Efficacy, Safety, and Gradual Discontinuation of Clonazepam in Panic Disorder: A Placebo-Controlled, Multicenter Study Using Optimized Dosages

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Background: The purpose of this multicenter, double-blind, placebo-controlled study was to evaluate the efficacy and safety of optimized dosages of clonazepam for the treatment of panic disorder and assess the tolerability of a schedule for gradual discontinuation.

Method: Adult patients with panic disorder with or without agoraphobia (DSM-III-R criteria) were randomly assigned to receive either placebo or clonazepam in individually adjusted doses over 3 weeks to approximate an optimal dosage, which was then maintained for an additional 3 weeks, amounting to a 6-week therapeutic phase. The daily dose range was 0.25 to 4.0 mg administered in 2 divided doses. In the following 7-week discontinuance phase, the doses were tapered gradually to cessation.

Results: At the therapeutic endpoint, clonazepam (N = 222) proved clinically and statistically superior to placebo (N = 216) in change in the number of panic attacks and in Clinical Global Impressions-Severity of Illness (CGI-S) and CGI-Change scores, Patient's Global Impression of Change scores, amount of fear and avoidance associated with phobic symptoms, and duration of anticipatory anxiety. The gradual tapering of clonazepam was not associated with symptoms suggestive of withdrawal syndrome. Although patients taking clonazepam experienced some clinical worsening compared with the status achieved at endpoint, particularly in terms of number of panic attacks, no deterioration was observed using their condition at baseline as point of reference. No overall evidence of rebound was found. All regimens were generally well tolerated. Somnolence was the main adverse event associated with clonazepam therapy. The percentage of patients who reported adverse events was higher in the clonazepam group than in the placebo group, as was the mean number of adverse events per patient.

Conclusion: In this placebo-controlled trial, clonazepam was an efficacious and safe short-term treatment of the symptoms of panic disorder. Discontinuance during and after slow tapering was well tolerated.

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For more than a decade, benzodiazepines, along with tricyclic antidepressants, have been the most established pharmacotherapy of panic disorder.[1] The efficacy of alprazolam, a high-potency benzodiazepine, in panic disorder was described in 1982,[2] substantiated by other investigators,[3,4] and confirmed in the Cross-National Collaborative Panic Study, a multicenter, placebo-controlled trial.[5] Subsequently, Chouinard et al.[6–8] reported on the efficacy of another benzodiazepine, clonazepam, in panic disorder. These findings were also confirmed in open-label studies[9–11] and in 2 double-blind, placebo-controlled studies.[1,12] There is additional evidence for the efficacy of other benzodiazepines, particularly diazepam[13] and lorazepam.[14]

Among the benzodiazepines now available in the United States, clonazepam has an affinity for central benzodiazepine receptors that is exceeded only by midazolam and triazolam.[15] Given its elimination half-life, with estimates ranging from 20 to 80 hours, clonazepam permits twice-daily dosing[16] and a more continuous control of anxiety than is possible with agents that have shorter half-lives, eliminating "clock-watching" between doses.[17–19] In addition, the long half-life of clonazepam may reduce the severity of the withdrawal syndrome during discontinuance compared with that associated with agents that have shorter half-lives, such as alprazolam.[20] Clonazepam has an onset of peak activity of 2 to 3 hours.[15] The results of pilot studies and open clinical trials[21,22] suggest that clonazepam has anxiolytic, antipanic, and antiphobic properties; those results were confirmed by 2 placebo-controlled studies.[1,12]

The objectives of this study were to assess (1) the effectiveness and safety of clonazepam compared with

placebo in the treatment of panic disorder with or without agoraphobia and (2) the tolerability of gradual discontinuation of clonazepam.

METHOD

The study protocol was approved by the institutional review board of each participating institution, and all patients gave written informed consent.

Study Design

The study was a multicenter, randomized, placebo-controlled, parallel-group trial with 3 phases: a 1-week single-blind placebo lead-in phase preceding the baseline evaluation, a 6-week double-blind therapeutic phase, and a 7-week discontinuance phase. The first 3 weeks of the therapeutic phase constituted the dose-optimization period and the remaining 3 weeks, the dose-maintenance period. The discontinuance phase consisted of a double-blind dose-tapering period followed by a 1-week single-blind placebo lead-out.

