Pharmacotherapy of Social Anxiety Disorder

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Antidepressants and high-potency benzodiazepines have been used successfully to treat patients with social anxiety disorder. This review considers the efficacy of irreversible and reversible inhibitors of monoamine oxidase, selective serotonin reuptake inhibitors, high-potency benzodiazepines, and beta-blockers and presents the response rates for each of these classes. Aspects of the social anxiety syndrome that are sensitive to drug treatment are discussed, and the data relating to relapse following treatment discontinuation are presented. Predictors for negative treatment outcome following completion of acute treatment trials are reviewed. *(J Clin Psychiatry 1998:59[suppl 17]:47–51)*

Social anxiety disorder/social phobia has been recognized as a discrete diagnostic condition that is associated with significant impairment in work, educational, social, and family function.[1] It is a distressing and often debilitating condition that is frequently allied with comorbid depression and alcohol and other substance abuse. The need for effective treatment strategies has been addressed in recent years, and in addition to the beta-blockers, which were initially considered of use in the treatment of performance-related anxiety, the efficacy of antidepressants and anxiolytics has been investigated.

The goals of pharmacotherapy for social anxiety disorder are to:

- relieve fearful affect and cognitions,
- reduce anticipatory anxiety,
- attenuate avoidance behavior,
- reduce the autonomic and physiologic symptoms of arousal and anxiety,
- and produce a concomitant improvement in disability and quality of life.

Pharmacotherapy with antidepressants (both reversible and irreversible monoamine oxidase inhibitors [MAOIs] and selective serotonin reuptake inhibitors [SSRIs]), with benzodiazepine anxiolytics, and with beta-blockers has been studied. This review presents the evidence in support of efficacy for each of these drug classes and considers, in addition, which aspects of the social anxiety syndrome are responsive to drug treatment. Predictors of drug response and relapse rates for drug discontinuation are also discussed.

PHARMACOTHERAPY

Monoamine Oxidase Inhibitors

The irreversible inhibitor of monoamine oxidase phenelzine has been studied in the treatment of social anxiety by at least 3 groups[2–4] in over 200 subjects, and in all of these clinical trials it produced a positive response with a rate of 63% to 75%, compared with a placebo response rate of about 20% or less. Although the efficacy of phenelzine in improving the symptoms of social anxiety has been clearly demonstrated, the need for caution when prescribing the drug due to its well-documented interaction with tyramine-containing food has limited its utility. As a result, phenelzine is rarely considered as a first-line treatment for social anxiety disorder.

Moclobemide, a reversible inhibitor of monoamine oxidase-A, has demonstrated equivocal efficacy in the treatment of social anxiety disorder. The results from 4 placebo-controlled clinical trials have now been published,[4–7] and whereas the earlier trials by Versiani et al.[4] and the International Multicenter Clinical Trial Group[7] have reported moclobemide to be more effective than placebo, the more recent studies have described less robust results (Figure 1). The large multicenter United States study[5] assessed fixed doses of moclobemide (75, 150, 300, 600, and 900 mg/day) in 523 subjects and noted that 35% of subjects taking the highest dose level and 33% of those taking placebo were considered responders at the end of the 12-week dosing period—a difference that was obvi-

