Prior Benzodiazepine Use and Buspirone Response in the Treatment of Generalized Anxiety Disorder

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Background: An earlier preliminary report suggested that prior treatment with benzodiazepines might predict a reduced response to buspirone in patients diagnosed with generalized anxiety disorder (GAD). To confirm or refute this hypothesis, the present data analysis was conducted.

Method: One large data set (N = 735) of GAD patients (DSM-III) treated with buspirone, a benzodiazepine, and a placebo was analyzed by dividing all patients into 3 prior benzodiazepine (BZ) treatment groups: no prior BZ treatment, recent (< 1 month) BZ treatment, and remote (≥ 1 month) BZ treatment. Using an intent-to-treat last-observation-carried-forward (LOCF) data set, acute 4-week treatment response was assessed in terms of clinical improvement, attrition, and adverse events as a function of these 3 prior benzodiazepine treatment groups.

Results: Patient attrition was significantly higher ($p < .05$) in the recent BZ treatment group than in the remote and no prior BZ treatment groups with lack of efficacy given as the primary reason by patients receiving buspirone but not benzodiazepine or placebo. In the buspirone group, adverse events occurred more frequently in the recent BZ treatment group than in the remote BZ treatment and no prior BZ treatment groups. Finally, clinical improvement with buspirone was similar to benzodiazepine improvement in the no prior BZ treatment and remote BZ treatment groups, but less than benzodiazepine improvement in the recent BZ treatment group, leading to the smallest buspirone/placebo differences in improvement in the recent BZ treatment group.

Conclusion: These data suggest that the initiation of buspirone therapy in GAD patients who have only recently terminated benzodiazepine treatment should be undertaken cautiously and combined with appropriate patient education.

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Almost none of the published treatment literature addresses the clinically relevant issue of predictors of response to anxiolytic treatment. Buspirone, a serotonin-1A (5-HT_{1A}) partial agonist, is a non-benzodiazepine anxiolytic that has demonstrated efficacy for the treatment of generalized anxiety disorder (GAD).[1–3] As such, it represents a clear treatment alternative to the benzodiazepines. Still, few prescriptive predictors that might guide a physician in choosing between a benzodiazepine and buspirone for the treatment of GAD have been empirically validated. We have previously suggested that higher levels of psychic anxiety might tend to predict a more favorable response to serotonergic drugs such as buspirone[1] or antidepressants such as imipramine[4] and venlafaxine[5,6] and that prominent somatic anxiety (especially in the absence of any subsyndromic depressive symptoms) might tend to predict a more favorable response to a benzodiazepine.[1,4]

We have also suggested in a preliminary report[7] that prior treatment with a benzodiazepine, with the duration of benzodiazepine-free episodes left undefined, might predict a reduced response to buspirone. We speculated at that time that previous benzodiazepine treatment might have prepared a patient to expect a swift onset of therapeutic action, a presence of sedation that highly anxious patients frequently interpret positively, and mild euphoric effects associated with benzodiazepines in a subset of patients[8,9] and that none of these 3 effects would occur during subsequent buspirone treatment, confounding patient expectations. Another factor contributing to the absence of these effects might also have been that some patients initiating buspirone treatment were still experiencing mild benzodiazepine discontinuation symptoms, symptoms that do not respond to buspirone therapy.[10,11] As medication-free time between prior benzodiazepine treatment and buspirone therapy increases, however, one may expect the previous benzodiazepine experience to become less important for patients treated with buspirone.

The purpose of the current report was to confirm or refute this hypothesis. To do so, we have examined a large data set that consists of all pooled results from all placebo-controlled studies comprising the evidence presented to the U.S. Food and Drug Administration (FDA) during the new drug approval process for buspirone. The availability of a

large data set permitted us to examine not only whether prior exposure to benzodiazepines constituted a negative predictor, but whether the timing of benzodiazepine treatment (recent or past) was a critical variable. In addition, we were interested in examining whether prior benzodiazepine treatment influenced tolerability and attrition from treatment. Finally, we wished to examine whether prior benzodiazepine treatment constituted a more general predictor of poor outcome to treatment (benzodiazepine, buspirone, or placebo) or a more specifically negative predictor of poor response to buspirone.

We hypothesized that remote benzodiazepine treatment should have significantly less effect on the anxiolytic response of buspirone than recent benzodiazepine treatment and that anxious patients who report no prior benzodiazepine therapy would achieve the highest overall response rate to buspirone therapy.

METHOD

Design

The available data for this report consist of the pooled results of the 8 double-blind, placebo-controlled trials (6 United States, 1 Canadian, 1 German) that comprised the original new drug approval submission to the FDA (data on file, Bristol-Myers Squibb). All patients with at least 1 week of data (last-observation-carried-forward [LOCF] data set, N = 735) were included in the data analysis. In 7 studies, the benzodiazepine was diazepam, in 1 it was clobazam. All 8 studies employed a 1-week, single-blind placebo washout period before randomization to 4 weeks of double-blind treatment with buspirone, diazepam, or placebo. Flexible dose titration was permitted up to a maximum daily dose of 30 mg of buspirone, 30 mg of diazepam, or 6 tablets of placebo administered t.i.d. The mean maximal daily dose across all studies was 20 mg for both active medications. GAD was diagnosed with the help of a semi-structured clinical interview using a DSM-III checklist (note that duration criteria of only 1 month is required for GAD and that DSM-III places a greater emphasis on somatic symptoms than does DSM-IV). All patients were evaluated at screening, baseline, and weeks 1, 2, and 4 of double-blind treatment. Outcome assessments included the Hamilton Rating Scale for Anxiety (HAM-A)[12] and the Clinical Global Impressions-Improvement (CGI-I)[13] scales.