Study Population

Candidates were eligible for the study if they (1) were outpatients who were willing to keep weekly appointments and daily panic attack diaries, (2) met the DSM-III-R criteria for a primary diagnosis of panic disorder with or without agoraphobia, (3) had an average of 4 or more panic attacks in the 4 weeks preceding randomization and scored 4 or higher on the Clinical Global Impressions-Severity of Illness scale (CGI-S),[23] (4) had not taken benzodiazepines or other psychotropic or psychoactive medication for 14 days or more before randomization, and (5) were over the legal age of consent. Women of childbearing potential could be enrolled if they were not pregnant, not lactating, and using an acceptable form of birth control. The diagnosis of panic disorder was established by the patient's scores on a version of the Structured Clinical Interview for DSM-III-R (SCID)[24] customized for the entry criteria used in this study and confirmed by a psychiatric interview. At this time, patients also identified the main phobia associated with their panic disorder.

The main exclusion criteria were (1) current or recent substance abuse disorder, including alcohol abuse; (2) a primary (in the sense of predominant) diagnosis of social phobia, obsessive-compulsive disorder, generalized anxiety disorder, or major depression; (3) a history of psychosis or bipolar disorder; (4) a recently begun cognitive-behavioral therapy to treat panic disorder; or (5) significant, unstable, or uncontrolled medical illness.

Administration of Study Medication

The study medications were clonazepam and identical-looking placebo tablets, which were ingested in the morning and the evening. All patients took placebo during the 1-week lead-in phase between screening and the baseline evaluation (week 0).

The therapeutic phase encompassed weeks 1 through 6. After being randomly allocated to a clonazepam or placebo treatment group, all patients took 0.25 mg/day of study drug for 3 days, followed by 0.5 mg/day for 3 days. During the remainder of the 3-week dose-optimization phase, the dosage could be increased by 0.5 or 1.0 mg/day every 3 days, according to the patient's response, until the optimized or maximum dosage (4.0 mg/day) was reached. Dosages could also be reduced in decrements of 0.5 mg b.i.d. Allowable dosages were 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, or 4.0 mg/day. The dosage in use at the end of dosing day 22 was maintained for the remaining 3 weeks of the therapeutic phase.

The discontinuance phase was begun upon completion of week 6 and proceeded until 1 week after the study drug was completely withdrawn. During this phase, dosages were reduced every 3 days in decrements of 0.5 mg/day for patients taking 1.5 mg/day or more and 0.25 mg/day for patients taking 1.0 mg/day or less. Upon completing withdrawal of the study drug, patients received placebo for 1 week.

Efficacy and Safety Assessments

At each visit, patients were given a diary to record any panic attacks between visits. For each attack, they noted the date, the number of symptoms, whether the attack was unexpected or not, its duration, and its intensity. They returned the completed diary at each subsequent visit so that the investigator could use it as an interview tool. An attack had to involve at least 4 symptoms to be logged as a panic attack.

Efficacy assessments included (1) change from baseline in the number of panic attacks, (2) distribution of scores and change from baseline in the CGI-S for panic disorder, (3) CGI-Change from baseline scale (CGI-C) scores for panic disorder,[23] (4) Patient's Global Impression of Change (PGI-C; same rating as the CGI except completed by patients) scores, (5) estimate of mean duration of anticipatory anxiety, (6) change from baseline in the fear (on an 11-point scale) and avoidance (on a 5-point scale) associated with the main phobia identified at baseline, (7) change from baseline in Work and Social Disability (WSD; unpublished) scale scores, and (8) change from baseline in Hamilton Rating Scale for Anxiety (HAM-A)[25] scores. Assessments (1), (2), and (6) were determined a priori to be the primary endpoints.

Safety assessments included monitoring of adverse events (any adverse change from the patient's pretreatment condition, including intercurrent illness, that occurred during the study irrespective of relationship to treatment), and measurements of blood pressure and heart rate. Routine hematologic and chemical tests and urinalysis were performed by a central laboratory.

Administration of the CGI-S, PGI-C, WSD, monitoring of adverse events, and measurements of blood pressure and heart rate took place at every scheduled visit throughout the therapeutic phase (weeks 0, 1, 2, 3, and 6), during the discontinuance phase when the daily dosage of study drug reached 2.0 mg (for those whose optimal dosage was > 2.0 mg/day) and 0 mg, and on completion of the 1-week placebo lead-out. The CGI-C was given at all of the above times except week 0. The HAM-A assessments and clinical laboratory tests were conducted at the screening visit (the week preceding week 0), at the conclusion of the therapeutic phase (week 6), and at the final study visit; at those particular visits, the Hamilton Rating Scale for Depression (HAM-D)[26] was also administered.

