Benzodiazepines and Anticonvulsants for Social Phobia (Social Anxiety Disorder)

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Both benzodiazepines and conventional anticonvulsants have been evaluated as treatments for social phobia (social anxiety disorder). Among the benzodiazepines, clonazepam is the best studied, although there is reason to expect that all benzodiazepine anxiolytics would be effective for this condition. Among the anticonvulsants, gabapentin and pregabalin, an analogue of γ-aminobutyric acid (GABA), have been shown to be more effective than placebo in double-blind studies. Other than a small negative open study of valproic acid for social phobia, there is a paucity of information on whether other anticonvulsants might be useful for this condition.

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Linking benzodiazepines and anticonvulsants together as treatments for social phobia, also known as social anxiety disorder, is less abstruse than it might appear since benzodiazepines have clearly defined antiseizure activity. U.S. Food and Drug Administration–approved uses of clonazepam include Lennox-Gastaut syndrome and akinetic and myoclonic seizures, and clorazepate is approved as adjunctive therapy for partial seizures. Parenteral diazepam and lorazepam are established treatments for status epilepticus. Be that as it may, the benzodiazepines have never been considered anticonvulsants per se and, consequently, they merit separate discussion.

BENZODIAZEPINES

It is only reasonable that these prototypical anxiolytics were studied as treatments for social phobia. After all, a survey done at the 1983 annual meeting of the American College of Cardiology[1] found that some presenters acknowledged taking diazepam to relieve their performance anxiety (a far greater number took a β-blocker). Diazepam (2 mg) did not fare as well when it was compared with nadolol (a β-blocker) and placebo in a single-dose, double-blind, crossover study of performance anxiety in 31 musicians.[2] Not only did diazepam fail to benefit performance that was assessed both subjectively and objectively, but it also caused minor worsening of performance.

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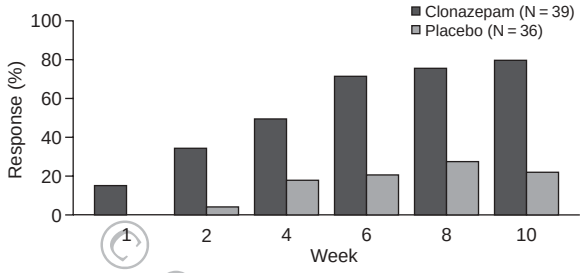
Alprazolam was the next benzodiazepine to arrive on the social phobia scene in the form of 2 open studies in the late 1980s. Lydiard et al.[3] described marked improvement in 4 socially phobic patients treated for varying lengths of time with doses ranging from 3 to 8 mg/day. In an 8-week study, Reich and Yates[4] found that all 14 socially phobic patients treated with alprazolam (maximum mean daily dose = 2.9 mg; range, 1–7 mg) were either very much or much improved. They also found that avoidant personality traits improved substantially in these patients.[5]

Alprazolam was last evaluated as a potential treatment for social phobia in a complex 12-week study[6] of 65 patients (26 with the generalized type) randomly assigned to (1) cognitive-behavioral therapy, (2) phenelzine and self-exposure, (3) alprazolam and self-exposure, and (4) pill-placebo and self-exposure. The mean alprazolam dose was 4.2 mg/day (range, 2.1–6.3 mg). There were no statistically significant differences among the 4 groups with regard to unequivocal response or in the primary outcome measures (perhaps because the beneficial effect of self-exposure was a common contaminating factor). In addition, 2 months after treatment ended, the relapse rate was highest in the alprazolam group.

Clonazepam has been the most extensively studied benzodiazepine for the treatment of social phobia. A cluster of encouraging open studies appeared in 1990 (5 subjects who all responded to a mean daily dose of 3 mg[7]; 10 patients receiving a mean dose of 2.75 mg/day [range, 1–6 mg/day] who improved substantially more than 10 non-treatment controls[8]; and 9 of 11 patients who responded to daily doses ranging from 0.7 to 3 mg[9]). More recently, Versiani et al.[10] found that 86.8% of 40 patients treated openly with clonazepam (mean daily dose = 4.8 mg) improved in a 16-week study. Despite the generous dosing, there were only 2 adverse event dropouts, both due to sexual dysfunction.

