Double-Blind, Placebo-Controlled Assessment of Combined Clonazepam With Paroxetine Compared With Paroxetine Monotherapy for Generalized Social Anxiety Disorder

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Background: Generalized social anxiety disorder (GSAD) is a pervasive form of social anxiety that affects approximately 5% of persons in the community. Among evidence-based pharmacologic treatments for the disorder, selective serotonin reuptake inhibitors (SSRIs) have become widely used and are known to be efficacious. Monotherapy with the benzodiazepine clonazepam is also efficacious for GSAD, but the adjunctive use of clonazepam with an SSRI to potentially improve outcomes has not been studied to date.

Method: Twenty-eight patients (22 men and 6 women) with DSM-IV–defined GSAD were randomly assigned to receive double-blind clonazepam (or placebo), 1.0 to 2.0 mg/day (divided b.i.d.) along with open-label paroxetine, 20 to 40 mg/day, for 10 weeks. A 2-week taper of double-blind medication was followed by an additional 8 weeks of open-label paroxetine treatment (during which the dose of paroxetine could be increased to a maximum of 50 mg/day). Twenty-three patients (82%) met DSM-IV criteria for avoidant personality disorder. The patients' mean ± SD age was 31.2 ± 7.7 years, and their mean duration of illness was 12.1 ± 5.8 years. Data were gathered from August 2001 to April 2002.

Results: Nineteen (68%) of 28 patients completed treatment. At the end of the 10-week double-blind treatment, there was a trend ($p < .06$) favoring the paroxetine/clonazepam group, who had a 79% response rate (Clinical Global Impressions-Global Improvement scale [CGI-I] score of 1 or 2) compared with a 43% response rate for the paroxetine/placebo group. However, no significant differences on other outcome measures were noted between the 2 groups in an intent-to-treat analysis, in terms of either very early (2–4 weeks) or not as early (5–10 weeks) responses during treatment. Dropout rates due to adverse events were rare (1 patient in each group), indicating that the paroxetine/clonazepam combination was well tolerated.

Conclusion: Coadministration of clonazepam with an SSRI, in contrast to findings in panic disorder, did not lead to more rapid resolution of symptoms in GSAD. On the other hand, there is some evidence that the clonazepam-added group had superior global outcomes (e.g., as measured on the CGI-I), although power to detect such differences in this study was small. These observations suggest that a role for adjunctive benzodiazepines in patients with GSAD (e.g., for augmenting SSRI partial response or nonresponse) is deserving of further controlled investigation.

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Social phobia (also known as social anxiety disorder) is a common anxiety disorder whose etiopathophysiology remains largely unknown. Epidemiologic and community-based studies have reported lifetime prevalence rates ranging from 2.4% to 13%.[1–3] The more debilitating form of the illness, generalized social anxiety disorder (GSAD), is characterized by pervasive fears of multiple performance and interactional situations, prominent physiologic/subjective symptoms, and substantial impairment in social and vocational functioning.[1] Currently, the selective serotonin reuptake inhibitors (SSRIs) are well established as a treatment for GSAD in view of available evidence regarding their efficacy, tolerability, and safety.[4]

Despite widespread use, response rates for GSAD peak at 50% to 70%, while only 20% to 30% of patients experience significant remission. As such, adjunctive medications may be useful in further improving outcomes. Owing to their rapid anxiolytic properties, benzodiazepines are commonly prescribed as concomitant or alternative agents in clinical practice. To date, only clonazepam,[5] alprazolam,[6] and bromazepam[7] have been studied under double-blind conditions. In a double-blind pilot study of clonazepam, Davidson et al.[1] demonstrated that clonazepam was statistically significantly superior to placebo in patients with GSAD (78% of responders receiving clonazepam vs. 20% receiving placebo). Despite evidence indicating their separate efficacy, the potential benefits of combining a benzodiazepine with an SSRI in GSAD have not been investigated. However, recent controlled data in

patients with panic disorder suggest that early coadministration of clonazepam with an SSRI may be a safe and clinically useful strategy for some patients and may accelerate response.[8]

The purpose of this study was to determine, under controlled conditions, whether early coadministration of the benzodiazepine clonazepam with the SSRI paroxetine might yield more rapid and/or robust improvement in social anxiety symptoms relative to the administration of paroxetine alone. Accordingly, we hypothesized that the combination would facilitate early reduction of social anxiety, avoidance, and associated physiologic symptoms, with gains sustained during continuation treatment with open-label paroxetine once the clonazepam was discontinued.