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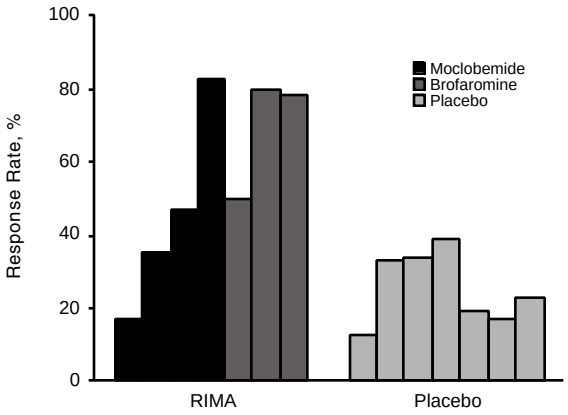
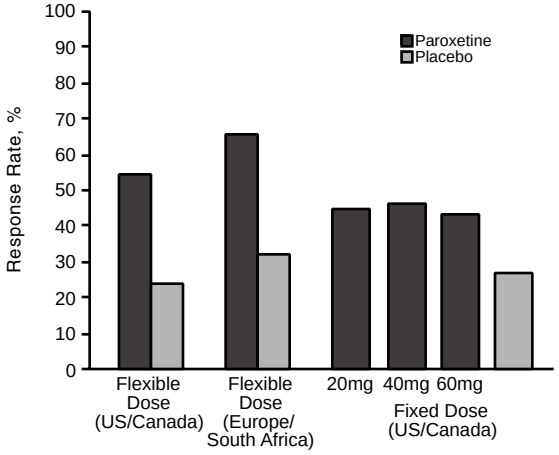
Figure 1. Response Rates for Moclobemide and Brofaromine (Reversible MAO Inhibitors) in Social Anxiety Disorder From Placebo-Controlled Trials*



*Data from references 4–10. In studies in the treatment of social anxiety disorder, RIMA treatment has, overall, elicited a higher response rate than placebo. However, improvement was shown to be less robust in more recent studies than in earlier studies. Abbreviation: RIMA=reversible monoamine oxidase inhibitor.

Figure 2. Response Rates for Paroxetine in Social Anxiety Disorder From Placebo-Controlled Trials*



*From reference 13 and SmithKline Beecham Pharmaceuticals, data on file, 1998.

ously not significant. Similarly, no separation between active drug and placebo was noted in the study by Schneier et al.,[6] in which 77 patients were randomly assigned to either moclobemide or placebo and a response rate as low as 17.5% was recorded for moclobemide, compared with 13.5% for placebo. Schneier et al. concluded that "small effect sizes for all outcome measures suggest that the magnitude of its [moclobemide's] clinical effect is small."[6(p70)]

Three studies have investigated the efficacy of brofaromine in placebo-controlled studies of 10 to 12 weeks' duration.[8–10] In a multicenter trial in the United States that included 102 patients with social anxiety, the response rate with brofaromine was approximately 50% compared with 19% in the placebo group.[9] Two further studies conducted in Europe[8,10] found a positive response to brofaromine which was significantly greater than that observed with placebo (see Figure 1).

Although brofaromine has produced more promising results than moclobemide, it is no longer commercially available. The limited clinical efficacy of moclobemide does not support its use as a first-line treatment for social anxiety disorder.

Selective Serotonin Reuptake Inhibitors

The most extensive database for the treatment of social anxiety disorder with any drug exists for paroxetine. Following initial promising results in 2 small open studies,[11,12] 3 large multicenter, placebo-controlled, clinical trials involving more than 850 patients with generalized social anxiety disorder were initiated and have recently been completed. Two of the studies were conducted in North America, and the third study was conducted in Europe and South Africa. All 3 studies involved a 12-week dosing period with paroxetine; 2 studies utilized a flexible dosing regimen in the 20- to 50-mg/day range, while the third was a dose-finding study (paroxetine 20, 40, and 60 mg/day).

Table 1. Improvement in Disability With Paroxetine in 3 Large Multicenter Studies*

Life Aspect	Flexible Dose (US/Canada) 20–50 mg	Flexible Dose (Europe/ South Africa) 20–50 mg	Fixed Dose (US/Canada) 20 mg	40 mg	60 mg
Work	0.8[a]	1.2[b]	0.8	0.6	0.6
Social	1.3[b]	0.7[a]	1.4[a]	0.8	1.1[a]
Family	0.4	1.0[b]	0.5	0.3	0.3

*From reference 13 and SmithKline Beecham Pharmaceuticals, data on file, 1998. Values shown are change in mean Sheehan Disability Scale scores (paroxetine minus placebo) from baseline to endpoint.
[a]p<.05; paroxetine vs. placebo.
[b]p<.001; paroxetine vs. placebo.