Analysis of Data

All efficacy data were analyzed for the end of the therapeutic phase (observed cases) and for the last postbaseline observation during the therapeutic phase (therapeutic endpoint). We present efficacy results using the therapeutic endpoint data compared with the baseline data for the intent-to-treat population. The intent-to-treat population included all randomized patients who took at least one dose of study medication and had both a baseline and at least one postbaseline efficacy assessment.

Analysis of variance (ANOVA) procedures were used to evaluate the data using the SAS Procedure General Linear Model.[27] For each analysis, the ANOVA model contained terms for "treatment effect," "center effect," and "treatment-by-center interaction." The least squares mean in the clonazepam group was compared with that in the placebo group. Two-sided p values, the least squares mean differences between the 2 groups, and 95% 2-sided confidence intervals based on the least squares mean differences were examined. Variables with categorical expressions of observations, such as the CGI-S and CGI-C ratings, were analyzed by means of the Cochran-Mantel-Haenszel test[28] stratified by center.

Because data for the change in the number of panic attacks did not satisfy the assumption of normality underlying the ANOVA model, rank transformation was used. Since the residuals of the rank-transformed data also were not normal, the data were further analyzed with the distribution-free Cochran-Mantel-Haenszel test to assess the difference between the treatment groups.

The analysis of data for the discontinuance phase involved only patients with data for week 6 and at least one subsequent evaluation. Data from the last assessment during this phase (discontinuance endpoint) were compared with week 6 data. No inferential analyses were performed for that phase.

Safety data were collected from all randomized patients who took at least one dose of study medication and had at least one postbaseline assessment of safety or efficacy. Any adverse event that was first seen or increased in severity after the first dose of study medication was included in the safety evaluation. The incidence of adverse events was calculated on the basis of the number of patients who reported a given event at least once.

RESULTS

Four hundred fifty-five patients were randomly assigned to treatment with clonazepam (N = 230) or placebo (N = 225) and met the requirements for safety evaluation; 438 patients met the requirements for the intent-to-treat population. Of the 222 intent-to-treat patients in the clonazepam group, 181 (82%) completed the therapeutic phase and 130 (59%) completed the discontinuance phase. Twenty-five (11%) patients failed to complete the entire study because of adverse events; other reasons for premature termination were lack of efficacy, 19 (9%); loss to follow-up, 13 (6%); patient withdrawal, 13 (6%); and "other," 22 (10%). Of the 216 intent-to-treat patients in the placebo group, 161 (75%) completed the therapeutic phase and 115 (53%) completed the discontinuance phase as well. Fifty (23%) patients failed to complete the entire study owing to lack of efficacy; other reasons for premature termination were loss to follow-up, 20 (9%); adverse events, 15 (7%); patient withdrawal, 6 (3%); and "other," 10 (5%).

The demographic and baseline disease characteristics of the clonazepam and placebo intent-to-treat groups were similar (Table 1). This was a predominantly young, female, white, and agoraphobic population. Few patients had concomitant depression at baseline. The 2 treatment groups presented similar baseline characteristics in terms of panic disorder, psychiatric comorbidity, and disability induced by the primary condition. The mean number of panic attacks at baseline for the clonazepam and placebo groups was 4.2 and 3.9, respectively, while the median number was 3.0 and 2.0, respectively. The study population was similar to that of the alprazolam Cross-National Collaborative Panic Study.[5]

During the therapeutic phase, at the end of up-titration, patients in the clonazepam group took a mean optimized dosage of 2.3 mg/day and a median dosage of 2.0 mg/day; the dosage range was 0.5 to 4.0 mg/day. Patients in the placebo group took a mean tablet equivalent of 3.0 mg/day and a median tablet equivalent of 4.0 mg/day.

Efficacy in Therapeutic Phase

At the therapeutic endpoint, 61.9% of the clonazepam patients were free of panic attacks, compared with 36.8% of the placebo patients ($p < .001$). The mean number of panic attacks was reduced from 4.2 at baseline to 1.5 at endpoint in the clonazepam group and from 3.9 to 2.2 in the placebo group ($p = .004$; Table 2). Throughout the therapeutic phase (weeks 1, 2, 3, and 6), patients treated

Table 1. Demographic and Baseline Characteristics: Intent-to-Treat Population[a]

