Prior Benzodiazepine Exposure and Benzodiazepine Treatment Outcome

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Background: We examined discontinuation symptoms following brief benzodiazepine therapy (8 weeks) and intermittent benzodiazepine therapy (2 weeks with at least 2 weeks without drug) and associations with prior benzodiazepine use. The hypothesis was that prior benzodiazepine use would predispose patients to more severe discontinuation symptoms.

Method: Data were drawn from 3 double-blind, randomized, placebo-controlled, published treatment trials: alprazolam for patients with premenstrual syndrome (PMS) and diazepam and lorazepam for patients with generalized anxiety disorder (GAD). The PMS group provided prospective daily symptom ratings, which allowed ongoing investigation of effects of prior treatment. In the GAD groups, taper outcome was examined after 8 weeks of benzodiazepine therapy as a function of prior benzodiazepine use and as a function of time since last prior benzodiazepine use. Symptom scores were analyzed using t statistics in the PMS group and analysis of covariance with 8-week scores as the covariate in the GAD groups.

Results: The PMS subjects reported no increase in symptom scores and no significant difference from placebo-treated subjects during taper and discontinuation of alprazolam in the follicular phase of each treatment cycle. In the GAD trials, the results of treatment discontinuation did not differ significantly as a function of presence or absence of prior benzodiazepine use or as a function of time since last benzodiazepine use.

Conclusion: These preliminary data fail to support the hypothesis that prior benzodiazepine use predisposes patients to more severe discontinuation symptoms when treatment is brief and doses are low.

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We have previously proposed that at least 50% of patients with chronic generalized anxiety disorder (GAD) and many other patients who experience anxiety sufficient to impair functioning would benefit from brief benzodiazepine treatment (up to 8 weeks) or intermittent therapy[1] (up to 2 weeks with at least 2 weeks without the drug at repeated intervals). This contention is now further supported by data from patients with premenstrual syndrome (PMS), whose cyclic patterns of 1 to 2 weeks of symptoms followed by 2 to 3 weeks of symptom remission in each menstrual cycle provide a model for intermittent therapies.

Of the drugs available for intermittent treatment of anxiety disorders, the benzodiazepines hold the advantage of rapid onset, consistent efficacy, ease of use, and a wide margin of safety when prescribed for only a few weeks.[2] However, these clear advantages are compromised by the problem of rebound anxiety with discontinuation of the benzodiazepine, which can occur following even 4 weeks of treatment.[3,4] Rebound phenomena frequently cannot be differentiated by the patient or the physician from the original anxiety and may often lead to unnecessary long-term drug therapy.

Alprazolam was an effective treatment for approximately 40% of clearly diagnosed PMS patients,[5] who took the medication repeatedly for 2-week intervals during the symptomatic premenstrual phase of the menstrual cycle and stopped taking the medication during the 2-week follicular phase of the cycle. These results contrasted with those of GAD patients, who were treated for 6 months with a benzodiazepine and experienced significantly more discontinuation symptoms if they had prior benzodiazepine use compared with patients with no prior benzodiazepine use.[6] We have now followed these intriguing findings by examining 3 data sets: (1) patients who met clearly defined criteria for PMS and were treated premenstrually only with alprazolam compared with oral micronized progesterone and placebo,[5] (2) GAD patients who were treated for 8 weeks with diazepam compared with gepirone and placebo,[7] and (3) GAD patients who were treated for 8 weeks with lorazepam compared with ipsapirone and placebo.[8,9] In the latter 2 studies, the diazepam results clearly showed that, after 8 weeks of treatment, abrupt discontinuation of diazepam resulted in significantly more discontinuation symptoms compared with

discontinuation of either gepirone or placebo, but no increase above baseline symptoms was observed.[7] Similarly, after 8 weeks of lorazepam treatment followed by a 50% taper for 4 days and then complete discontinuation, lorazepam produced significantly more discontinuation symptoms than placebo or ipsapirone.[8,9]

This report further examines discontinuation symptoms in relation to the intermittent dosing that was prescribed for the PMS patients and in relation to prior benzodiazepine use in the GAD patients. In the PMS trial, the subjects experienced symptoms premenstrually only, and none had been taking benzodiazepines prior to the trial. Therefore, the PMS group allowed prospective observation of both the first ending of benzodiazepine use and repeated dosing at approximately 2-week intervals not confounded by a possible return of original anxiety symptoms. In the 2 GAD trials, patients who had stopped benzodiazepine treatment more than 1 month before the trial were compared with patients who stopped benzodiazepine treatment at 1 month or less before the trial, and these groups were compared with benzodiazepine-naive patients to determine the association of prior benzodiazepine use with discontinuation symptoms. The data reported here were not examined in the previous reports of these trials.