Response rates to paroxetine (as assessed by the proportion of patients "much" or "very much improved" on the Clinical Global Impressions-Improvement scale) are illustrated in Figure 2. In all 3 studies, a significantly greater proportion of patients receiving paroxetine treatment were rated as responders compared with those receiving placebo.

The effect of paroxetine treatment on the patient's ability to undertake routine daily activities was assessed using the Sheehan Disability Scale, which covers areas relating to work, social, and family life. A positive improvement in social functioning with paroxetine was observed in all 3 clinical trials and in work situations in 2 of the trials. As these are aspects of the subject's life that are particularly troubled by social anxiety, this represented a considerable improvement in quality of life (Table 1).

For the other members of the SSRI drug class, only limited clinical data are available in the form of small controlled trials, open studies, or case series. Two small placebo-controlled studies have reported initial findings with sertraline[14] and fluvoxamine[15] in patients with social anxiety. The sertraline trial was a crossover, flexible-dose (50–200 mg/day) design and included only 10 patients; nevertheless, a 50% response rate was observed with sertraline, compared with only 9% or 10% with placebo. In a 12-week, placebo-controlled trial in 30 subjects with social anxiety disorder, a substantial improvement was observed in 46% of patients receiving fluvoxamine (150 mg/day) compared with only 7% receiving placebo. An open study with fluoxetine in 16 patients reported that 10 of the patients were considered to be responders at the end of treatment,[16] while a case series describing 3 patients with social anxiety disorder treated with citalopram has suggested that this drug also has efficacy in this condition.[17] Double-blind studies will be needed to further investigate these findings.

In conclusion, controlled data supporting the efficacy of paroxetine, sertraline, and fluvoxamine in the treatment of social anxiety disorder are available, although by far the most extensive database exists for paroxetine. Preliminary findings with the other SSRIs need to be further validated in large, controlled studies.

Benzodiazepines

There have been 2 main studies of the efficacy of benzodiazepines in the treatment of social anxiety disorder. Alprazolam was compared with phenelzine and cognitive-behavioral group treatment in a placebo-controlled study of 65 subjects.[2] The response rate for alprazolam was modest at approximately 38%, compared with 20% for placebo. Furthermore, patients who were treated with phenelzine were rated by clinicians as showing greater improvement on a measure of work and social disability than patients treated with either alprazolam or placebo.

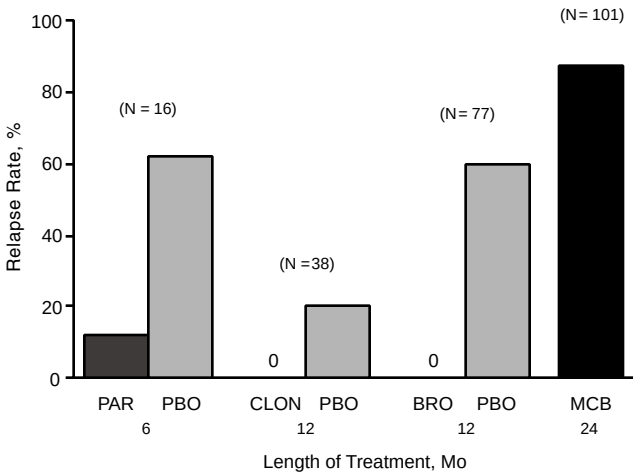
A more robust response to clonazepam was reported in a placebo-controlled clinical trial in 75 subjects with social anxiety.[18] A 78% response rate was observed with clonazepam over the 10-week trial, compared with a 20% response rate with placebo.

In conclusion, only limited data are available to support the efficacy of the benzodiazepines in the treatment of social anxiety disorder, and whereas 1 of the 2 main studies provides positive data, the other study, with alprazolam, suggests only modest levels of efficacy.