The Davidson group at Duke University has done the most extensive evaluation of clonazepam for social pho-

Figure 1. Response Rates for Clonazepam Versus Placebo in Social Phobia[a]



[a]Data from Davidson et al.[12] All comparisons statistically significant at $p < .02$.

Table 1. Common Adverse Events in a 10-Week, Double-Blind, Placebo-Controlled Study of Clonazepam for Social Phobia[a]

Adverse Event	Clonazepam[b] (%)	Placebo (%)	p Value
Anorgasmia	44	6	< .0001
Unsteadiness	62	21	< .0001
Forgetfulness	44	21	< .03
Poor concentration	35	15	< .05
Dizziness	29	0	< .001

[a]Data from Davidson et al.[12]
[b]Only unsteadiness and dizziness were persistent and more severe than with placebo. Other side effects were more frequent but mild.

bia. In 1991, they reported an open-label study[11] of 26 patients treated for a mean of 11.3 months (range, 1–29 months) with a maximum mean daily dose of 2.1 mg.A total of 84.6% of the patients (22/26) were rated as very much or much improved on the Clinical Global Impressions scale (CGI). It was reassuring to note that the mean daily dose of clonazepam at the time of final evaluation had actually decreased to 0.94 mg. The majority of patients (57.7%) had side effects consistent with a benzodiazepine that were managed mainly by dose reduction. The stage was now set for a double-blind, placebo-controlled study.

Davidson et al.[12] randomly assigned 75 patients with social phobia (DSM-III-R) to clonazepam (N = 39) or placebo (N = 36) in a 10-week double-blind study. On the basis of an intent-to-treat analysis of global improvement (response defined as much or very much improved), 78% benefited from clonazepam and only 20% from placebo (Figure 1). The mean daily dose of clonazepam at week 10 was 2.4 mg. About 25% of both groups failed to complete the study, but none of these premature terminations appeared to be due to adverse events. Side effects from clonazepam did outstrip those from placebo and included unsteadiness, forgetfulness, poor concentration, dizziness, and anorgasmia (Table 1). Anorgasmia in 44% of the clonazepam-treated patients (versus 5.8% receiving placebo) was a particularly striking finding. Fortunately, only unsteadiness and dizziness differed significantly from placebo with regard to both frequency/persistence and severity. All in all, the investigators found clonazepam to be an effective and generally well-tolerated treatment for social phobia.

Two years later, the Duke group[13] conducted a retrospective follow-up of these patients and was able to contact 56% of the original subjects (39 from the clonazepam group and 36 from the placebo group) and interview them by self-report questionnaire (N = 56) and telephone (N = 55). On follow-up, those who had received clonazepam in the double-blind study had significantly lower social phobia symptom scores than those who had received placebo. Whether this was due to the 10-week double-blind exposure to clonazepam or to the fact that substantially more of these patients persisted with some type of treatment over the intervening 2 years was unclear. The group as a whole (both clonazepam and placebo) did better with regard to health and disability functioning than comparable groups from a variety of other studies. For example, the patients had fewer sick days in the last 3 months (0.5 vs. 3.0), fewer medical visits in the last 6 months (1.1 vs. 2.3), and a lower average score on the Liebowitz Disability Scale (7.2 vs. 29.1). The authors suggested that this may have been due to "an overall enhancement of mental and physical health resulting from participation in a treatment protocol."[13]

The final look at clonazepam came in the form of a discontinuation study[14] involving patients who had responded favorably to 6 months of open-label treatment at a mean daily dose of less than 2.0 mg. Thirty-six patients were then randomly assigned under double-blind conditions to either continued clonazepam or taper/discontinuation with placebo substitution for 5 months. No one in the clonazepam group relapsed, but 21.1% in the placebo group experienced a worsening of symptoms. The low relapse rate in the placebo group suggested a continued benefit following discontinuation of open-label clonazepam, especially since the study excluded concomitant cognitive-behavioral therapy. The authors concluded that long-term clonazepam is a safe and effective treatment for social phobia.

