

High-Potency Benzodiazepines: Recent Clinical Results

Georges Moroz, M.D.

As high-potency benzodiazepines, essentially alprazolam, clonazepam, and lorazepam, have been used to treat anxiety disorders for almost 2 decades, most efficacy and safety data appeared several years ago. The release of new formulations of 2 of them, clonazepam and alprazolam, invites review of these broadly effective anxiolytics. Clonazepam has recently become available in a lyophilized wafer that disintegrates when exposed to saliva and enhances ease of administration without altering its pharmacology, as shown by bioequivalence studies. Two U.S. multicenter trials carried out in the 1990s, among others, have provided strong confirmatory evidence for the use of clonazepam in panic disorder. Other recently published data on clonazepam pertain to its use as augmentation therapy with selective serotonin reuptake inhibitors and in the prevention of recurrences of major depressive disorder. A new, extended-release formulation of alprazolam now allows for once-daily rather than t.i.d. or q.i.d. dosing. With extended release, the blood drug concentrations of alprazolam remain within the therapeutic window for several hours, which should reduce fluctuation in therapeutic effect and curb the clock-watching phenomenon between doses. The literature concerning the use of this new formulation of alprazolam in panic disorder is reviewed. (*J Clin Psychiatry* 2004;65[*suppl* 5]:13–18)

Since high-potency benzodiazepines, mainly alprazolam, clonazepam, and lorazepam, have been used to treat anxiety disorders for almost 2 decades, most efficacy and safety data appeared several years ago. Today, benzodiazepines remain one of the most broadly effective pharmacologic treatments for anxiety disorders.¹ Clonazepam has recently become available in an orally disintegrating tablet, and alprazolam has recently been marketed in an extended-release formulation. The availability of these new formulations of clonazepam and alprazolam has awakened new interest in these agents, signaling the need for a literature review of the most relevant recent clinical studies.

SELECTED CLONAZEPAM STUDIES

Clonazepam has a strong affinity and specificity for the benzodiazepine binding sites located on postsynaptic receptors for the inhibitory neurotransmitter γ -aminobutyric acid²; in addition, unlike many other benzodiazepines, clonazepam up-regulates the serotonin-1 and -2 (5-HT₁ and 5-HT₂) receptors. This serotonergic effect may underlie the

drug's antimyoclonic and some of its psychotropic effects. Clonazepam has high bioavailability (90%). Plasma concentrations peak at 1 to 4 hours after oral dosing. Liposolubility is low, hence a low volume of distribution. The elimination half-life is 30 to 40 hours. Clonazepam has no active metabolite, and primary metabolism occurs via the cytochrome P450 3A substrate. The pharmacokinetics of clonazepam are not significantly affected by the selective serotonin reuptake inhibitors (SSRIs) fluoxetine or sertraline, both of which have been studied in combination or augmentation therapy with clonazepam.

The new formulation of clonazepam, the orally disintegrating tablet, is essentially a lyophilized wafer that enhances ease of administration without altering pharmacology. In its manufacture, a solution of polymers, saccharides, and clonazepam is placed into a mold, frozen, and dehydrated. The result is a tablet-shaped wafer that disintegrates when exposed to saliva. Bioequivalency studies (data on file, Roche Laboratories, Nutley, NJ) have established that the wafers have the same pharmacokinetic parameters (area under the curve and maximum plasma concentration) as the regular clonazepam tablet.

The ability of a single dose of clonazepam to prevent carbon dioxide (CO₂)-induced panic attacks was documented in a randomized double-blind study by Nardi et al.³ One hour after a single dose of 2 mg of clonazepam or placebo, 22 medication-free panic disorder patients inhaled 35% CO₂, which is known to provoke panic in people with panic disorder. In the clonazepam group, 2 patients (18%) experienced a mild panic attack due to the CO₂ challenge. In the placebo group, 9 patients (81%) had a moderate-to-severe panic attack.