Beta-Blockers

The beta-blockers have been used by performing artists to decrease performance-related anxiety[19] owing to their ability to attenuate some of the autonomic symptoms associated with arousal and anxiety (e.g., tachycardia, tremor, sweating). However, the beta-blockers have limited efficacy in the treatment of generalized social anxiety disorder, a view that is supported by the findings of a placebo-controlled comparison of atenolol and phenelzine in 74 patients with social anxiety disorder.[3] Overall response rates for atenolol were not significantly different from placebo, whereas phenelzine was superior to both of the other treatments. Atenolol has also been compared with behavioral therapy in a placebo-controlled trial conducted in 72 subjects; the response to atenolol did not differ from that of placebo.[20]

Figure 3. Relapse Prevention With Maintenance Therapy With Paroxetine, Clonazepam, Brofaramine, Moclobemide, and Placebo*



*Data from references 9, 12, 22, and 23. Abbreviations: BRO=brofaromine, CLON =clonazepam, MCB =moclobemide, PAR = paroxetine, PBO=placebo.

RELAPSE PREVENTION

Relapse Rates

Four clinical studies have investigated the rate of relapse following treatment discontinuation (Figure 3). Stein et al.[12] conducted an 11-week open-label study of paroxetine in 36 patients with generalized social anxiety disorder and then randomly assigned the responders to continue, double-blindedly, taking the same dose of drug or placebo (after a taper period) for a further 12 weeks. The relapse rate for those patients who were switched to placebo was 62%, whereas only 12% of those who continued with paroxetine relapsed. These results support the view that relapse rates can be high if medication is discontinued too early and suggest that treatment periods in excess of 3 months are required.

A considerably lower level of relapse was observed when patients were continued on pharmacotherapy for a period of 6 months before switching to placebo. On completion of a 6-month open-label trial with clonazepam (1–2.5 mg/day), patients were randomly assigned either to continue for 6 more months on drug treatment or to

withdraw very slowly to placebo.[21] There was a 0% relapse rate in those who remained on treatment with the drug for 12 months, whereas 20% of those patients who switched from clonazepam to placebo relapsed during the 12-month period.

On completion of a 12-week, placebo-controlled trial of brofaromine in 77 subjects with social anxiety, a 9-month follow-up treatment period was undertaken.[8] The authors noted that while the brofaromine group improved further, 60% of the placebo responders from the acute treatment period relapsed during the 9-month follow-up.[8]

The design of such treatment discontinuation trials appears to be of critical importance. Following 2 years of open-label treatment with moclobemide (N = 101), the drug was abruptly withdrawn and a relapse rate of 88% was observed.[22] This high level of relapse even after 2 years of treatment would appear to reflect, at least in part, the dependency on the therapist and/or treatment program that develops in a patient over such a prolonged period, and perhaps reflects the abrupt discontinuation of the medication.

Candidates for Long-Term Pharmacotherapy

Although there is a relative paucity of information on the long-term treatment of social anxiety disorder, from the preceding section on relapse it is clear that maintenance therapy for periods of up to 1 year can maintain improvement and reduce the rate of subsequent relapse. Indications for long-term pharmacotherapy include patients with persistent ongoing significant symptoms, the presence of comorbidity, the presence of early onset with severe avoidant personality, and a prior history of relapse.

WHICH ASPECTS OF SOCIAL ANXIETY DISORDER RESPOND TO DRUG THERAPY?

The symptoms most feared by patients are the physiological ones,[15] trembling in particular, but also blushing. This raises the question of whether the physiologic symptoms, which often drive the patient to treatment, do in fact respond to pharmacotherapy.

Two rating scales include an assessment of physiologic symptoms. The Brief Social Phobia Scale (BSPS) is an observer-based scale that considers the different domains of social anxiety—fear, avoidance, and physiologic arousal[23]—whereas the Social Phobia Inventory (SPIN) is a new self-rating scale that also assesses physiologic symptoms (J.R.T.D., unpublished data, 1998).

