improved, 3 = minimally improved, and 4 through 7 for patients unchanged or worse. Most studies have classified responders as patients rated much or very much improved at last observation. The most commonly used continuous measure of social phobia severity has been the Liebowitz Social Anxiety Scale (LSAS).⁶ The LSAS rates severity of anxiety and avoidance on 4-point scales for 24 different social or performance situations, and it is well validated.⁷ Unless otherwise stated, results reviewed here for each trial will pertain to the intent-to-treat sample of all patients randomized.

IRREVERSIBLE MONOAMINE OXIDASE INHIBITORS

As was described above, irreversible MAOIs were one of the first classes of medications studied in social phobia, and the efficacy of phenzelzine has now been established in 4 double-blind, placebo-controlled studies (Figure 1).⁸⁻¹¹ There is also some evidence from direct comparisons suggesting that phenzelzine has advantages in efficacy over

some other active treatments, including the benzodiazepine alprazolam, the β -blocker atenolol, the RIMA moclobemide, and CBT.

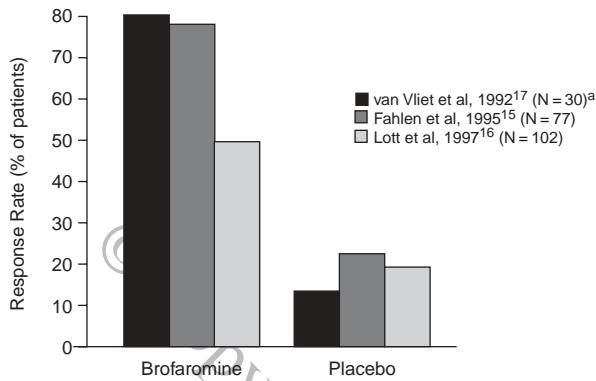
The most recent published study of phenzelzine for social phobia compared it with cognitive-behavioral group therapy (CBGT), placebo, and an educational-supportive therapy control group (N = 133).⁸ Both phenzelzine and CBGT were superior to control conditions, and phenzelzine was superior to CBGT on some measures after both 6 and 12 weeks of treatment. Most phenzelzine-treated patients maintained their gains during a 6-month continuation of treatment, and about half remained well during the 6 months after treatment was discontinued.¹² In a prior study, Liebowitz et al.⁹ compared phenzelzine and atenolol in outpatients (N = 74), most of whom had the generalized subtype of social phobia. After 8 weeks of treatment, 64% of patients were much improved on phenzelzine treatment, significantly more than the 23% treated with placebo ($p = .003$) and 30% treated with atenolol ($p = .02$).

Phenzelzine was compared with moclobemide (a RIMA not currently marketed in the United States) and placebo in a double-blind trial in Brazil (N = 78).¹⁰ After 8 weeks of treatment, both phenzelzine and moclobemide were significantly superior to placebo. After 16 weeks of treatment, 73% of patients receiving phenzelzine and 54% of patients receiving moclobemide were much improved, significantly more than the 12% of patients receiving placebo ($p < .001$ and $p < .001$, respectively).

Phenzelzine, alprazolam, pill placebo, and CBGT were compared over 12 weeks of treatment (N = 65) in a study conducted at the National Institute of Mental Health.¹¹ This study differed from those above in that few patients had the generalized subtype, and treating clinicians actively encouraged all patients to enter phobic situations each week. By categorical outcome (response vs. nonresponse), the authors found a trend toward superiority for phenzelzine ($p = .09$). They identified unequivocal improvement in 69% of the phenzelzine arm, compared with 38% of the alprazolam arm, 24% of the CBGT arm, and 20% of the placebo arm. There were few other group differences, however. At follow-up 2 months after discontinuation of treatment, phenzelzine patients retained most of their improvement and were significantly less impaired than were alprazolam- or placebo-treated patients.

Selegiline, another irreversible MAOI, at daily doses ≤ 10 mg is specific for monoamine oxidase B (MAO-B). The MAO-B isozyme is known to degrade dopamine, norepinephrine, and phenylethylamine, but ingested tyramine is deaminated by monoamine oxidase A (MAO-A); this specific inhibition allows for relaxation of MAOI dietary restrictions with low-dose selegiline use. Simpson et al.¹³ conducted a 6-week open trial of low-dose selegiline in 16 subjects, most with generalized social phobia (N = 12). The response rate was only 33% (3/9) among completers, lower than in studies of MAOIs that inhibit both MAO-A and

Figure 2. Response Rates in Placebo-Controlled Studies of Brofaromine for Social Phobia^a



^aResults based on self-assessment.