*From the Department of Clinical Science,
Hoffmann-La Roche, Inc., Nutley, NJ.*

*This article is derived from the roundtable meeting
"Revisiting the Use of High-Potency Benzodiazepines," which
was held July 11, 2003, in Boston, Mass., and supported by an
unrestricted educational grant from Solvay Pharmaceuticals.*

*Corresponding author and reprints: Georges Moroz, M.D.,
Department of Clinical Science, Hoffmann-La Roche, Inc.,
340 Kingsland St., Nutley, NJ 07110
(e-mail: georges.moroz@roche.com).*

Multicenter Panic Disorder Studies

Two U.S. multicenter trials^{4,5} carried out in the 1990s provided strong evidence for the use of clonazepam in panic disorder. They confirmed the efficacy and safety findings of earlier studies conducted by Chouinard's and Rosenbaum's groups,^{6,7} established the dose-response characteristics of the drug in panic disorder, and provided a schedule for the discontinuation of clonazepam after 6 or 9 weeks of treatment; furthermore, they documented a comprehensive therapeutic effect on the main clinical components of panic disorder: panic attacks, phobic fear and avoidance, anticipatory anxiety, and disability; and finally, they formed the basis for the U.S. Food and Drug Administration labeling of clonazepam.

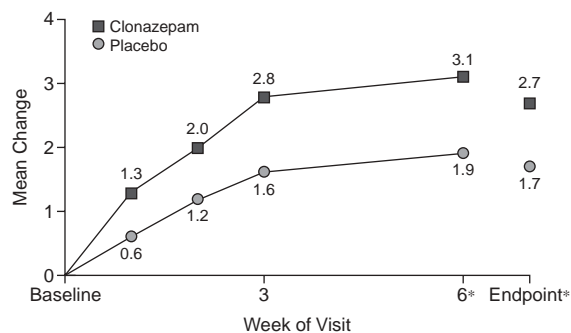
Both studies^{4,5} tested a dose range of 0.5 to 4 mg/day of clonazepam in comparison with placebo. The first⁴ was a 6-week flexible-dose study that allowed for dose adjustments in conditions close to clinical practice, while the other⁵ was a 9-week fixed-dose study (including a titration period of up to 3 weeks) designed to provide dose-response characterization for efficacy and tolerability. In both studies, treatment was followed by a discontinuation phase entailing a double-blind taper.

In both studies,^{4,5} key outcome variables included the number of panic attacks over the last 7 days; the scores for Clinical Global Impressions-Severity of Illness scale (CGI-S) and -Change From Baseline scale (CGI-C) for panic disorder; ratings of phobic avoidance and anticipatory anxiety, also measured by the CGI-C; fear and avoidance associated with the patient's main phobia as identified at baseline (measured on an 11-point and a 5-point scale, respectively); and proportion of time spent experiencing anticipatory anxiety each day. Both patient populations were to meet a DSM-III-R primary diagnosis of panic disorder with or without agoraphobia, to have experienced at least 4 panic attacks over the previous 4 weeks, and to be moderately ill at baseline according to CGI-S scores. A concomitant secondary diagnosis of mood or anxiety disorder was allowed.

In the flexible-dose study (N = 438),⁴ 222 subjects were randomly assigned to clonazepam and 216 to placebo. The treatment groups were demographically and clinically similar. The mean age of the population was about 37 years. In each group, approximately 64% of patients were women and approximately 73% were agoraphobic. In the clonazepam group, patients had a mean of 4.2 panic attacks (median = 3.0) over the previous 4 weeks; in the placebo group, the mean number of panic attacks over the previous 4 weeks was 3.9 (median = 2.0). The mean and median dosages of clonazepam in the active arm were 2.3 mg/day and 2.0 mg/day, respectively.

The characteristics of the patient population in the fixed-dose study⁵ were very similar to those in the flexible-dose study.⁴ Seventy-nine percent of the 404 subjects had agoraphobia and 56% were women. Their mean age was

Figure 1. Mean Reduction in Number of Panic Attacks From Baseline in Flexible-Dose Study^a



^aAdapted from Moroz and Rosenbaum.⁴ Numerical increase on x-axis indicates reduction in number of panic attacks.

*Statistically significant difference ($p < .01$) at week 6 and endpoint.