Characteristic	Clonazepam (N = 222)	Placebo (N = 216)
Sex		
Female	141 (64)	140 (65)
Male	81 (36)	76 (35)
Age at entry, y		
Mean ± SD	36.7 ± 11.3	36.8 ± 11.4
Range	18–74	18–68
Race		
White	188 (85)	197 (91)
Black	21 (9)	16 (7)
Other	13 (6)	3 (1)
Primary diagnosis		
Panic disorder		
With agoraphobia	162 (73)	160 (74)
Without agoraphobia	60 (27)	56 (26)
Comorbidity		
Major depression	13 (6)	11 (5)
Social phobia	13 (6)	13 (6)
Obsessive-compulsive disorder	2 (1)	1 (0)
Generalized anxiety disorder	35 (16)	33 (15)
Mean duration of condition, y	8.3	8.9
No. of panic attacks		
Mean ± SD	4.2 ± 4.2	3.9 ± 3.9
Median	3.0	2.0
CGI-S rating		
Moderately ill	113 (51)	115 (53)
Markedly ill	80 (36)	75 (35)
Severely ill	26 (12)	26 (12)
Most severely ill	3 (1)	0 (0)
HAM-A total score, mean ± SD	20.9 ± 8.5	21.0 ± 9.3
HAM-D total score, mean ± SD	10.5 ± 4.4	10.3 ± 4.4

[a]All values shown as N (%) unless specified otherwise. Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression.

with clonazepam had greater changes from baseline in the mean number of panic attacks than did patients treated with placebo. The between-group differences were statistically significant ($p = .004$) at both week 6 and endpoint (Figure 1).

The CGI-S, a 7-item scale, was used to assess the severity of the panic disorder; subjects were ranked as normal (1), borderline ill (2), mildly ill (3), moderately ill (4), markedly ill (5), severely ill (6), or among the most severely ill patients (7). As required by the protocol, all patients were moderately ill or worse at baseline, and the distribution of patients in each category was similar for the 2 treatment groups. At the therapeutic endpoint, 79.4% of patients in the clonazepam group and 54.2% of patients in the placebo group had at least 1 unit of improvement from baseline (see Table 2), and approximately 45% of patients in the clonazepam group were normal or borderline ill compared with approximately 22% of patients in the placebo group. The difference in the distribution of CGI-S ratings between the 2 groups at endpoint (Figure 2) was statistically significant ($p < .001$).

Using the CGI-C, the investigators evaluated the change from baseline with respect to panic disorder, phobic avoidance, and anticipatory anxiety. Each of the 3 components was rated separately on a 7-point scale ranging from very much improved to very much worse. The percentage of clonazepam-treated patients who were much improved or very much improved was significantly higher ($p < .001$) than that of placebo patients for each component (see Table 2).

Patients used the 7-point PGI-C to estimate the global change in their condition from that at the screening evaluation. Significantly more ($p < .001$) clonazepam-treated patients than placebo patients considered themselves much improved or very much improved at endpoint (see Table 2).

The severity of fear associated with the main phobia specified by patients at the screening evaluation was scored on a scale ranging from 0 (none) to 10 (extreme), and the frequency with which they avoided the main phobia was rated on a 5-point scale ranging from never to always. At endpoint, the mean severity of fear associated with the main phobia was significantly lower ($p < .0001$) in the clonazepam group than in the placebo group (see Table 2). In addition, more patients in the clonazepam group reported no avoidance of their main phobia at endpoint (31% vs. 17%) (see Table 2), and the distribution of responses for the frequency of avoidance showed significant drug-placebo differences ($p = .001$).

The mean duration of anticipatory anxiety represents the percentage of time a patient spent experiencing anticipatory anxiety during the preceding week. At endpoint, it showed a significantly larger decrease ($p < .001$) in the clonazepam group than in the placebo group (see Table 2).

Patients used the 5-point WSD scale to estimate the extent to which their panic disorder interfered with work and social activities (1 = no complaints, 5 = symptoms radically change or prevent normal work or social activities). At baseline, 84% of the patients in both treatment groups reported that their panic disorder interfered with their normal work and social activities. At endpoint, that percentage had dropped to 40% for the clonazepam group versus 60% for the placebo group, a statistically significant difference ($p < .001$).

Decreases in the HAM-A ratings at endpoint, indicative of reduced anxiety, were significantly ($p < .001$) greater in the clonazepam group than in the placebo group (see Table 2).