METHOD

Design

This was a double-blind, placebo-controlled study of patients with DSM-IV–defined GSAD. The study protocol was approved by the Human Research Protection Program of the University of California San Diego School of Medicine, and all subjects gave written informed consent to participate. Data were gathered from August 2001 to April 2002. The Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition,[9] (modified by the authors to include additional social phobia situational probes) was used to confirm a diagnosis of GSAD. On completion of screening procedures, all patients (N = 28) were treated with flexible-dose, open-label paroxetine (starting dose = 20 mg/day, target dose = 40 mg/day). In addition, patients were randomly assigned to receive either active clonazepam (0.5 mg twice daily orally for 1 week, then 1.0 mg twice daily orally for 9 weeks) (N = 14) or placebo (N = 14), followed by 2 weeks of tapered doses. After the taper period, open-label paroxetine (maximum dose of 50 mg/day) was continued for a further 8 weeks.

Subjects

Subjects were recruited using local newspaper advertisements. To be eligible, participants were required to meet DSM-IV criteria for GSAD, have a minimum score of at least 20 on the Liebowitz Social Anxiety Scale (LSAS),[10] be between 18 and 65 years of age, have no serious medical history, and have taken no psychotropic medications for at least 14 days prior to randomization. Participants who had received benzodiazepines in the 4 weeks prior to randomization were precluded from participation. Further, patients were excluded if they had any other psychiatric, medical, or neurologic disorder that was deemed to be "primary" in terms of clinical significance (e.g., schizophrenia, bipolar disorder, alcohol abuse/dependence); concurrent major depressive disorder was not an exclusion criterion. Other exclusion criteria were any clinically significant abnormal laboratory or electrocardiogram findings at the screening visit or judgment that the patient was a serious suicidal or homicidal risk. Women who were pregnant, lactating, or not using an acceptable method of contraception were also ineligible.

Outcome Measures

Patients were evaluated at 10 study visits (baseline and weeks 1, 2, 4, 6, 10, 12, 14, 16, and 20) by means of efficacy and safety measures. Primary efficacy variables included (1) proportion of responders as determined by the Clinical Global Impressions-Global Improvement scale (CGI-I),[11] by which a responder was defined as very much improved (CGI-I score = 1) or much improved (CGI-I score = 2) based solely on social anxiety symptoms, and (2) mean change from baseline in LSAS and Brief Social Phobia Scale (BSPS) scores.[12] Secondary efficacy variables comprised mean change from baseline scores on the Beck Depression Inventory (BDI),[13] Clinical Global Impressions-Global Severity scale (CGI-S),[11] and the Sheehan Disability Scale (SDS).[14] Adverse events and dropouts were monitored clinically by the study psychiatrist. The Physicians Withdrawal Checklist[15] was used to assess for benzodiazepine withdrawal at weeks 12 and 14.

Statistical Analysis

Intent-to-treat (ITT) analyses with the last observation carried forward were conducted for all subjects who had taken at least 1 dose of medication and had received at least 1 postbaseline evaluation (N = 28). The 2 ITT groups were compared on baseline demographic (age, gender, ethnicity, marital status), clinical (mean duration of illness in years, percentage of patients with major depressive disorder, percentage of patients with avoidant personality disorder), efficacy (LSAS, BSPS, CGI-S, BDI), and safety measures (adverse events and withdrawal symptoms) using Fisher exact tests for categorical variables and independent t tests for continuous variables. For the primary efficacy variable of CGI-I response, Fisher exact tests were used to compare the groups at each timepoint. Comparison of the frequency of endorsed adverse events (including withdrawal symptoms) between the groups was performed using Fisher exact tests. In addition, multivariate and repeated-measures analysis of variance (ANOVA) (general linear model) was conducted on both primary and secondary efficacy measures at all timepoints with group and time as main effects. All tests were 2-tailed, and the α level was set at .05.

RESULTS

Baseline demographic and clinical characteristics of the 2 ITT groups are shown in Table 1. In both groups, subjects were predominantly male, white, and single, with