37 years, with a mean of 4.0 panic attacks (median = 2.0) over the previous 4 weeks. Subjects were randomly assigned to receive either placebo or 1 of 5 fixed daily dosages of clonazepam: 0.5 mg, 1 mg, 2 mg, 3 mg, or 4 mg.

Despite different designs, the studies yielded convergent efficacy results. In the flexible-dose study,⁴ 61.9% (N = 218) of clonazepam-treated patients were panic free at endpoint compared with 36.8% (N = 212) of placebo-treated patients ($p < .001$). Among patients who were not panic free, the mean number of panic attacks from baseline to endpoint declined significantly ($p = .004$) more in the clonazepam group than in the placebo group (Figure 1). On CGI-S scores at endpoint, 79.4% of patients who received clonazepam versus 54.2% of patients who received placebo had improved by at least 1 unit of measure. Compared with placebo-treated patients, a significantly ($p < .001$) higher percentage of clonazepam-treated patients were "much" or "very much" improved at endpoint on each of the 3 CGI-C measures: panic disorder, phobic avoidance, and anticipatory anxiety. Data showed a statistically significant ($p < .001$) reduction from baseline to endpoint in severity of symptoms associated with the primary phobia in the clonazepam group compared with the placebo group. There was likewise a statistically significant ($p < .001$) drug-placebo difference at endpoint in the frequency distribution of avoidance ratings. The number of patients experiencing anticipatory anxiety decreased from 28% to 15% in the clonazepam group and from 27% to 21% in the placebo group ($p < .001$).

The fixed-dose study⁵ allowed for dose-response characterization. The minimal effective dose of clonazepam was found to be 1 mg/day for both panic attacks and phobic fear. Linear regression analysis showed a flat dose-response curve from 1 to 4 mg/day for effect on panic attacks. Overall, patients who received the 1 mg/day dose of clonazepam showed the most consistent significant differences from the placebo group in number of panic attacks,

phobic fear and avoidance, CGI-S and CGI-C scores, and intensity of anticipatory anxiety.

In both studies,^{4,5} the tolerability of clonazepam was comparable to that established for other benzodiazepines. In the flexible-dose study, 4 adverse events were reported at least twice as frequently by patients taking clonazepam than by those taking placebo: somnolence (45.7% vs. 16.4%), depression (9.6% vs. 2.7%), irritability (7.8% vs. 3.6%), and ataxia (7.0% vs. 0.4%). In the fixed-dose trial, there was a higher incidence of adverse events among patients receiving 3 or 4 mg/day of clonazepam. Those adverse events with a clearly dose-related incidence were somnolence and ataxia. Depression, dizziness, fatigue, and irritability occurred more frequently with clonazepam than with placebo but did not reveal a dose-related pattern.

Both study designs^{4,5} incorporated a period of taper entailing dose decrements every 3 days: decrements of 0.25 mg in the fixed-dose study⁵ and of 0.5 mg (followed by 0.25 mg once a dose threshold of 1 mg/day was reached) in the flexible-dose study.⁴ Most patients in the fixed-dose study⁵ tolerated discontinuation well, with the most frequently reported adverse events being headache (4%–22% in the clonazepam groups vs. 4% in the placebo group) and insomnia (2%–13% vs. 4%). The ranges of event occurrence in the clonazepam groups did not suggest any apparent relationship to dosage. During discontinuation, patients who had received clonazepam experienced an increase in mean number of panic attacks per week (ranging from 0.6 to 1.5 in the 3-mg and 4-mg groups) compared with mean number of panic attacks at week 6, whereas that parameter remained stable in the placebo group during that phase. Compared with baseline, there was no evidence of rebound (a return and worsening of symptoms) in this short-term study, in terms of both number of panic attacks and CGI-S scores at the final visit.

During the discontinuation phase of the flexible-dose study,⁴ the only 2 adverse events with notable drug-placebo differences in occurrence were insomnia (7.2% vs. 2.5%) and nausea (5.5% vs. 1.2%). There was no evidence of rebound at discontinuation endpoint as gauged by number of panic attacks and CGI-S scores; however, in comparison with the last week of treatment, the clonazepam group did show a greater increase in panic attacks at discontinuation endpoint (2.7 compared with 0.9 at week 6) than did the placebo group (1.8 compared with 1.5 at week 6). It should be noted that limitations in the measurement process during this discontinuation phase may have affected its interpretability, particularly the small number of patient visits (and thus the infrequent measures taken) and the absence of an a priori checklist of symptoms associated with withdrawal.