Efficacy Assessments in the Discontinuance Phase

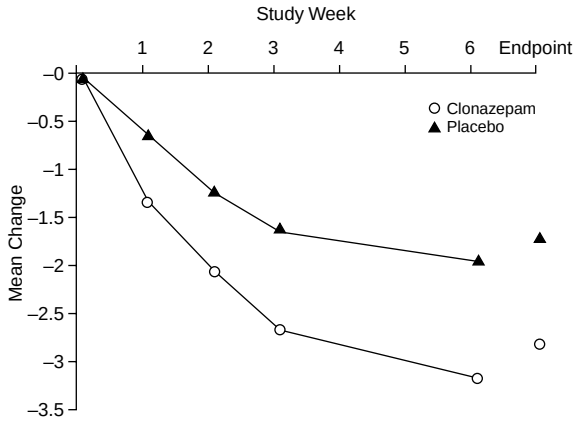
Descriptive statistics comparing the patients' condition at the discontinuance endpoint with that at the therapeutic endpoint were available for patients who had both a week 6 evaluation and at least one evaluation in the discontinuance phase (Table 3). The clonazepam group showed a greater increase in the mean number of panic attacks at discontinuance endpoint (from 0.9 to 2.7) than did the placebo group (from 1.5 to 1.8). Similarly, the evolution

Table 2. Baseline and Endpoint Efficacy Variables by Treatment Group[a]

Efficacy Variable	Clonazepam Baseline (N = 222)	Clonazepam Endpoint (N = 218)	Placebo Baseline (N = 216)	Placebo Endpoint (N = 212)	Clonazepam vs. Placebo, p Value at Endpoint
Mean no. of panic attacks	4.2	1.5	3.9	2.2	< .01
% Patients panic-free	0.9	61.9	0.5	36.8	< .001
% Patients with at least 1 unit of improvement from baseline on the CGI-S	…	79.4	…	54.2	…
CGI-C score, % patients much or very much improved					
Panic disorder rating	…	69	…	40	< .001
Phobic avoidance rating	…	53	…	27	< .001
Anticipatory anxiety rating	…	61	…	33	< .001
PGI-C score, % patients much or very much improved compared with condition at screening	…	70	…	42	< .001
Mean severity of fear associated with main phobia	6.9	3.8	7.0	5.1	< .0001
% Patients with no avoidance of their main phobia	13	31	7	17	…
Mean duration of anticipatory anxiety (% of time)	27.7	14.8	26.6	21.0	< .001[b]
Mean HAM-A total score	20.9	11.0	21.0	15.0	< .001[b]

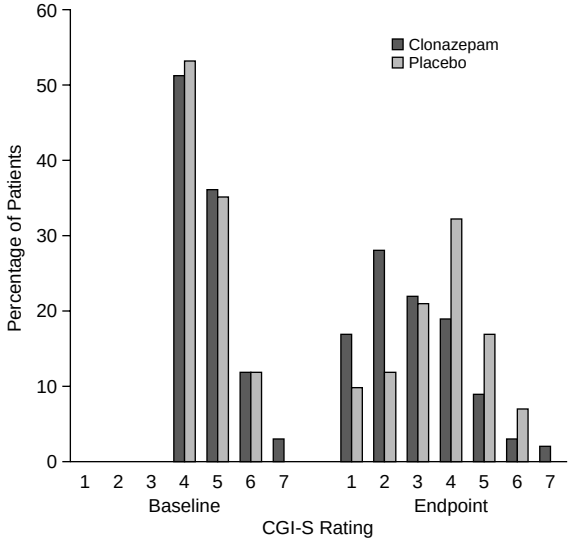
[a]Abbreviation: PGI-C = Patient's Global Impression of Change.
[b]Decrease from baseline to endpoint values significantly greater for clonazepam-treated patients than for placebo-treated patients.

Figure 1. Mean Change in Number of Panic Attacks by Week of Visit[a]



[a]The mean number of panic attacks at baseline was 4.2 in the clonazepam group and 3.9 in the placebo group. Mean change is the decrease in number of attacks from baseline at the on-treatment timepoints. The differences at week 6 and at endpoint were statistically significant (p = .004), based on the Cochran-Mantel-Haenszel procedure applied to the rank-transformed data.

Figure 2. Distribution of Ratings on the CGI-S at Baseline and Endpoint[a]



[a]The severity of panic disorder was rated on a scale ranging from 1 = normal to 7 = most severely ill. The difference at endpoint was statistically significant (p < .001), based on the Cochran-Mantel-Haenszel procedure.

in CGI-S ratings between the therapeutic and the discontinuance endpoints indicated stability in the placebo group and increasing severity in the clonazepam group.