Table 1. Comparison of Baseline Demographic and Clinical Variables in ITT Sample

Characteristic	Clonazepam/ Paroxetine (N = 14) N (%)	Placebo/ Paroxetine (N = 14) N (%)		p[a]
Gender, male	11 (79)	11 (79)		.68
Ethnicity, white	13 (93)	10 (71)		.16
Marital status, never married	12 (86)	11 (79)		.50
Major depressive disorder	2 (14)	1 (7)		.50
Avoidant personality disorder	12 (86)	11 (79)		.50
Alcohol abuse/ dependence	0 (0)	0 (0)		…
	Mean ± SD	Mean ± SD	t	p
Age, y	29.9 ± 8.4	32.6 ± 6.9	–.93	.36
Duration of illness, y	11.1 ± 6.1	13.1 ± 5.5	–.91	.37
LSAS total	94.6 ± 25.8	95.2 ± 24.5	–.07	.95
BSPS total	51.6 ± 10.8	51.1 ± 9.7	.13	.89
CGI-S score	4.6 ± 0.7	4.8 ± 0.8	–.78	.44
BDI total	12.1 ± 7.5	14.2 ± 6.9	–.73	.47
SDS total	19.2 ± 4.9	17.8 ± 4.5	.79	.43

[a]Fisher exact test used for categorical variables.
Abbreviations: BDI = Beck Depression Inventory, BSPS = Brief Social Phobia Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, ITT = intent to treat, LSAS = Liebowitz Social Anxiety Scale, SDS = Sheehan Disability Scale.

a mean duration of GSAD of approximately 11 years and a comorbid diagnosis of avoidant personality disorder. Most subjects had scores of less than 15 on the BDI at baseline, indicating low levels of depressive symptoms.

Nineteen (68%) of 28 randomized patients completed the study. Of the 9 dropouts, 4 were in the clonazepam/paroxetine group (29% dropout rate) and 5 were in the placebo/paroxetine group (36% dropout rate). Seven (78%) of 9 patients dropped out because of noncompliance (being lost to follow-up), while 2/9 patients dropped out because of adverse events (1 clonazepam/paroxetine patient and 1 placebo/paroxetine patient).

Efficacy Variables

At the end of the double-blind period (10 weeks), 17/28 patients (61%) in the sample were classed as responders, and at treatment endpoint (20 weeks) this comprised 20/28 patients (71%). At week 10, 11/14 (79%) in the clonazepam group versus 6/14 (43%) in the placebo/paroxetine group were treatment responders, indicating a trend toward significance (Fisher exact test, p = .06). Post hoc power analysis revealed that the study had only 50% power to detect between-group differences of this magnitude and that a future study would require a total of 70 subjects (35 in each group) to have 90% power for this comparison.

There were no significant between-group differences in response status at any other timepoint (Table 2). Further, multivariate analysis and repeated-measures ANOVA conducted separately for LSAS (Figure 1), BSPS, CGI-S, and BDI scores showed no significant group-by-time interactions, providing no evidence of superior efficacy of clonazepam/paroxetine over placebo/paroxetine on primary or secondary outcome measures either early or later in the study. At both weeks 10 and 20, the clonazepam/paroxetine group demonstrated greater reductions in LSAS, BSPS, and SDS sum scores from baseline than the placebo/paroxetine group (the converse was true for BDI sum scores), although statistical comparisons showed only trend or no differences.

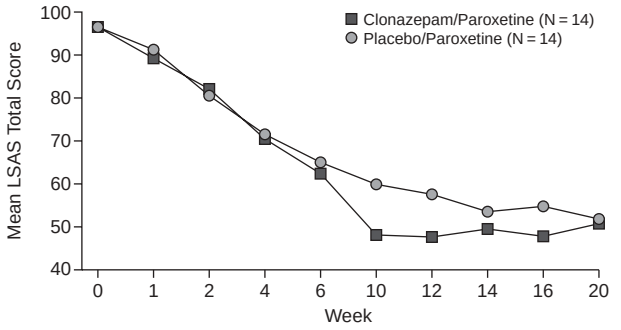
Effect sizes for the treatment groups were calculated for each outcome measure at weeks 10 and 20. As seen in Table 3, effect size at week 10 was 1.72 for the clonazepam/paroxetine group versus 0.97 for the placebo/paroxetine group. At week 20, effect sizes were 1.89 and 1.16, respectively. To allow comparison with published estimates of effect sizes for paroxetine and clonazepam, we used the following method to compute the effect size: the difference in the mean score change from baseline

Table 2. Treatment Responders in ITT Sample: Clinical Global Impressions-Global Improvement Change Score

Week	Clonazepam/ Paroxetine, N (%) (N = 14)	Placebo/ Paroxetine, N (%) (N = 14)	p Value[a]
1	1 (7)	0 (0)	.52
2	2 (14)	0 (0)	.24
4	5 (36)	4 (29)	.50
6	7 (50)	5 (36)	.42
10[b]	11 (79)	6 (43)	.06
12[c]	10 (71)	6 (43)	.13
14	11 (79)	8 (57)	.21
16	12 (86)	8 (57)	.10
20	12 (86)	8 (57)	.10

[a]Fisher exact test was used.
[b]End of double-blind phase.
[c]End of taper phase.
Abbreviation: ITT = intent to treat.