Classification of Prior Benzodiazepines Use

Patients were assigned to 1 of 3 prior benzodiazepine (BZ) use groups using the following criteria: (1) the no prior BZ treatment group, with no documented history of any benzodiazepine treatment in the previous 5 years (treatment history prior to 5 years prestudy was not systematically queried, and therefore was not considered reliable); (2) the remote BZ treatment group, with patients reporting benzodiazepine treatment terminated 1 month or more prior to study entry (≥ 1 month benzodiazepine-free); and (3) the recent BZ treatment group, which included all patients reporting benzodiazepine treatment discontinued only within the 4 weeks immediately prior to study entry (< 1 month benzodiazepine-free). Treatment groups were compared in anxiolytic efficacy, discontinuation rates, and incidence of adverse experiences during the 4-week acute treatment phase.

Table 1. Demographic Data and Clinical Characteristics of Patient Sample[a]

Characteristic	Buspirone (N = 252)	Benzodiazepine (N = 248)	Placebo (N = 235)
Age, y			
Mean	39	37	38
Range	19–64	18–67	18–66
Sex, % female	63	61	64
Age at onset, mean, y	31	30	31
Present episode ≥ 6 mo, %	51	47	48
HAM-A score at baseline, mean	25	26	26

[a]Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

Statistical Analysis

Analyses of variance (ANOVA) of change scores were used for continuous variables (change in HAM-A score), and the Cochran-Mantel-Haenszel general association test was used for discontinuous variables, i.e., global improvement (marked or moderate vs. all other scores), ≥ 40% improvement in HAM-A score, discontinuation rates, and adverse events. p Values were interpreted conservatively as 2-tailed and corresponded to response rates from the Cochran-Mantel-Haenszel general association test for discontinuous variables and from t tests for continuous variables. Endpoint (LOCF) analyses were utilized for this report.

RESULTS

Study Population

Demographic information is given in Table 1. Two hundred fifty-two patients received buspirone; 248, benzodiazepine; and 235, placebo. Ages were similar across treatment groups, as were the male/female distribution, mean age at onset, duration of present episode, and HAM-A scores at baseline. No statistically significant differences were found among the 3 prior BZ treatment groups in any of the variables tested and given in Table 1.

Patient Attrition

Table 2 gives patient discontinuation rates during 4 weeks of acute treatment for the 3 prior BZ use groups. Buspirone patients in the recent BZ treatment group dropped out of the study significantly more frequently than patients in the remote BZ treatment and the no prior BZ treatment groups, primarily for lack of efficacy (re-

Table 2. Attrition During 4 Weeks of Acute Treatment[a]

		Prior Benzodiazepine Treatment Groups		
Study Treatment	N	No	Remote	Recent
Buspirone	252	37/135 (27%)[b]	9/43 (21%)[c]	31/74 (42%)[b,c]
Benzodiazepine	248	28/131 (21%)	14/47 (30%)	14/70 (20%)
Placebo	235	42/121 (35%)	21/48 (44%)	26/66 (39%)

[a]Statistically significant ($p < .05$) differences were found only in the buspirone group.
[b]No prior benzodiazepine (BZ) vs. recent BZ ($\chi^2 = 4.57$, df = 1, $p < .04$).
[c]Remote BZ vs. recent BZ ($\chi^2 = 5.31$, df = 1, $p < .03$).

Table 3. Adverse Events[a] With Buspirone as a Function of Prior Benzodiazepine Treatment Group (%)

	Prior BZ Treatment Groups			p Value		
Adverse Events	No (N = 135)	Remote (N = 43)	Recent (N = 74)	Recent vs No	Remote vs No	Recent vs Remote
Patients reporting any events	41	63	61	.009	NS	.022
Individual events						
Nervousness	4	5	14	.012	NS	NS
Excitement	0	0	5	.015	NS	NS
Dizziness	10	16	22	.021	NS	NS
Depression	2	2	8	.070	NS	NS
Insomnia	2	5	8	.070	NS	NS
Fatigue	4	2	11	.090	NS	NS

[a]Any event that differed at any comparison (< .10) by either chi-square or Fisher exact test.