Comparisons of the patients' condition at the discontinuance endpoint with the original baseline condition (at week 0) were made for all patients who participated in the discontinuance phase, irrespective of whether they had week 6 data. The proportion of patients who had more panic attacks at discontinuance than at baseline was similar in the 2 groups: 22.8% (43/189) in the clonazepam group and 18.9% (32/169) in the placebo group, implying an absence of rebound phenomenon with discontinuance of clonazepam. Similarly, among the patients who participated in the discontinuance phase, 55.8% (106/190) of

those treated with clonazepam and 56.6% (98/173) of those treated with placebo had at least one unit of improvement on the CGI-S at the discontinuance endpoint; on the other hand, in the same patient population, 4.8% (9/187) of those treated with clonazepam and 3.5% (6/173) of those treated with placebo had worsened by at least one unit on the CGI-S panic disorder scale by the discontinuance endpoint.

Table 3. Comparison of Patients' Condition at Discontinuance Endpoint With Condition at Therapeutic Endpoint by Treatment Group

	Clonazepam		Placebo	
Variable	Therapeutic Endpoint	Discontinuance Endpoint	Therapeutic Endpoint	Discontinuance Endpoint
No. of panic attacks	(N = 168)		(N = 143)	
Mean	0.9	2.7	1.5	1.8
Median	0.0	1.0	1.0	1.0
Patients rated markedly to most severely ill on CGI-S	(N = 169)		(N = 144)	
N (%)	12 (7)	38 (22)	25 (17)	31 (22)

Efficacy and Baseline Agoraphobia

At baseline, the population consisted of 322 patients with agoraphobia (74%) and 116 nonagoraphobic patients (26%). At endpoint, patients with agoraphobia showed marked drug-placebo difference, with 68% of the clonazepam group having ratings of "normal," "borderline ill," or "mildly ill" versus 37% of the placebo group receiving similar ratings. In contrast, for the nonagoraphobic population, the drug-placebo differences for the same CGI-S ratings were much less (70% vs. 63%).

Safety

All reported adverse events were considered in the safety analysis regardless of their relationship to the study drug. At least one adverse event was reported by 87.8% of patients in the clonazepam group and by 72.9% of patients in the placebo group. The mean number of adverse events was 3.5 in the clonazepam group and 2.2 in the placebo group. The principal difference between the clonazepam and the placebo treatment groups was in the incidence of neuropsychiatric adverse events. Two hundred thirty-one such events were reported among the 230 patients receiving clonazepam, in contrast to 136 events among the 225 patients receiving placebo.

The 12 specific adverse events listed in Table 4 were reported by at least 5% of the patients in at least one treatment group. All but headaches were reported more often in the clonazepam group than in the placebo group. Somnolence was the most frequent complaint in the clonazepam group and was reported almost 3 times more often in this group than in the placebo group (45.7% of patients vs. 16.4%). Three other adverse events were reported at least twice as frequently by patients receiving clonazepam compared with patients receiving placebo: depression (9.6% vs. 2.7%), irritability (7.8% vs. 3.6%), and ataxia (7.0% vs. 0.4%).

Most of the adverse events in the clonazepam group, particularly somnolence, had their onset during the first 3 weeks of treatment. During the discontinuance phase, insomnia (7.2% vs. 2.5%) and nausea (5.5% vs. 1.2%) were the only adverse events showing noticeable drug-placebo differences.

Table 4. Adverse Events Reported in ≥ 5% of Patients in at Least One Treatment Group in the Safety Population (irrespective of relationship to study drug)

	Clonazepam (N = 230)		Placebo (N = 225)	
Adverse Event	N	%	N	%
Somnolence	105	45.7	37	16.4
Headache	45	19.6	52	23.1
Upper respiratory infection	31	13.5	21	9.3
Fatigue	28	12.2	15	6.7
Nausea	26	11.3	13	5.8
Depression	22	9.6	6	2.7
Dizziness	20	8.7	13	5.8
Irritability	18	7.8	8	3.6
Insomnia	16	7.0	12	5.3
Ataxia	16	7.0	1	0.4
Influenza	15	6.5	14	6.2
Sinusitis	12	5.2	10	4.4

Adverse events led to early withdrawal for 25 patients treated with clonazepam and 15 patients treated with placebo. These were essentially neuropsychiatric events. Depression was the reason for withdrawal for 9 clonazepam-treated patients and 2 placebo-treated patients, somnolence was the reason for withdrawal for 6 clonazepam-treated patients and 3 placebo-treated patients, and anxiety was the reason for withdrawal for 3 patients in each group. Seven patients taking clonazepam experienced serious adverse events: 2 cases of suicidal ideation and 1 case each of pancreatitis, thrombophlebitis, alcohol intolerance, hemorrhoids, and chest pain. There were no deaths. With respect to blood pressure or pulse rate, no noticeable trends were observed in either treatment group. No trends of clinical relevance were observed in laboratory results, including hematologic tests and liver function tests.