Overall, the 2 trials^{4,5} led to the conclusion that a dosage of 1 to 2 mg/day of clonazepam (with b.i.d. intake) provided a good balance of efficacy and tolerability in the treatment of panic disorder. The tolerability of clonazepam

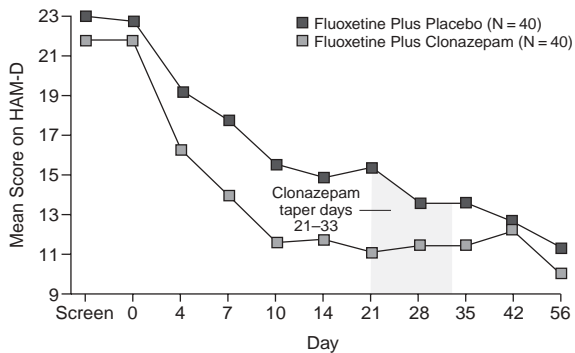
was similar to that of other benzodiazepines. A taper schedule based on 3-day decrements was well tolerated and was not associated with rebound.

Augmentation Studies

Continuing research^{8,9} on clonazepam examined its action in combination with other psychotropic medications commonly prescribed to anxious and/or depressed patients, such as SSRIs. Because SSRIs require several weeks to achieve full efficacy, it is plausible that augmentation with fast-acting benzodiazepines may reduce a patient's time to response and facilitate rapid clinical stabilization. To test this hypothesis, Goddard et al.⁸ studied clonazepam in coadministration with sertraline in a population of 50 patients with moderate to severe panic disorder. Patients received flexible-dose, open-label sertraline (titrated toward a target dose of 100 mg/day) for the duration of the 12-week study. Additionally, these patients were randomly assigned to receive either 0.5 mg of clonazepam or placebo t.i.d. for the first 4 weeks of the trial; afterward, clonazepam or placebo doses were tapered over 3 weeks. Twenty-five percent of patients receiving clonazepam and 38% of patients receiving placebo dropped out of the study before endpoint; these percentages did not represent a statistically significant difference in completion rates between groups.

Primary efficacy measures in this study⁸ were based on the 7-item Panic Disorder Severity Scale (PDSS). Response to treatment (defined by a $\geq 50\%$ improvement in PDSS scores) was experienced by 41% of patients receiving clonazepam plus sertraline versus 4% of patients receiving placebo plus sertraline, a statistically significant difference ($p = .003$), by the end of week 1. By the end of week 3, these numbers had risen to 63% of clonazepam patients and 32% of placebo patients ($p = .05$). There were, however, no statistically significant differences in response status between groups at week 2 or at weeks 4 through endpoint. The total PDSS scores indicated superior efficacy with clonazepam plus sertraline compared with placebo plus sertraline at weeks 1 and 2. Safety data and dropout rates suggested that clonazepam in coadministration with sertraline, and clonazepam discontinuation, were well tolerated. Both treatment groups reported adverse events in a similar pattern and at a similar frequency, with the exception of diarrhea, which was reported exclusively by patients receiving clonazepam and mostly during drug taper. The authors concluded that coadministration of clonazepam and sertraline provide rapid stabilization of symptoms in panic disorder. These findings contrasted with those of a previous study¹⁰ that combined alprazolam and imipramine during the initial phase of treatment for panic disorder; in that study, more patients responded to imipramine combined with placebo than to imipramine combined with alprazolam, mainly due to the inability of some patients to taper off alprazolam during the 2-week discontinuation period.