Before closing the book on benzodiazepines, we shall look at a 12-week study in which Versiani and others,[15] incorporating double-blind placebo-controlled conditions, enrolled 60 patients with social phobia (DSM-III-R) and found bromazepam (21 mg/day) to be more effective than placebo. Contrary to what might have been expected with a benzodiazepine, a statistically significant separation from placebo did not occur until week 8. The Liebowitz Social Anxiety Scale (LSAS) scores decreased an impressive 62.2 points with bromazepam treatment and only 5.6 points with placebo. The drug is not available in the United States.

So where does this leave us with regard to benzodiazepines for treating social phobia? Since these drugs are no longer protected by patent, and since no new ones appear to be in the pharmaceutical pipeline, it is unlikely that ben-

zodiazepines will undergo further formal studies for this indication. Although clonazepam is the best studied of these drugs and, therefore, likely to be a first choice if a benzodiazepine were to be used, it is probable that any drug in this class could be an effective treatment for social phobia. There is a general sense among clinicians that long-term use of benzodiazepines is to be frowned upon (despite research including the above-mentioned clonazepam study that has found long-term use both effective and safe). Some positive aspects of benzodiazepines include established efficacy, a relatively rapid onset of action (bromazepam excluded), good tolerability, overdose safety, and dose flexibility. On the downside are side effects such as sedation, incoordination, and sexual dysfunction; abuse potential; discontinuation difficulties; adverse interactions with alcohol and other drugs; and ineffectiveness for comorbid conditions such as depression.

ANTICONVULSANTS

The investigation of conventional anticonvulsants for treating social phobia has been limited to studies of valproate, gabapentin, and pregabalin.

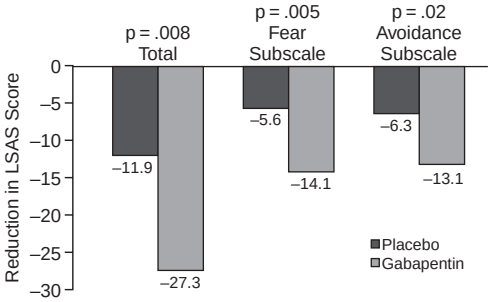
Valproate

Valproate can be disposed of quickly, at least if a presentation at the 6th World Congress of Biological Psychiatry in 1999 is substantiated.[16] Sixteen patients with DSM-IV–diagnosed generalized social phobia were treated with 500 to 1500 mg/day of valproic acid over 1 to 9 months, and all 16 considered the drug to be ineffective. Although only 3 patients had serum valproate concentrations measured, the levels in all 3 were within the therapeutic range.

Gabapentin

Gabapentin advanced to the forefront of mood stabilizers for social phobia with the 1999 publication of a 2-site, double-blind, placebo-controlled study of 69 adults.[17] The rationale for studying this drug for social phobia was 2-fold. First, in the human epilepsy trials, improved mood, reduced anxiety, and increased social well-being were noted. Second, the drug performed favorably in animal models of anxiety that included the rat conflict test, the rat elevated X-maze, and the marmoset human threat test (a marmoset is a small [weight: 300–500 g, length (without tail): 14–19 cm] New World monkey known formally as *Callithrix jacchus*). Within a flexible-dose design, patients were treated for 14 weeks with doses ranging from 900 to 3600 mg/day. The mean maximum daily dose was 2868 mg, with 56% of patients receiving 3600 mg and 77% receiving at least 2100 mg. In the drug and placebo groups, mean age at onset of illness was 12 and 13 years and mean duration of illness was 22 and 25 years, respectively. In addition to a DSM-IV diagnosis of social phobia, a minimum score of 50 was required on the LSAS (the primary outcome measure). All randomized patients who received at least one double-blind dose of study drug were included in the last-observation-carried-forward outcome analysis.