Two of the 22 patients receiving clonazepam who experienced depression as an adverse event required treatment versus 1 of the 6 corresponding patients receiving placebo. These patients were predominantly females: 19 of 22 in the clonazepam group and 5 of 6 in the placebo group. Diagnostic categorizations, i.e., how many met the criteria for a DSM-III-R diagnosis of major depression, are not available on the records from which the database was created.

Considering the entire intent-to-treat population at endpoint, the mean HAM-D scores had decreased by 3.4 points in the clonazepam group and 1.6 points in the placebo group. An analysis of item 3 of the scale (suicidal ideation) indicates that an identical proportion (0.5%) of patients in both treatment groups had a change from a baseline score of 0 or 1 to a postbaseline score of 3 or 4. Similarly, there was no significant drug-placebo difference in the number of patients who experienced a postbaseline increase in their item 3 score: 29 (14%) of 209 versus 21 (11%) of 199, respectively ($p = .365$, based on the 2-sided Fisher exact test).

DISCUSSION

The results of this study provide consistent evidence of clonazepam's efficacy in the short-term treatment of panic disorder and of its superiority over placebo in the study's efficacy outcomes. Placebo-treated patients demonstrated modest improvement in all efficacy variables, as was seen in the Cross-National Collaborative Panic Study.[5] However, in the absence of a group of untreated controls, it is not possible to distinguish between a true versus a perceived placebo effect.[29] Such nonspecific effects as the natural course of panic disorder, the regression toward the mean, and, possibly, inadvertent behavioral interventions during the study could have contributed to the perceived placebo effect.

The evidence of efficacy, assessed on the basis of drug-placebo differences, encompassed 3 categories of outcomes: global ratings of the condition (CGI-S for panic disorder, CGI-C for panic disorder, PGI-C, and HAM-A), assessments of the main components of panic disorder (panic attacks, phobia-induced fear and avoidance, and anticipatory anxiety), and evaluation of the disabling effect of the condition. The CGI-S and CGI-C results exemplify the global drug effect; at endpoint, 45% of patients receiving clonazepam (vs. 22% receiving placebo) were categorized normal or borderline ill, and 69% of patients receiving clonazepam (vs. 40% receiving placebo) were rated much or very much improved. The effect on panic is illustrated by a median reduction of 2.0 panic attacks per week in the clonazepam group (vs. 1.0 in the placebo group) and by respective endpoint rates of 62% versus 37% of patients free of panic attacks. Similar drug-placebo differences emerged in the ratings of phobic fear, phobic avoidance, and anticipatory anxiety.

The efficacy results in this trial are consistent with those reported in previously published placebo-controlled studies. Beauclair et al.[12] observed significant differences after 4 weeks of double-blind treatment in 29 patients with respect to number of panic attacks, CGI-S scores, and HAM-A scores. The mean daily dose of clonazepam was 2.3 mg during the last 3 weeks of that trial. In the trial by Tesar et al.,[1] 72 patients were randomly assigned to either clonazepam (N = 26), alprazolam (N = 24), or placebo (N = 22) for a 6-week treatment. At endpoint, statistically significant differences between both drugs and placebo were observed in the number of panic attacks, the CGI-S scores, the overall phobic distress, and the disability ratings; on the other hand, no significant drug-placebo difference was found in the daily duration of anticipatory anxiety. The baseline categorization as agoraphobic or nonagoraphobic was relevant for the global rating results, as drug-placebo differences were much greater in agoraphobic patients.

A unique feature of this study was the assessment of a schedule for gradually tapering the clonazepam dosage during the 7-week discontinuance phase. The number of panic attacks and the CGI-S scores at the discontinuance endpoint were compared with those both at the therapeutic endpoint and at the original baseline. In comparison with the placebo group, clonazepam-treated patients experienced some degree of clinical deterioration with regard to their condition at therapeutic endpoint, but did not revert to their baseline status. Thus, most patients tolerated the gradual cessation of clonazepam without suffering the rebound commonly associated with the discontinuation of benzodiazepines. Moreover, the discontinuance phase was not associated with the high dropout rates or the emergence of adverse events that would have pointed to poor tolerability. Among the patients taking clonazepam who completed the therapeutic phase, 28.2% (51/181) dropped out during the discontinuance phase, a figure similar to the one observed in the placebo group (28.6%, 46/161). Concerning adverse events emerging during that phase, insomnia (7.2% vs. 2.5%) and nausea (5.5% vs. 1.2%) were the only ones showing noticeable drug-placebo differences.