Figure 2. Scores on the HAM-D Over 8 Weeks for Patients Taking Fluoxetine Plus Clonazepam or Fluoxetine Plus Placebo^a



^aReprinted with permission from Smith et al.⁹
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Acute augmentation with clonazepam has also been examined in the treatment of major depressive disorder. Smith et al.⁹ tested the effectiveness of fluoxetine augmented with clonazepam versus fluoxetine alone in 80 moderately or markedly depressed patients. All 80 patients were treated for 8 weeks with fluoxetine at 20 mg/day, which was raised to 40 mg/day after 6 weeks if necessary. One half of these patients were randomly assigned to also receive 0.5 mg h.s. of clonazepam or placebo; the dose could be increased to 1.0 mg h.s. by day 10 if needed, which was the case for 60% of patients receiving clonazepam. From days 10 to 21, patients maintained their adjusted dosages. Both clonazepam and placebo were then tapered to discontinuation over days 21 to 33.

Patient response was assessed on the basis of the 17-item Hamilton Rating Scale for Depression (HAM-D) scores and CGI-Improvement (CGI-I) scores.⁹ Significantly lower HAM-D scores were observed in the clonazepam group at days 7, 10, and 21 (Figure 2). Subsequently (days 28 to 56), there was no significant difference between groups. There was actually a slight increase in HAM-D score after taper of clonazepam (days 35 and 42). A similar pattern was seen with response defined as reduction by at least 50% from HAM-D baseline score, with significantly more responders taking clonazepam at days 7 (30% vs. 13%), 14 (48% vs. 25%), and 28 (58% vs. 38%). Also, a CGI-I score of "much" or "very much" improved was achieved by 35% of clonazepam patients versus 13% of placebo patients at day 7 and by 55% of clonazepam patients versus 33% of placebo patients at day 14, both significant differences; the respective percentages were 65% versus 45% at day 28. After day 28, there was a numerical but not a statistically significant difference in response between the 2 groups. Overall, these results suggest that most of the benefit from the combination therapy was derived early in treatment. Patients receiving clonazepam experi-

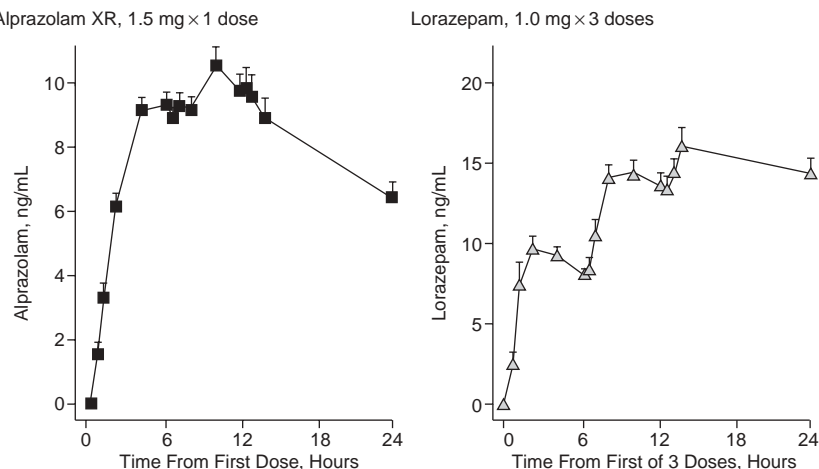
enced more sedation, less sleep impairment, and less anxiety than did patients receiving placebo, but none of these differences was found to be statistically significant. During taper, 10 patients in the placebo group and 4 patients in the clonazepam group experienced emerging or worsening adverse events. The authors concluded that clonazepam plus fluoxetine is superior to fluoxetine alone in symptomatic relief of major depressive disorder during the first 3 weeks of treatment. Patients receiving clonazepam augmentation achieved in 10 days the same improvement in HAM-D scores that patients receiving fluoxetine alone reached by day 56. Further, augmentation of fluoxetine with clonazepam seemed to help suppress the anxiety and insomnia sometimes associated with initial SSRI treatment.