In 2 separate placebo-controlled trials of an anticonvulsant and an antidepressant, improvement in the 3 different symptom clusters (fear, avoidance, and physiologic symptoms) was assessed using both the BSPS and the SPIN (reference 23 and J.R.T.D., unpublished data, 1998). The 2 active treatments produced an improvement in all 3 symptom clusters compared with placebo when assessed using either scale. This finding supports the view that the physiologic symptoms of social anxiety are also sensitive to drug treatment.

Table 2. Overall Comparison of Drug Groups in Generalized Social Anxiety Disorder*

Drug Class	Overall Efficacy	Tolerance	Serious Risks	Speed of Onset	Effectiveness for Comorbid Depression/ Anxiety
MAOI-IRs	++	–	++	+	+
MAOI-Rs	±	+	±	+	+
SSRIs	++	+	–	+	+
Benzodiazepines	+	+	–	++	–
Beta blockers[a]	–	+	–	–	–

*Abbreviations: MAOI-IRs =irreversible, nonselective monoamine oxidase inhibitors; MAOI-Rs = reversible, selective MAOI-A inhibitors; SSRIs = selective serotonin reuptake inhibitors. Symbols: ++ =strong, + =acceptable, ± =equivocal, –= minimal/poor.
[a]Of limited benefit: used only in performance-related social anxiety.

The sensitivity of fearful cognitions to treatment with pharmacotherapy has been evaluated in a placebo-controlled trial of clonazepam.[18] The benzodiazepine reduced the score on the Negative Evaluation Scale[24] by week 6 of treatment, whereas placebo was ineffective (clonazepam, 25.5 to 15.4; placebo, 25.3 to 13.0; $p < .0001$).

PREDICTORS OF OUTCOME

Although social anxiety disorder is thought to be a chronic disorder, little is known about its long-term course in patients who engage in acute treatment studies. Sutherland et al.[25] conducted a 2-year follow-up study of 56 subjects who had participated in a brief, placebo-controlled treatment trial of clonazepam. Two variables were found to be significant predictors of long-term outcome: baseline severity of illness (whether it be social anxiety symptoms, interpersonal sensitivity, anxiety, or depression) and the original treatment condition. Subjects with less severe symptoms at baseline and the group treated with clonazepam during the acute treatment trial manifested a superior outcome 2 years later. Alcohol abuse was associated with a poor outcome in a study of 32 patients who entered a 1-year drug treatment trial with tranylcypromine,[26] and a positive family history for social anxiety disorder has also been linked with negative outcome. Interestingly, Slaap et al.[27] noted that nonresponders in clinical trials with brofaromine and fluvoxamine had a higher systolic blood pressure and a higher heart rate than did responders. This might be taken to indicate that nonresponders have higher baseline levels of sympathetic arousal. Finally, personality disorder, which is either borderline or passive-dependent in nature, was also a negative predictor.[27]

CONCLUSIONS

Controlled efficacy data are available for the antidepressants (SSRIs and MAOIs) and the high-potency ben-

zodiazepines in the treatment of social anxiety disorder (Table 2). The largest body of clinical evidence supports the efficacy of paroxetine in this condition, and it is rapidly being considered as a first-line treatment. The need for treatment-associated dietary restrictions with the irreversible MAOI phenelzine has limited its utility as first-line pharmacotherapy for social anxiety disorder, and recent data published with moclobemide have suggested that this drug has only modest efficacy. Brofaromine is no longer available. The high-potency benzodiazepine clonazepam is also effective in social anxiety disorder; however, concerns over its use in patients who abuse alcohol and its lack of activity in treating comorbid depression may ultimately restrict its use to patients without these comorbidities.

Drug names: alprazolam (Xanax), atenolol (Tenormin), clonazepam (Klonopin), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate).

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