MAO-B. Tranylcypromine, a nonspecific irreversible MAOI like phenelzine, appeared effective in a single open trial,¹⁴ with 79% of patients rated as experiencing moderate or marked improvement.

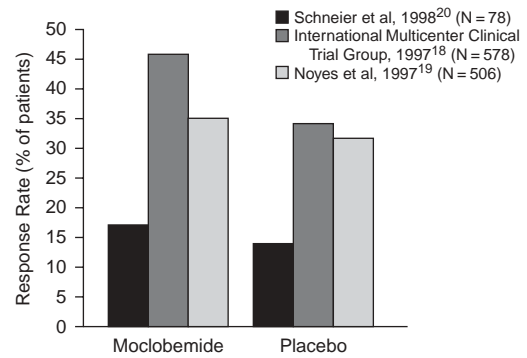
In summary, MAOIs, of which phenelzine is best studied, may be the most efficacious class of medications for social phobia. They are often held in reserve for refractory patients because of the inconvenience of required dietary restrictions and the risk of a potentially dangerous hypertensive reaction. The low-tyramine diet prohibits most cheeses and a variety of other foods, beer, and red wines. Sympathomimetic medications and other antidepressants must also be avoided. Additionally, adverse effects at effective doses (usually 45–90 mg/day for phenelzine) are common, including postural hypotension, sedation, sexual dysfunction, and weight gain. Nevertheless, many patients who find their response to phenelzine superior to that from other treatments are more than willing to put up with its drawbacks.

REVERSIBLE INHIBITORS OF MONOAMINE OXIDASE

The dietary restrictions and relatively high rate of adverse effects of irreversible MAOIs have spurred further research into less problematic related compounds. Two newer MAOIs, moclobemide and brofaromine, are selective for the A isoenzyme of monoamine oxidase and bind to monoamine oxidase reversibly. The features of these RIMAs result in a much lower risk of hypertensive crisis from tyramine-containing foods and consequently less need for dietary caution. In addition, these RIMAs appear to be generally better tolerated than the irreversible MAOIs. Unfortunately, however, they are not without drawbacks.

Three double-blind studies found brofaromine, which may also have SSRI activity, more effective than placebo

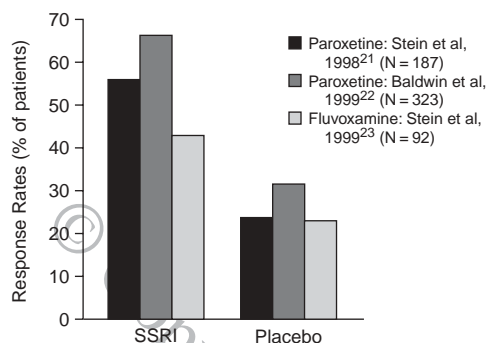
Figure 3. Response Rates in Placebo-Controlled Studies of Moclobemide for Social Phobia



for social phobia (Figure 2).^{15–17} In one clinical trial,¹⁵ 78% (of 77 patients) responded to brofaromine, compared with a placebo response rate of 23% ($p < .001$). A second randomized controlled trial found that among 102 individuals with social phobia, 50% of those receiving brofaromine versus 19% of those receiving placebo were rated significantly improved ($p = .001$).¹⁶ Effect size for magnitude of improvement was moderate, and the mean score on the LSAS (62.6) remained in the symptomatic range at study completion. In a smaller clinical trial ($N = 30$), 80% of brofaromine patients, but only 14% of those receiving placebo, considered themselves responders.¹⁷ Despite these encouraging findings, brofaromine is not marketed and currently remains unavailable.

The controlled trial of moclobemide, phenelzine, and placebo¹⁰ described above demonstrated encouraging results, with a 54% response rate for moclobemide, but this magnitude of response has not been replicated in subsequent trials (Figure 3).^{18–20} A multicenter controlled trial of moclobemide¹⁸ found only modest efficacy for moclobemide (600 mg/day) in a very large sample ($N = 578$). After 12 weeks, 47% of the moclobemide sample versus 34% of the placebo group were rated very much improved ($p = .002$); reductions in social phobia symptoms were 38% and 25%, respectively, in this group. A second large multicenter study ($N = 506$)¹⁹ found no evidence of efficacy for moclobemide for social phobia in a fixed dose-response placebo-controlled trial. The response rate was 35% for individuals taking 900 mg/day of moclobemide, compared with 32% of those taking placebo (NS). Consistent with these findings, a National Institute of Mental Health–sponsored trial²⁰ recently found minimal efficacy for moclobemide ($N = 77$, mean maximum daily dose = 728 mg). At week 8, response rates were 17.5% for the moclobemide group versus 13.5% for the placebo group. As mentioned earlier, moclobemide is marketed in Canada and in Europe, but not in the United States.