Figure 1. Mean LSAS Scores (ITT population)[a]



[a]Data are from the last observation carried forward. Differences in change from baseline between the clonazepam/paroxetine and placebo/paroxetine groups were analyzed by means of repeated-measures 2-way analyses of variance (df = 2.5).
Abbreviations: ITT = intent to treat, LSAS = Liebowitz Social Anxiety Scale.

Table 3. Comparison of Primary and Secondary Outcome Measures in the Clonazepam/Paroxetine and Placebo/Paroxetine Groups (ITT sample)[a]

Outcome Measure	Week 0 Mean (SD)	Week 10[b] Mean (SD)	Week 20[c] Mean (SD)	Week 10 Group Effect Size[d]	Overall Trial Effect Size[e]	Week 20 Group Effect Size[d]
LSAS						
Clonazepam/paroxetine	94.6 (25.8)	43.6 (28.5)	40.7 (35.6)	1.7		1.9
Placebo/paroxetine	95.2 (24.5)	59.9 (34.2)	48.0 (39.1)	1.0	0.5	1.2
BSPS						
Clonazepam/paroxetine	51.6 (10.8)	23.2 (15.9)	21.4 (18.6)	1.7		1.9
Placebo/paroxetine	51.1 (9.7)	32.5 (17.7)	27.6 (18.5)	1.0	0.5	1.3
BDI						
Clonazepam/paroxetine	12.1 (7.5)	5.5 (8.5)	5.1 (6.2)	0.6		0.7
Placebo/paroxetine	14.2 (6.9)	7.4 (5.6)	2.7 (3.4)	1.1	0.4	2.3
SDS						
Clonazepam/paroxetine	19.2 (4.9)	8.9 (7.8)	9.6 (9.2)	1.6		1.3
Placebo/paroxetine	17.8 (4.5)	11.7 (7.1)	9.9 (6.2)	0.8	0.6	1.2

[a]Differences (week 0 – week 10 and week 0 – week 20) in primary and secondary outcome measures between groups were not statistically significant.
[b]End of double-blind phase.
[c]End of treatment.
[d]Effect size per group was calculated using the change in mean score from baseline divided by the standard deviation of the change.
[e]Effect size for the trial was calculated using the difference in the mean score change from baseline between clonazepam and placebo groups divided by the standard deviation of the change in the placebo group.
Abbreviations: BDI = Beck Depression Inventory, BSPS = Brief Social Phobia Scale, ITT = intent to treat, LSAS = Liebowitz Social Anxiety Scale, SDS = Sheehan Disability Scale.

Table 4. Most Frequently Reported Adverse Events and Withdrawal Symptoms (Physicians Withdrawal Checklist)

Event	Clonazepam/ Paroxetine, N (%) (N = 14)	Placebo/ Paroxetine, N (%) (N = 14)
Adverse events		
Somnolence*	14 (100)	10 (71)
Anxiety	8 (57)	3 (21)
Increased sweating	7 (50)	3 (21)
Fatigue	6 (43)	8 (57)
Headache	5 (36)	5 (36)
Insomnia	5 (36)	5 (36)
Dizziness	4 (29)	6 (43)
Low mood	7 (50)	2 (14)
Dry mouth	3 (21)	5 (36)
Jitteriness*	6 (43)	1 (7)
Withdrawal symptoms	(N = 12)	(N = 9)
Anxiety	8 (67)	2 (22)
Diaphoresis*	6 (50)	0 (0)
Insomnia	3 (25)	2 (22)
Tremor	4 (33)	1 (11)
Headache	3 (25)	3 (33)
Fatigue, lethargy	3 (25)	3 (33)

*$p < .05$ vs. placebo.

between clonazepam/paroxetine and placebo/paroxetine groups divided by the standard deviation of the change in the placebo group. Comparing the mean change in social anxiety scores (on the LSAS) in patients treated with clonazepam versus patients treated with placebo, the effect size was 0.5. On the basis of work by Cohen,[16] this corresponds to a "medium" effect size.