Among the limitations affecting the analysis and interpretation of the discontinuance data are the endpoint analysis and the small number of visits during that phase: together, they may have reduced the reporting of clinical deterioration and adverse events, particularly in patients who may have dropped out before a visit captured their worsening condition. Furthermore, the lack of an a priori classification of discontinuation syndromes, using the concepts of recurrence, rebound, and withdrawal (with corresponding definitions),[30] reduces the interpretability of the results. It is possible that the actual incidence of rebound, a phenomenon with quick onset and of limited duration, may have been underestimated as a result of the sparsity of assessments. Finally, given the long half-life of clonazepam, it would have been useful to gather clinical observations for more than a week beyond taper-to-zero dose.

The safety and tolerability results of the study are consistent with the well-known safety profile of benzodiazepines as a class. Somnolence, which is due to the sedative effects of benzodiazepines, was the most prominent adverse event associated with clonazepam. No major

safety problems arose during the trial. Clinically significant drug-placebo differences were evident in the overall frequency of adverse events, in the frequency of neuropsychiatric adverse events, and in the incidence of the following specific adverse events: somnolence, depression, irritability, and insomnia. Most adverse events were evident in the first 3 weeks of treatment during the dose-optimization part of the therapeutic phase; in the discontinuance phase, insomnia was the main adverse event, affecting 7.2% of patients receiving clonazepam (vs. 2.5% of patients receiving placebo).

Depression was the adverse event that most often led to early termination (9 cases in the clonazepam group and 2 in the placebo group), and the drug-placebo ratio of incidences was more than 2-fold. It should be pointed out, however, that depression was reported as an adverse event, not as a clinically established diagnosis, so that no DSM-III-R categorization is available; furthermore, no overall upward move was observed in the HAM-D ratings, and there was no significant between-group difference in suicidal ideation. With respect to depression, the results of this trial stand in contrast to 2 other placebo-controlled clonazepam studies. Beauclair et al.[12] found that clonazepam had a greater beneficial effect than placebo on depressive symptoms associated with panic disorder. In a comparison of clonazepam, alprazolam, and placebo for the treatment of panic disorder, Tesar et al.[1] reported that all 3 treatment groups had modest improvements in Beck Depression Inventory scores. In that study, none of the patients in the clonazepam or placebo groups reported treatment-emergent depression. Benzodiazepine-associated depression is a recognized phenomenon and has also been observed during alprazolam treatment of panic disorder.[31] Additional confounding factors such as the high incidence of depressive disorder in this patient population and the possible unmasking of depressive symptoms associated with the decrease in anxiety make it difficult to evaluate whether clonazepam has a causal role. A 1-year follow-up in a cohort of 50 patients[19] indicated that, in practice, clonazepam-associated depression responds favorably to dosage reduction, addition of an antidepressant, or substitution with alprazolam.

This study's main limitation is its duration, which did not allow for an evaluation of the dosage, therapeutic effect, and tolerability of clonazepam beyond several weeks. Panic disorder is a chronic condition, and most patients are treated for much longer than 6 weeks. Furthermore, the assessment of the potential for tolerance and dependence would have required a long-term study. Similarly, the clinical effects of discontinuation of clonazepam after long-term exposure have not been studied in controlled trials. Uncontrolled trials evaluating long-term exposure to clonazepam[32] suggest that most patients maintain a therapeutic benefit without an increase in dose or safety problems.

CONCLUSION

This multicenter, placebo-controlled study confirms the efficacy and tolerability of clonazepam for the treatment of panic disorder, with or without agoraphobia. Patients receiving placebo had a modest response in all efficacy variables, but those receiving clonazepam had clinically and statistically significantly better responses in all efficacy variables. The slow taper of clonazepam was not accompanied by symptoms suggestive of withdrawal syndrome, although an increase in the number of panic attacks was observed during that phase. No serious safety problems were encountered.

Drug names: alprazolam (Xanax and others), clonazepam (Klonopin and others), diazepam (Valium and others), lorazepam (Ativan and others), midazolam (Versed), triazolam (Halcion).

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