Figure 4. Response Rates in Placebo-Controlled Studies of Selective Serotonin Reuptake Inhibitors (SSRIs) for Social Phobia



SELECTIVE SEROTONIN REUPTAKE INHIBITORS

SSRIs have emerged as a first-line treatment for social phobia on the basis of several recent large placebo-controlled trials (Figure 4).²¹⁻²³ Paroxetine was initially studied in a 12-week open trial²⁴ of patients with generalized social phobia and yielded a response rate of 77%. After double-blind, randomized discontinuation of 16 patients, 63% of those switched to placebo relapsed, versus only 13% of patients who continued on paroxetine treatment. These findings of efficacy were confirmed in a multicenter, randomized, 11-week controlled trial (N = 187) of paroxetine in generalized social phobia.²¹ Paroxetine was effective in 55% of patients, compared with 24% for placebo ($p < .001$; mean daily dose of paroxetine = 37 mg). A multicenter 12-week controlled trial²² in Europe (N = 323) also reported efficacy, with a response rate of 66% for paroxetine versus 32% for placebo ($p < .001$). These findings resulted in paroxetine's becoming the first medication approved by the FDA for the indication of social phobia.

Fluvoxamine has also been studied as a treatment for social phobia in a multicenter, randomized controlled trial (N = 92).²³ Significantly more patients responded to fluvoxamine treatment (43%, mean daily dose = 202 mg) than placebo (23%; $p = .04$). An earlier, small controlled trial had also found fluvoxamine to be efficacious.²⁵ A small double-blind crossover-design study²⁶ of sertraline versus placebo in social phobia (N = 12) also found significant effects for active medication.

Other SSRIs have been studied in open trials only. Fluoxetine was the first SSRI studied for social phobia. Three open trials²⁷⁻²⁹ with fluoxetine found evidence of efficacy in social phobia. A naturalistic open trial³⁰ of citalopram (N = 22) noted improvement in 86% of patients, some of whom met the criteria for comorbid major depression (45%) and panic disorder (23%).

For the generalized subtype of social phobia, the SSRIs have emerged as the likely treatment of choice because of

their established efficacy and lower risk of adverse events. These agents have the additional benefits of antidepressant efficacy for frequently concomitant depression and relative safety when used in patients with a history of substance abuse. Although paroxetine is the only medication currently approved for the treatment of social phobia by the FDA, there is no evidence that the other SSRIs differ in efficacy. Dosage appears similar to the standard doses used for depression, and the most common side effects include nausea, sedation, and sexual dysfunction.

OTHER ANTIDEPRESSANTS

Studies of other antidepressants are currently limited to open trials. A retrospective chart review³¹ observed that venlafaxine (mean daily dose = 147 mg) was effective in 8 of 9 patients with social phobia, 5 of whom had previously failed to respond to a moderate dose of an SSRI. A second open trial³² of venlafaxine in 12 outpatients with a history of nonresponse to SSRIs observed a response rate of 83%. An open trial³³ of nefazodone (N = 23, mean dose = 435 mg/day) found a response rate of 70% over a 12-week period among patients with generalized social phobia. There are also case reports of effective treatment with bupropion.³⁴ If the efficacy of these antidepressants is confirmed in controlled trials, these agents hold promise as alternatives to SSRIs, second-line treatments for patients who do not respond to SSRIs or cannot tolerate them because of sexual dysfunction (nefazodone and bupropion), and augmenters of partial response to SSRIs (bupropion).

BUSPIRONE

Although not generally considered an antidepressant, buspirone will be reviewed here as another serotonergic agent (in this case, acting at the serotonin-1A receptor) that has been studied for social phobia. Buspirone first appeared promising in a pair of open trials,^{35,36} one of which³⁶ found a higher response rate (67%) among patients who tolerated a dose of 45 mg/day or greater. Two subsequent controlled trials^{37,38} using relatively low doses of buspirone have failed to confirm its efficacy. In one of these trials,³⁷ neither buspirone alone (mean daily dose = 30 mg) nor its combination with CBT was superior to placebo or CBT for musicians with performance anxiety and predominantly nongeneralized social phobia. Another controlled trial³⁸ (N = 30) with moderately symptomatic individuals with social phobia found minimal response rates for both placebo (13%) and buspirone (27%) in doses up to 30 mg daily. Finally, Van Ameringen and colleagues³⁹ conducted an uncontrolled augmentation study in which buspirone (mean dose = 45 mg/day) was added to SSRI treatment in 10 partial responders and produced modestly positive results. Improvement as measured by the CGI was noted in 70% of patients, but no sig-

nificant changes were noted on continuous outcome measures of anxiety and avoidance.