METHOD

The subject selection criteria and procedures are fully described in previous reports. In the alprazolam group,[5] subjects with PMS were randomly assigned to treatment with alprazolam (N = 55) or placebo (N = 54) for 3 months of double-blind treatment with 3 additional months of optional maintenance (double-blinded). The demographic characteristics did not significantly differ between the alprazolam- and placebo-treated groups. The mean ± SD age of the subjects was 34 ± 6 years; the mean duration of PMS was 10 ± 8 years. Eighty-two percent had education beyond high school; 62% reported a family history of mental illness as recorded in the medical history.

Alprazolam was administered under double-blind conditions from day 18 of the menstrual cycle to the first day of menses, with a taper on the first 2 menstrual days. The initial dose was 0.75 mg/day, taken in divided doses 3 times daily. The dose could be increased to 1 mg/day in the first cycle and further increased to a maximum of 3 mg/day in the second and third cycles. The mean ± SD alprazolam dose after 3 months of treatment was 1.5 ± 0.5 mg/day. Subjects continued the same dose taken at the end of the 3 months of acute treatment for the 3 months of maintenance.

Symptom severity was assessed by subjects' daily ratings of premenstrual symptoms, using the University of Pennsylvania Daily Symptom Rating form (DSR).[10] Each of 17 symptoms was rated daily on a 5-point scale ranging from 0 (none) to 4 (severe). The ratings for each day were summed for a total daily score. A mean of the total daily score was obtained for the premenstrual and postmenstrual days indicated. The pretreatment mean of the DSR scores in the 3 screen cycles was 36 ± 34 postmenstrually (days 5–10) and 144 ± 53 premenstrually (days 23–28) ($p < .001$).

In the diazepam group,[7] 41 patients with GAD were randomly assigned to 8 weeks of double-blind treatment, 20 with prior benzodiazepine use and 21 with no prior benzodiazepine use (pretaper daily doses were 18.0 ± 11.2 and 21.2 ± 11.7 mg, respectively). The demographic characteristics did not differ between the prior use and no prior use groups. The mean age of the subjects was 43 ± 15 years; 59% had an episode duration of ≥ 1 year; 61% were female.

In the lorazepam group,[8,9] 55 patients with GAD were randomly assigned to 8 weeks of double-blind treatment: 13 with prior benzodiazepine use and 42 with no prior benzodiazepine use (pretaper daily doses were 3.9 ± 1.2 and 3.6 ± 1.2 mg, respectively). The demographic background characteristics did not differ between the 2 groups. The mean age of the subjects was 40 ± 12 years; 24% had an episode duration of ≥ 1 year; 38% were female. Outcome measures in both GAD trials were the Hamilton Rating Scale for Anxiety (HAM-A)[11] and the Physicians' Withdrawal Checklist (PWC).[12]

In the PMS study,[5] the mean DSR scores were compared between the alprazolam and placebo groups using Student t tests. In the GAD studies,[7–9] symptom scores in each of the treatment groups were analyzed using analysis of covariance with the 8-week scores as the covariate. Background variable comparisons were tested with t statistics for continuous variables and with the chi-square test for frequency distributions. In all analyses, results were considered significant at $p < .05$ with 2-tailed interpretation. The statistical software package was SAS.[13]