Prophylaxis of Depression

A recent publication pertains to the use of clonazepam in the prophylaxis of depressive episodes.¹¹ A retrospective chart review at a lithium clinic included 15 patients with unipolar depressive disorder who were not benefiting from or could not tolerate lithium treatment. Their mean age was 43 years, and the mean duration of the disorder was 11 years. These patients received adjunctive clonazepam or clonazepam alone at a mean dose of 2 mg/day and were observed for 2.7 years prior to treatment and 1.1 years afterward. The mean \pm SD number of yearly depressive episodes experienced by these patients dropped from 1.5 ± 2.9 before clonazepam treatment to 0.3 ± 0.5 during treatment with clonazepam, a significant decline ($p = .026$). Eleven of the 15 patients had no relapse during the follow-up period of 1.1 years. This intriguing study has obvious limitations, including small sample size, possible selection bias, open-label clonazepam administration, and asymmetry between the pre- and post-intervention observation times. As a retrospective chart review, it lacks an experimental design but invites possible duplication in prospective and controlled conditions.

SELECTED ALPRAZOLAM STUDIES

Alprazolam in its conventional formulation is readily absorbed, with peak plasma concentrations occurring 1 to 2 hours after oral administration. Because the mean elimination half-life of this high-potency benzodiazepine is a relatively brief 11.2 hours, the conventional formulation requires multiple daily dosing. However, an extended-release (XR) formulation of alprazolam recently became available, allowing for once-daily rather than t.i.d. or q.i.d. dosing. The maximum plasma concentration is decreased as a result of the slow release from a methylcellulose matrix, and the time to maximum plasma concentration is delayed; therefore, the blood drug level remains within the therapeutic window for several hours.¹² The expected clinical result is reduced fluctuation in therapeutic effect, which should help to curb breakthrough anxiety and the clock-watching

Figure 3. Blood Drug Concentration of Alprazolam XR and Lorazepam^a

^aAdapted with permission from Busto et al.¹³

phenomenon between doses. On the other hand, the elimination half-life of the new formulation is the same as that of the originally marketed compressed tablet.

Busto et al.¹³ measured the pharmacokinetics of 1.5 mg/day of alprazolam XR (referred to in this and other studies as alprazolam sustained release [SR]), lorazepam 1 mg t.i.d., bromazepam 3 mg t.i.d., and placebo in 13 healthy volunteers. The plasma concentration peak plateau for alprazolam SR started 6 hours postdose, whereas the initial peaks for lorazepam and bromazepam started 1 to 2 hours postdose (Figure 3). Once the peak plateau was reached, blood drug concentration was better sustained for alprazolam SR than for lorazepam and bromazepam.

Schweizer et al.¹⁴ conducted a double-blind, placebo-controlled clinical trial to determine the efficacy and safety of alprazolam SR in an anxious population. Patients (N = 194) met DSM-III-R diagnoses of agoraphobia with panic attacks or panic disorder with limited phobic avoidance. At baseline, the mean number of major panic attacks per week was 6.3 for patients assigned to the alprazolam SR group and 6.0 for patients assigned to placebo. Mean baseline global phobia score for each group was 6.9 on a scale of 1 to 10, suggesting moderate-to-marked phobic avoidance. Patients underwent a 1-week placebo washout. They were then randomly assigned to 6 weeks of treatment with either alprazolam SR (1-mg tablets) or placebo. Patients treated with the active agent were initially given 1 mg/day, increased over 3 weeks as tolerated to a maximum of 10 mg/day, with the mean highest dose of alprazolam being 4.7 mg/day. At the end of the treatment phase, patients were tapered off medication at a rate of 1 mg every 3 to 4 days for up to 5 weeks. There was subsequently a 2-week drug-free phase.

Results¹⁴ showed that with regard to weekly frequency of panic attacks, a statistically significant treatment effect favoring alprazolam SR was seen at week 1 and sustained

throughout the study. At week 6, 74 patients (85%) taking alprazolam SR were panic free versus 37 patients (61%) taking placebo, a significant difference between groups ($p < .01$). Other outcome measures on which alprazolam SR showed significantly greater efficacy than did placebo were the Hamilton Rating Scale for Anxiety (HAM-A), CGI, and phobia scores. In fact, alprazolam SR was a more effective treatment than was placebo across all study measures by last-observation-carried-forward (LOCF) analysis except the global phobia scale, the HAM-D, and the Sheehan Patient-Rated Anxiety Scale.

The placebo group had a significantly ($p < .01$) higher dropout rate than did the alprazolam SR group.¹⁴ The main adverse events occurring more frequently with alprazolam SR than with placebo were drowsiness (88% vs. 39%) and incoordination (35% vs. 2%).