SOME GENERAL PRINCIPLES OF TREATMENT

Antidepressants have come to represent a valuable part of the social phobia treatment armamentarium, which currently includes other medications, such as clonazepam and gabapentin, and cognitive-behavioral therapies. The rational basis for preferential selection of a treatment modality is limited, however, because of the small number of trials comparing effective treatments and the lack of empirical data about patient characteristics that might predict responsiveness to specific treatments.

Clinically, antidepressants in general and SSRIs in particular may be the treatment of choice for patients with generalized social phobia who prefer medication to psychotherapy or who have marked depression or other comorbidity that is responsive to antidepressants. The antidepressants appear to work more quickly than CBT⁸ and lack the abuse potential of benzodiazepines. The MAOI phenelzine appears to result in a greater magnitude of improvement than does CBT.⁸ On the other hand, patients need to be informed that on discontinuation of antidepressants there seems to be a substantial rate of relapse. Although some patients do maintain gains, CBT may offer long-term advantages in this respect.¹² The combination of antidepressant and CBT has been little studied. Nevertheless, it seems reasonable that pretreatment with antidepressants might enable fearful patients to engage in CBT, and active encouragement of exposure to specific situations may potentiate response to antidepressants. In highly avoidant patients, experience suggests that more formal exposure instructions, cognitive retraining, and social skills training may be necessary to maximize response to drug treatment.

Patients with social phobia can usually start with standard doses of antidepressant and do not seem particularly susceptible to early hyperstimulation unless they have comorbid panic disorder. Antidepressant response in social phobia is typically seen by the third or fourth week of treatment, but occasionally does not become clinically apparent until 8 weeks or more. Given that as many as half of the patients in short-term clinical trials of SSRIs do not achieve a clinically significant response, it seems reasonable to switch medications if no benefit is seen during a 6- to 8-week initial trial or to consider dosage increase or augmentation in the case of a partial response that has reached a plateau. When improvement occurs, progress may continue over a period of months or more, as patients gradually confront and master situations they have been avoiding. Optimal duration of treatment has received little study, but many clinicians will attempt to discontinue medication 6 to 12 months after a patient has achieved a stable plateau of improvement. There are no established

predictors of which patients will maintain gains after discontinuation of treatment, and long-term treatment may be required to maintain benefits for some.

Most responders to antidepressants experience a marked improvement in social phobia symptoms, including less anxiety and avoidance; this improvement is reflected in improved occupational and/or social functioning. It is relatively uncommon, however, for individuals with chronic generalized social phobia to experience complete remission, as might be seen in patients with uncomplicated panic disorder. Many patients with social phobia will be reassured by the notion that medication treatment is unlikely to transform their personality into something alien to them, but rather is more likely to lift the cloud of anxiety that prevents their individuality from coming through.

Anecdotal and open-trial evidence suggests that some SSRI nonresponders may benefit from switching to venlafaxine or an MAOI. A 2-week washout period (5 weeks for fluoxetine) is required before starting an MAOI after an SSRI because of the risk of serotonin syndrome. Other options include switching to clonazepam, gabapentin, or another SSRI. Partial responders to an SSRI may benefit from buspirone augmentation, as has been supported by 1 open trial,³⁹ or possibly by augmentation with clonazepam, gabapentin, bupropion, or as-required use of β -blockers. Antidepressant side effects in social phobia are similar to those seen in treatment of depression, but occasionally may be particularly distressing if they cause symptoms that increase self-consciousness (e.g., increased sweating, sexual dysfunction in a patient with performance fears associated with social phobia).

CONCLUSION

The past decade has seen the application of several classes of antidepressants to the treatment of social phobia. SSRIs have emerged as a first-line treatment for the generalized subtype of social phobia. Standard MAOIs have been shown to be highly effective for social phobia, and research continues on second-generation MAOIs, which may be more acceptable to patients. Preliminary reports suggest that newer antidepressants, including venlafaxine, bupropion, and nefazodone, may also have a role in the treatment of social phobia.

Drug names: alprazolam (Xanax and others), atenolol (Tenormin and others), bupropion (Wellbutrin), buspirone (BuSpar), citalopram (Celexa), clonazepam (Klonopin and others), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), selegiline (Eldepryl and others), sertraline (Zoloft), tranylcypromine (Parnate), venlafaxine (Effexor).

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