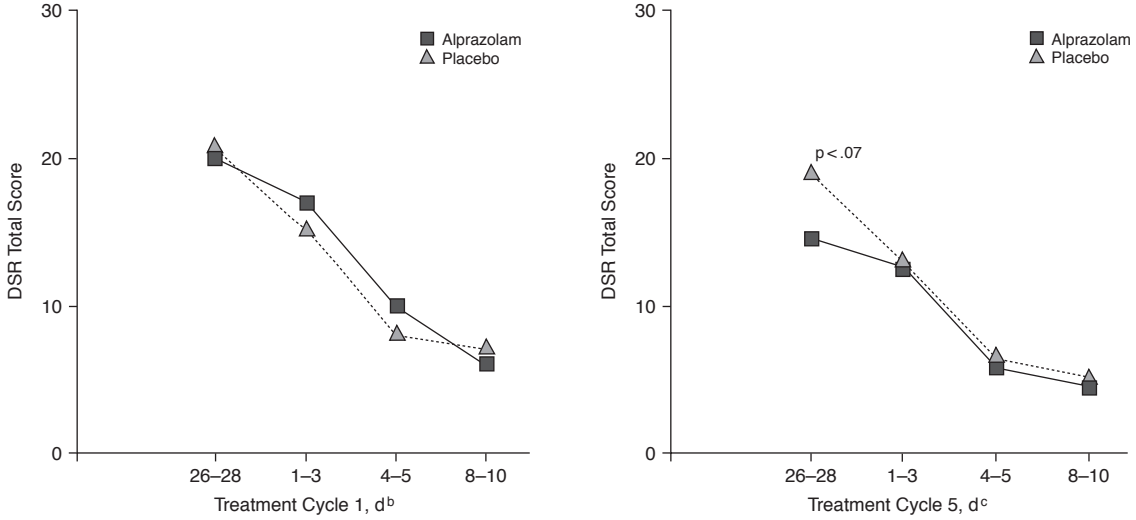
RESULTS

Intermittent Alprazolam Use in PMS

Figure 1 shows the total DSR scores for the last premenstrual days, the discontinuation period, and subsequent postmenstrual days after 1 month and 5 months of double-blind therapy. Comparing the response of alprazolam versus placebo, the data clearly indicate that patients for whom alprazolam was prescribed for 14 days and stopped with a 1- to 2-day taper developed no discontinuation symptoms.

Review of each of the 17 DSR symptoms showed that only the insomnia item evidenced an increase after tapering and stopping alprazolam on days 1 to 3 of the menstrual cycle following the first treatment period. The increase in insomnia was greater in the alprazolam group compared with the placebo-treated subjects, but did not reach statistical significance with the Bonferroni correc-

Figure 1. Total Daily Symptom Rating (DSR) Scores for Alprazolam- and Placebo-Treated Groups[a]



[a]Data from Freeman et al.[5] DSR scores are means of the sum of daily symptom ratings for the days indicated. Seventeen symptoms were rated 0 (none) to 4 (severe); range, 0–68 per day.
[b]Treatment cycle 1: alprazolam N = 55, placebo N = 54.
[c]Treatment cycle 5: N = 35 in each group.

Table 1. Severity of Discontinuation Symptoms After 8 Weeks of Benzodiazepine Therapy for Generalized Anxiety Disorder as a Function of Presence or Absence of Prior Benzodiazepine Use[a]

	Prior Diazepam Use[b]				Prior Lorazepam Use[c]			
Measure	Yes (N = 20)	No (N = 21)	F[d] (df = 2,40)	p Value	Yes (N = 13)	No (N = 42)	F (df = 2,54)	p Value
HAM-A peak during taper	11.7 ± 8.5	17.4 ± 9.3	3.36	.08	16.2 ± 9.1	17.1 ± 8.8	0.00	.99
PWC peak during taper	9.5 ± 9.1	14.1 ± 9.9	2.26	.14	18.9 ± 14.2	21.2 ± 17.0	0.18	.67

[a]Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, PWC = Physicians' Withdrawal Checklist.
[b]Data from Rickels et al.[7]
[c]Data from Cutler et al[8] and Mandos et al.[9]
[d]Analysis of covariance with score at 8 weeks as the covariate; mean ± SD scores (unadjusted) are shown.

tion, and subsequently decreased in each treatment period and did not differ from placebo-treated subjects. Insomnia is a possible withdrawal symptom, but this single finding among 17 daily-rated symptoms, which diminished rather than increased over time, could also be due to chance.

To determine whether subjects dropped out because of discontinuation symptoms, we reviewed the reasons for dropout and reported side effects in each treatment cycle. No subject was withdrawn from the study because of adverse events. No subject requested to continue taking alprazolam beyond the 2-week intervals of each menstrual cycle as prescribed by the protocol. Only 2 subjects said that the reason for dropping out of the study was side effects. The side effects reported by all dropouts (N = 20) included fatigue (N = 11), swelling (N = 5), breast tenderness (N = 3), increased appetite (N = 2), and one each for dizziness, diarrhea, constipation, and increased cycle length, but no symptoms viewed as discontinuation symptoms. Forty percent (8/20) of the dropouts experienced no side effects.

Taper Outcome After 8 Weeks of Benzodiazepine Treatment for GAD

In both the diazepam and the lorazepam trials, the results of treatment discontinuation did not differ significantly as a function of presence or absence of prior benzodiazepine use (Table 1). We then compared patients whose previous benzodiazepine use occurred more than 1 month before study treatment with those who had used benzodiazepines within 1 month (but not within 2 weeks) before entering the 8-week double-blind treatment phase of the study. The prediction was that patients who had stopped taking their benzodiazepine within the previous month would have more severe discontinuation symptoms than patients who had stopped benzodiazepine use more than 1 month ago.[14,15] This prediction was not confirmed. HAM-A scores at peak during taper showed a pattern opposite to the prediction. In the lorazepam study, the patients who stopped benzodiazepine use within a month of the study had less severe symptoms at peak during taper compared with the subjects who discontinued benzodiaze-

pine use more than 1 month before the study ($F = 7.03$, $df = 2,12$; $p = .02$). The corresponding comparison in the diazepam group showed a trend in the same direction, with recent discontinuers having the less severe symptoms, but did not reach statistical significance ($F = 2.43$, $df = 2,19$; $p = .14$). These preliminary data suggest that the duration of prior benzodiazepine use for these conditions has no bearing on discontinuation symptoms.