Table 4. Clinical Improvement After 4 Weeks of Treatment (LOCF data set) as a Function of Anxiolytic Treatment and Prior Benzodiazepine Treatment Group

				p Value vs Placebo	
Rating Scale	Buspirone (N = 252)	Benzodiazepine (N = 248)	Placebo (N = 235)	Buspirone	Benzodiazepine
HAM-A (40% improved)					
No prior BZ	62[a]	65	33	.001	.001
Remote BZ	56	62	27	.006	.001
Recent BZ	46[a]	73	35	.184	.001
Global improvement (much/very much improved)					
No prior BZ	59[b]	61	31	.001	.001
Remote BZ	56	60	25	.003	.001
Recent BZ	41[b]	69	26	.065	.001

[a]$\chi^2 = 4.5$, df = 1, $p < .05$.
[b]$\chi^2 = 5.99$, df = 1, $p < .02$.

cent BZ treatment group, 23% attrition; remote BZ treatment group, 7% attrition; no prior BZ treatment group, 10% attrition; $p < .05$). In contrast, no relationship between the 3 prior BZ treatment groups and attrition was found for the benzodiazepine and placebo groups.

Adverse Events

Table 3 gives adverse events for buspirone divided by the 3 prior BZ treatment groups for any event in which one group comparison was significant at least at the $p < .10$ level. The recent BZ treatment group reported the most and the no prior BZ treatment group the least side effects, with remote BZ treatment group being generally closer to the no prior BZ treatment group than to the recent BZ group. For patients receiving benzodiazepine or placebo study treatment, no differences in adverse event rates were found among the 3 prior BZ treatment groups; therefore data are not given. With all patient groups, most adverse events were recorded as mild or moderate.

Clinical Improvement

Table 4 gives response rates for an endpoint (LOCF) analysis of the HAM-A (≥ 40% improvement from baseline) and data on global improvement (percent of very much and much improved patients) within each of the 3 prior BZ treatment groups. For patients in the no prior BZ treatment group, similar improvement rates in the HAM-A were achieved for both buspirone and benzodiazepine. It should be noted, however, that both active medications caused significantly more clinical improvement than placebo in all 3 prior BZ treatment groups, including the recent BZ group, even if it only reached a trend level ($p < .10$).

Data on global improvement provided very similar results. As seen in the HAM-A data, benzodiazepine response in all 3 groups was similar and clearly positive, and the placebo response in all 3 groups was also similar, but lower than the benzodiazepine or buspirone response. In contrast, buspirone response was affected by the prior BZ treatment group and was lowest in the recent BZ treatment group.

DISCUSSION

The early observation by Schweizer et al.[7] that a history of prior benzodiazepine treatment affects buspirone treatment outcome negatively is confirmed by the present report. Discontinuation rates, adverse events, and efficacy ratings all support the fact that buspirone patients who only recently had stopped benzodiazepine therapy (recent BZ treatment group) did less well on all 3 outcome measures than patients without prior benzodiazepine treatment history. Clinical response to buspirone treatment in patients in the remote BZ treatment group was more similar to response in the no prior BZ treatment group than to that of the recent BZ treatment group. Finally, patient response to diazepam and to placebo was not differentially affected by prior benzodiazepine treatment status, suggesting that prior use of benzodiazepines was not simply a more general predictor of negative outcome.

The current report benefits from the availability of a large sample size, but is necessarily limited by the retro-

spective nature of the data analysis. In addition, no systematic assessment was made of the presence or severity of possible benzodiazepine withdrawal, so caution must be exercised in making any inferences about whether attrition or clinical outcome was influenced by the presence, at least in the early stages of study treatment, of a mild or covert withdrawal syndrome.

With these caveats in mind, the results of the study suggest that recent treatment with a benzodiazepine tends to reduce the anxiolytic benefit of buspirone. This reduction in efficacy appears to be associated with an increase in side effects, as well as an increase in attrition from treatment. It is possible but not probable that increased rates of side effects and attrition are attributable to overt benzodiazepine discontinuation symptoms, since these side effects are present only in the buspirone and not in the placebo group. It is probably much more likely that buspirone and its major metabolite 1-PP exacerbate covert benzodiazepine withdrawal symptoms via their noradrenergic activity in patients only recently discontinued from benzodiazepine therapy.[14–16] In addition, these adverse events may further remind former benzodiazepine-treated patients that they are now missing the early onset of action of efficacy, sedative effects, and mild euphoria so frequently experienced with benzodiazepines and that their absence may counterbalance at least some of the anxiolytic effects of buspirone.

One may speculate that similar adverse effects related to recent benzodiazepine experience may also occur with other non-benzodiazepine serotonergic agents, such as imipramine[4] or venlafaxine,[5,6] the most recently marketed antidepressant for the treatment of GAD.

From the patient-management perspective,[17] the data presented in the current report suggest that initiation of treatment with buspirone in patients who only recently terminated benzodiazepine treatment should be undertaken cautiously and be accompanied by patient education to set proper expectations for treatment. The possibility of increased adverse events in the first few weeks of treatment and the inability of buspirone to treat benzodiazepine discontinuation symptoms should be discussed with the patient. If attrition can be avoided, the chance of long-term benefit from buspirone therapy is likely to increase. Only further research can provide data on whether or not similar precautions are necessary for other serotonergic anxiolytic agents when switching a patient from a benzodiazepine to such agents.

Drug names: buspirone (BuSpar), diazepam (Valium and others), venlafaxine (Effexor).

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