During the taper and drug-free phases, the alprazolam group had transiently greater severity of anxious symptoms; an increase in the HAM-A scores above baseline level was observed in 43% of alprazolam patients (vs. 24% of placebo patients) during taper.¹⁴ During the discontinuation phase, patients stopping alprazolam had a significantly higher rate of adverse events compared with patients stopping placebo; this was particularly the case for nervousness (28% vs. 13%), headache (25% vs. 7%), diarrhea (20% vs. 2%), sleep problems (19% vs. 5%), and cognitive impairment (19% vs. 5%).

In a multicenter, double-blind clinical trial reported by Pecknold et al.,¹⁵ 184 patients who met DSM-III-R criteria for panic disorder with extensive phobic avoidance were randomly assigned to receive alprazolam XR once a day, the regular formulation of alprazolam (differentiated in the study from the XR version as CT, or compressed tablet) q.i.d., or placebo at a flexible dosage over 6 weeks. Dosage was initiated at 2 mg/day and increased by 1 mg/day per week until the patient reached optimal improvement or experienced dose-limiting side effects. At week 6, the mean dose of alprazolam CT was 3.95 mg/day, while the mean dose of alprazolam XR was 4.35 mg/day.

Both active treatments showed similar efficacy and showed significant superiority over placebo on several outcome measures at endpoint (LOCF analysis) such as the CGI-S, the CGI-I, the phobia rating (using the Marks-Mathews Phobia Scale), and work-related disability.¹⁵ Significant drug-placebo differences in the number of panic attacks occurred in the first week of treatment but were not maintained beyond that timepoint for alprazolam XR. In the following weeks, only alprazolam CT continued to

show a significant reduction in number of panic attacks compared with placebo. Week by week analysis of survivor data indicated that the panic factor (i.e., number of panic attacks times the duration of the attack times the intensity) was significantly reduced in both active drug groups relative to placebo in the first 2 weeks of treatment only. No significant differences were detected between alprazolam XR and alprazolam CT in the analysis of endpoint data, although patients treated with alprazolam CT had lower panic factor scores at all weeks. At endpoint, significant differences were observed between the CT and placebo groups and between the CT and XR groups in percentage of patients who were panic free, but the difference between the XR and placebo groups did not reach significance. For the HAM-A scores, endpoint analysis showed significant superiority for the CT formulation (but not for alprazolam XR) over placebo. Two adverse events occurred in a significantly greater proportion with the 2 active treatments than with the placebo: drowsiness and incoordination.

The discontinuation phase was reported in a separate publication.¹⁶ Taper lasted 16 weeks and was followed by a post-discontinuation evaluation 4 weeks after its completion. Similar results in terms of relapse and withdrawal symptoms were observed in both active groups, CT and XR, with a robust return of symptoms (panic attacks and generalized anxiety) during the late-discontinuation phase; this may be a correlate of both formulations having the same elimination half-life. At post-discontinuation, however, the symptoms of anxiety had subsided, so that the incidences were similar in the active groups and the placebo group.

CONCLUSION

High-potency benzodiazepines have been used for about 2 decades and remain a key component in the pharmacotherapy of anxiety disorders, particularly panic disorder. Over the last 10 years, publication on this class of drugs has mostly concerned alprazolam's extended release formulation and clonazepam in the treatment of panic and social anxiety disorders and as augmentation therapy with SSRIs. Clonazepam has recently become available in an orally disintegrating tablet, which enhances ease of administration without altering pharmacology, as bioequivalence with the regular clonazepam tablets has shown. Two U.S. multicenter trials^{4,5} carried out in the 1990s and reviewed herein provided strong confirmatory evidence for the use of clonazepam in panic disorder, established its dose-response characteristics, and documented the good tolerability of a schedule of discontinuation after short-term treatment. As augmentation therapy with SSRIs, clonazepam has been studied in combination with sertraline for the treatment of panic disorder and with fluoxetine for the treatment of major depressive disorder.