Figure 2. Reduction in Score on the Liebowitz Social Anxiety Scale (LSAS) for Gabapentin Versus Placebo in Social Phobia[a]



[a]Data from Pande et al.[17]

Gabapentin was statistically superior to placebo on the LSAS (total score, fear subscale, and avoidance subscale; Figure 2). The mean change in LSAS total score from baseline to endpoint exceeded that for placebo by 15.4 points. This outcome was similar to the 16.0-point difference found by Stein et al.[18] for paroxetine in social anxiety disorder. Gabapentin also outperformed placebo when response was determined by (1) a ≥ 50% decrease on the LSAS total score (32% vs. 14%) or (2) a CGI-Change scale score of 1 (very much improved) or 2 (much improved) (38% vs. 17%).

In contrast to the relatively rapid anxiolytic effect of gabapentin often noted in clinical practice, in this study it took the drug 2 weeks to outperform placebo. Additional observations included a greater drug/placebo difference in men (due to a high placebo response in women at one of the treatment sites) and a better response in patients 35 years of age or older.

Overall, 62% of the patients receiving gabapentin (N = 21) and 51% receiving placebo (N = 18) completed the study. Early termination due to adverse events occurred in 7 patients receiving gabapentin (21%) and 4 patients receiving placebo (11%). Side effects on gabapentin treatment were consistent with its known side effect profile and included somnolence, dizziness, and dry mouth.

The mechanism of action of gabapentin in social phobia is unknown. Although it is not converted to γ-aminobutyric acid (GABA), does not bind to $GABA_A$ or $GABA_B$ receptors, and does not bind to benzodiazepine receptors, it does cause a dose-dependent increase in brain GABA levels as measured by magnetic resonance spectroscopy in humans.[19] Other possible mechanisms include competition with the system L amino acid transporter, indirect inhibition of voltage-dependent sodium channels, and binding to the $\alpha_2\delta$ subunit of the L-type calcium channel.[20,21] As with many psychiatric drugs, the clinical

efficacy of gabapentin has become established well before a convincing explanation for its effectiveness.

Pregabalin

Hovering in the wings has been an analogue of the neurotransmitter GABA, *S*-(+)-3-isobutyl GABA, or pregabalin. A recently completed study of pregabalin in social phobia was presented at a 1999 scientific meeting.[22] The results were encouraging since the drug was more effective than placebo. Details of this study will become available once the definitive article is published. Additional work is underway to further evaluate the merits of pregabalin as a treatment for social phobia (as well as for a number of other disorders).

CONCLUSION

Benzodiazepines appear to be effective treatment for social anxiety disorder, although the placebo-controlled studies to support this assumption have been limited to clonazepam and bromazepam. Among the anticonvulsants, positive placebo-controlled studies with gabapentin[17] (published) and pregabalin (submitted for publication) support efficacy for both these medications.

Drug names: alprazolam (Xanax and others), clonazepam (Klonopin and others), clorazepate (Tranxene and others), diazepam (Valium and others), gabapentin (Neurontin), lorazepam (Ativan and others), paroxetine (Paxil), phenelzine (Nardil), valproic acid (Depakene and others).

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Question and Answer Session

Question: Can you provide more information about bromazepam? Is it currently being investigated for approval in the United States? If so, can you describe the studies? If not, why not?

Dr. Jefferson: Bromazepam is widely available elsewhere in the world, including Canada, but not in the United States. This can be explained by several factors. First of all, bromazepam has been in use for quite a while, so it probably no longer has a patent life. In addition, it has no particularly distinguishing features, and there is an overabundance of benzodiazepines in this country. Consequently, it is unlikely that bromazepam will ever be available in the United States.

Question: You mentioned that benzodiazepines have good tolerability, yet there was a 44% rate of anorgasmia in the Duke clonazepam study.[1] Can you comment on this?

Dr. Jefferson: The 44% rate of anorgasmia with clonazepam in the Duke study, versus 5.8% with placebo, was based on an anytime occurrence during the study. When clonazepam was compared with placebo at the end of the study relative to baseline, the rates were 22.8% and 2.9%, respectively. According to the authors, anorgasmia was one of the side effects with clonazepam that differed significantly from placebo in terms of frequency and persistence, but not in terms of severity. Unsteadiness and dizziness were the only adverse effects with clonazepam that did differ significantly from placebo in terms of both frequency/persistence and severity.

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