Medication Dose, Adverse Events, and Withdrawal Symptoms

The fixed-dose titration of clonazepam to 2.0 mg was well tolerated, with both the clonazepam/paroxetine group (N = 12) and placebo/paroxetine group (N = 9) attaining this mean ± SD dose equivalent by the end of week 4. By the end of week 10 (i.e., the end of the double-blind period), the mean ± SD daily dose of paroxetine was 40.0 ± 0.0 mg in the clonazepam/paroxetine group (N = 12) and 38.9 ± 3.3 mg in the placebo/paroxetine group (N = 9) ($p = .35$). At study end (week 20), there was no significant difference between the groups in the mean ± SD daily dose of paroxetine (40.0 ± 4.7 mg in the clonazepam/paroxetine group vs. 35.6 ± 7.3 mg in the placebo/paroxetine group, $p = .14$). The 2 groups had a similar profile of adverse events, with only 2 events (somnolence, jitteriness) occurring at significantly higher rates than placebo (Table 4). Other common treatment-emergent adverse events for which clonazepam/paroxetine had an excess over placebo/paroxetine by at least 10% were nausea, anxiety, increased sweating, restlessness, decreased libido, delayed ejaculation, and anorgasmia. In contrast, dry mouth, decreased appetite, dizziness, and fatigue had at least a 10% greater incidence in the placebo/paroxetine group. In general, adverse events were of mild-to-moderate intensity.

During the tapering phase, common symptoms reported by both groups included anxiety, headache, and fatigue. Diaphoresis was endorsed by 6/12 patients (50%) in the clonazepam/paroxetine group and none in the placebo/paroxetine group.

DISCUSSION

On the basis of the absence of statistically significant between-group differences on primary and secondary efficacy measures in the first 4 weeks of the study, these data do not demonstrate superior early outcomes (i.e., acceleration of benefits) in adults with GSAD when

clonazepam is coadministered with paroxetine. However, the trend toward differences in overall CGI-I outcome (clonazepam/paroxetine, 79% vs. placebo/paroxetine, 43%) observed at week 10 and the decrease of greater than 50% in LSAS scores in the clonazepam plus paroxetine group suggest that differences may have been significant in a larger sample, and this possibility is clearly deserving of further study. In addition, these gains appeared to persist to week 20 in the clonazepam plus paroxetine group after clonazepam withdrawal.

The effect sizes for the clonazepam/paroxetine and placebo/paroxetine groups were approximately 1.7 and 1.0, respectively. These findings compare to other published placebo-controlled trials of paroxetine monotherapy[17–19] in which effect sizes in the widely varying range of 0.3 to 2.2 have been reported[20] and also to the single placebo-controlled trial of clonazepam monotherapy[5] in which the effect size was 1.0. Although it is difficult to make direct comparisons across studies of varying design, the large effect size for the adjunctive clonazepam group is encouraging and should spur larger, controlled studies to confirm its potential advantages.

The 2 treatment groups were generally comparable in the pattern and frequency of adverse events and withdrawal symptoms (during benzodiazepine taper). The fixed dose of clonazepam and flexible dose of paroxetine were well tolerated, with only 2 patients dropping out due to adverse events. Adding clonazepam to paroxetine produced greater somnolence, which might be expected, but also jitteriness, which was unexpected.

Our failure to observe significant differences in efficacy across most measures may be attributable, in part, to the relatively low dose of clonazepam, and certainly to the small sample size. The power to detect between-group differences for CGI-I outcomes at week 10 was less than 50%, indicating that the study was underpowered to detect between-group differences. In the future, if such a study is undertaken, a larger sample size (i.e., a minimum of 70 subjects) would be required. Thus, while these findings suggest some promise for this combination to effect improved outcomes in GSAD, they should be treated as exploratory.

Although benzodiazepines are not considered a first-line choice as a monotherapy for long-term use in GSAD in view of concerns about physical dependence and withdrawal on discontinuation, they may be useful in other contexts (e.g., to augment treatment for SSRI partial responders or nonresponders). Thus, while routinely prescribing clonazepam for all patients receiving paroxetine for GSAD is probably not optimal, the findings do suggest that various ways of combining the 2 drugs should be pursued. Perhaps future studies would do well to use a targeted strategy, for example, adding clonazepam later in treatment only for those with suboptimal responses to antidepressant treatment. Clinically, this approach would be preferred because this combination could then be reserved for nonresponders or partial responders, and patients who respond adequately would not be unnecessarily exposed to benzodiazepines. Given the relatively high rates of nonresponse (and even higher rates of nonremission) in GSAD, this particular combination strategy, as well as other strategies for treating refractory GSAD, should be further evaluated under double-blind, placebo-controlled conditions.

Drug names: alprazolam (Xanax and others), clonazepam (Klonopin and others), paroxetine (Paxil and others).

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