Alprazolam has recently become available in an extended-release formulation that allows for once-daily rather than t.i.d. or q.i.d. dosing. With extended release, the blood drug concentrations of alprazolam remain within the therapeutic window for several hours, which may reduce the risks of breakthrough anxiety and clock watching. This new formulation does not alter the compound's elimination half-life, and the clinical correlates of discontinuation are similar to those of the immediate-release alprazolam.¹⁴ Clinical research¹⁴ in panic disorder reviewed herein documented the efficacy of alprazolam XR in that indication.

Drug names: alprazolam (Xanax and others), clonazepam (Klonopin and others), diazepam (Valium and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lorazepam (Ativan and others), sertraline (Zoloft).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, alprazolam is not approved by the U.S. Food and Drug Administration for augmentation of imipramine, and clonazepam is not approved for the treatment of depression or for augmentation of fluoxetine or sertraline.

REFERENCES

- Weinberger DR. Anxiety at the frontier of molecular medicine. *New Engl J Med* 2001;344:1247-1249
- Greenblatt DJ, Miller LG, Shader RI. Clonazepam pharmacokinetics, brain uptake, and receptor interactions. *J Clin Psychiatry* 1987;48(suppl 10):4-9
- Nardi AE, Valença AM, Nascimento I, et al. Double-blind acute clonazepam vs. placebo in carbon dioxide-induced panic attacks. *Psychiatr Res* 2000;94:179-184
- Moroz G, Rosenbaum JF. Efficacy, safety, and gradual discontinuation of clonazepam in panic disorder: a placebo-controlled, multicenter study using optimized dosages. *J Clin Psychiatry* 1999;60:604-612
- Rosenbaum JF, Moroz G, Bowden CL, et al. Clonazepam in the treatment of panic disorder with or without agoraphobia: a dose-response study of efficacy, safety, and discontinuance. *J Clin Psychopharmacol* 1997;17:390-400
- Chouinard G, Annable L, Fontaine R, et al. Alprazolam in the treatment of generalized anxiety and panic disorders: a double-blind placebo-controlled study. *Psychopharmacology (Berl)* 1982;77:229-233
- Spier SA, Tesar GE, Rosenbaum JF, et al. Treatment of panic disorder and agoraphobia with clonazepam. *J Clin Psychiatry* 1986;47:238-242
- Goddard AW, Brouette T, Almai A, et al. Early coadministration of clonazepam with sertraline for panic disorder. *Arch Gen Psychiatry* 2001;58:681-686
- Smith WT, Londborg PD, Glaudin V, et al. Short-term augmentation of fluoxetine with clonazepam in the treatment of depression: a double-blind study. *Am J Psychiatry* 1998;155:1339-1345
- Woods SW, Nagy LM, Koleszar AS, et al. Controlled trial of alprazolam supplementation during imipramine treatment of panic disorder. *J Clin Psychopharmacol* 1992;12:32-38
- Winkler D, Willeit M, Wolf R, et al. Clonazepam in the long-term treatment of patients with unipolar depression, bipolar and schizoaffective disorder. *Eur Neuropsychopharmacol* 2003;13:129-134
- Klein E. The role of extended-release benzodiazepines in the treatment of anxiety: a risk-benefit evaluation with a focus on extended-release alprazolam. *J Clin Psychiatry* 2002;63(suppl 14):27-33
- Busto UE, Kaplan HL, Wright CE, et al. A comparative pharmacokinetic and dynamic evaluation of alprazolam sustained-release, bromazepam, and lorazepam. *J Clin Psychopharmacol* 2000;20:628-635
- Schweizer E, Patterson W, Rickels K, et al. Double-blind, placebo-controlled study of a once-a-day, sustained-release preparation of alprazolam for the treatment of panic disorder. *Am J Psychiatry* 1993;150:1210-1215
- Pecknold J, Luthe L, Munjack D, et al. A double-blind, placebo-controlled, multicenter study with alprazolam and extended-release alprazolam in the treatment of panic disorder. *J Clin Psychopharmacol* 1994;14:314-321
- Pecknold J, Alexander PE, Munjack D. Alprazolam-XR in the management of anxiety: discontinuation. *Psychiatr Ann* 1993;23(suppl 10):38-44