DISCUSSION

These preliminary data refute the hypothesis that prior benzodiazepine use, given either continuously or intermittently, predisposes patients to more severe discontinuation symptoms following brief benzodiazepine therapy. In fact, the data show that even for a short half-life benzodiazepine such as alprazolam, up to 2 weeks of treatment can be offered over multiple time periods when the brief treatment period is followed by at least 2 weeks with no benzodiazepine medication.

When GAD patients were treated for at least 8 weeks with a benzodiazepine, discontinuation symptoms clearly occurred, although the symptoms were relatively mild. In the lorazepam group, in which the patients were seen weekly, the symptoms were clearly more marked 4 days after starting the taper than after 10 days, when they did not differ from the symptoms reported in the placebo group.[9] Therefore, it appears that benzodiazepine treatment even up to 8 weeks does not increase the risk of severe discontinuation symptoms. Although discontinuation symptoms did occur in this time frame, they were mild, of brief duration, and typically manageable.

In keeping with the known patterns of withdrawal for shorter versus longer half-life benzodiazepines,[12] the short half-life drugs were tapered at discontinuation in these studies, whereas the longer half-life drug was stopped abruptly. Lorazepam was tapered for 4 days at half the dose while diazepam was discontinued with no taper. With the taper adjustment for the short half-life, withdrawal symptoms subsided at about the same time in both GAD groups, regardless of the half-life of the medication. In both treatment groups, peak withdrawal symptoms were reported at the 1-week visit after ending treatment, the withdrawal symptoms were less severe than the baseline symptom levels, and the withdrawal symptoms subsided by the 2-week visit.

We had previously found that discontinuation symptoms were more marked in patients with prior benzodiazepine use.[6] Again, the previous study examined longer-term treatment (6 months), in contrast to the present studies, in which treatment was of brief duration (2–8 week treatment periods). On the basis of present data, we speculate that prior benzodiazepine use has less bearing for short treatment periods than for longer durations of use. Regardless of prior use, the present results do not pertain to longer durations of benzodiazepine treatment, which have well-documented discontinuation problems, e.g., 6 months of treatment with clorazepate[6] or any benzodiazepine use for 1 year or longer.[12]

The results with PMS patients, who had no history of sedative, alcohol, or drug abuse and were symptomatic only 1 to 2 weeks in each month, suggest that intermittent administration of benzodiazepines can be a useful treatment for PMS and GAD. Although serotonergic antidepressants are an effective treatment for a larger proportion of PMS patients,[16,17] the response rate to selective serotonin reuptake inhibitors is approximately 60%, leaving a still-sizeable patient group who may benefit from other medications such as benzodiazepines. Conversely, when anxious patients must be treated for more than 8 weeks rather than for a brief time period, the physician should consider anxiolytics other than benzodiazepines, such as buspirone[18] or antidepressants.[19]

It is important to emphasize that the findings pertain to the diagnoses studied, i.e., generalized anxiety disorder and premenstrual syndrome. Benzodiazepines should not be given to patients with current or past substance abuse or clear comorbid personality disorders. While the GAD studies in this report included patients 19 to 78 years of age, the age data are insufficient to indicate prescription for the elderly. Also, these results relate only to the doses used, which were equivalent in the 3 studies (1 mg of alprazolam = 2 mg of lorazepam or 10 mg of diazepam). Further study is needed to determine whether these findings pertain to higher doses.

In conclusion, these preliminary data suggest that for anxiety problems that can be appropriately treated in a short time interval with low-to-moderate benzodiazepine doses, benzodiazepine use for 2 weeks or less has few withdrawal symptoms, whereas 8 weeks of use has mild and manageable withdrawal symptoms, in contrast to the well-documented withdrawal problems that occur with longer periods of benzodiazepine use. Prior benzodiazepine use does not appear to affect withdrawal in short-term use, again in contrast to longer periods of use in which prior benzodiazepine use is associated with greater withdrawal problems. In all cases, when benzodiazepines are prescribed, the physician should discuss discontinuation management with the patient at the outset. Moreover, medication for anxiety should be prescribed not as a panacea for all the patients' problems, which cannot be solved by drug treatments alone, but as an agent to reduce anxiety and enable more effective problem solving by patients themselves. Even today, after more than 30 years of use, the benzodiazepines have not been replaced as the treatment of choice for brief treatment of anxious patients.[1]

Drug names: alprazolam (Xanax and others), buspirone (BuSpar), clorazepate (Tranxene), diazepam (Valium and others), lorazepam (Ativan and others).

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