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Psychomotor Performance of Long-Term Benzodiazepine Users Before, During, and After Benzodiazepine Discontinuation

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Abstract

Long-term (mean, 8 years) users of benzodiazepines (BZs) were administered a small battery of cognitive tests on three occasions (before BZ taper, and 5 and 12 weeks post taper) as part of their BZ discontinuation program. Ninety-six patients had 5-week and 77 patients had 12-week data. For taper successes, BZ-free status was confirmed by weekly BZ plasma level determinations. Age and education, as well as baseline test scores, were used as covariates for all data analyses. Patients who successfully tapered off BZ were able to complete symbol copying (SC) and digit symbol substitution (DSST) tasks faster than patients still taking BZ ($p < 0.05$). In addition, using an adjective check list, patients with taper success, i.e., BZ-free patients, reported lower levels of mental and physical sedation and higher levels of tranquilization ($p < 0.05$) than did patients still taking BZ. These results were confirmed in two multiple regression analyses with SC and DSST as the dependent variables. Higher baseline, younger age, and successful taper status (off BZ) were selected as significant independent predictors of SC and DSST scores. In summary, cognitive functions improved for many long-term BZ users after discontinuing their BZ intake. (J Clin Psychopharmacol 1999;19:107-113)

DESPITE AN INTENSIVE SEARCH for new, nonbenzodiazepine anxiolytics [1,2] and despite the observation that antidepressants such as imipramine may have anxiolytic properties, [3,4] the benzodiazepines (BZs) are still the main psychopharmacologic treatment of patients with anxiety of a generalized nature (i.e., adjustment disorder, generalized anxiety disorder [GAD], anxiety not otherwise specified, panic disorder, social phobia), irrespective of the duration of these symptoms. [5] Although most patients are prescribed BZs for the short-term and thus do not

experience significant problems when discontinuing their BZ therapy gradually, there are a significant number of patients who are treated for prolonged periods of time. And although rebound anxiety may occur in patients who abruptly discontinue after 4 weeks BZ treatment, [6,7] BZ discontinuation after 6 months of therapy or more causes discontinuation (withdrawal) symptoms in a significant number of BZ users. [8]

There has been concern that long-term use of BZs may lead to prolonged cognitive and generalized intellectual impairment long after the BZ has been discontinued. [9-11] Further support for the possible occurrence of long-term (not temporary) negative effects of BZs on cognition were provided by Lader and associates, [12] who reported abnormal computed tomographic [CT] scans in long-term BZ users. However, these data could not be confirmed by other investigators. [13,14] Furthermore, Lucki and associates [15] failed to confirm "significant detrimental effects" of BZs in long-term BZ users.

Lucki and associates [15] tested 43 long-term users of BZs (average duration, 5 years) on a battery of behavioral tasks, cognitive tests, and subjective mood rating scales. They observed that the performance of long-term BZ users did not differ significantly from age and sex-matched anxious, untreated subjects, except that the Critical Flicker Fusion (CFF) thresholds were lower and subjective ratings of tranquilization were higher in the long-term BZ users. When 22 long-term BZ users were reexamined to determine the short-term drug effect in such patients, it was found that the short-term administration significantly increased CFF threshold and improved, not worsened, digit symbol substitution test (DSST) performance. Yet, just as in nontreated anxious patients, short-term BZ administration impaired delayed recall of verbal material. It also increased subjective ratings of tranquilization and reduced subjective ratings of physical sedation. These results suggest that tolerance develops selectively to different behavioral and subjective effects and that tolerance fails to develop to the anxiolytic effects of BZ, to the reduction of CFF threshold, and to the impairment of short-term memory that lasts for a few hours after an acute BZ dose. It is interesting that the same authors also found no statistically significant effects, with the exception of CFF reduction, between the initial examination of long-term BZ users and an examination of the same patients during their BZ withdrawal period.

Sakol and Power [16] assessed 12 long-term BZ patients before and during 4 weeks of gradual BZ withdrawal and compared them with 10 healthy control subjects. Although the patient and control groups differed significantly before BZ withdrawal in cognitive and behavioral tests, with BZ patients showing impaired performance, the patient and control groups did not differ after withdrawal. Thus, some evidence was provided by these authors that decreasing BZ intake leads to an improvement of previously impaired cognitive performance.

Golombok and associates [17] studied cognitive impairment in long-term BZ users. The authors compared 50 patients who were currently taking BZs for at least 1 year with 34 patients who had stopped taking BZs and with a matched control group of subjects who had never taken BZs, or at least not during the previous year. On the basis of correlational data, the authors reported that patients taking BZs for prolonged periods of time performed poorly on tasks involving visual spatial ability and sustained attention, such as DSST and symbol copying (SC) tests, compared with control subjects and with patients who had been able to become BZ-free. The authors postulated that these findings were consistent with a deficit in posterior cortical cognitive function observed in long-term BZ users. Global measures of intellectual functions such as memory and reaction time were not impaired.

In 1994, Tata and associates [18] reported on the lack of cognitive recovery after withdrawal from long-term BZ use. Their study involved 21 patients who completed a standardized 4-week inpatient BZ withdrawal regimen after having been on a mean diazepam dose of 45 mg/day and who then stayed abstinent for at least 6 months. They compared these results with those of 21 normal control subjects who were taken from the Department of Psychology volunteer pool. The authors reported significant impairment in verbal learning and memory, psychomotor, and visuo-motor and visuoconceptual abilities. In contrast to the earlier studies discussed, their patients were on higher (2 to 3 times) daily BZ doses than the subjects in the other studies. Their main finding was that patients had significantly lower DSST scores than the control subjects, and that over time, these scores improved slightly as patients remained off BZs, whereas control subject scores did not change. Yet even after 6 months of follow-up, there were still statistically significant differences between raw DSST scores, with patients having lower scores than control subjects (patients, 46; controls, 63). The authors concluded that consistent cognitive deficits were still present 6 months after BZ withdrawal.

Because of these divergent findings in the literature with regard to the possible detrimental effect of long-term BZ use on cognitive functions, our research group incorporated a short battery of tests into the BZ discontinuation program conducted at the University of Pennsylvania. Patients were tested at baseline before BZ discontinuation was initiated, and 5 and 12 weeks after BZ discontinuation was completed. At these later two time periods, we had two patient groups: those who were successfully tapered, and those who were unsuccessful in their taper attempt. It was believed that these data should provide information on the long-term effect of BZs, even after BZ discontinuation. On the basis of earlier data and to simplify the test battery, we used CFF, SC, and DSST as cognitive measures and assessed the self-report of sedation and tranquilization with an analog mood scale. In this study, we did not assess delayed memory effects because we had clearly demonstrated earlier that detrimental effects of a short-term dose of a BZ on delayed memory was present for several hours even in those patients who had been on BZ for 10 years or more. [15]

Method

Behavior test battery

Long-term BZ users who participated in a BZ discontinuation program and who were taking either diazepam, lorazepam, or alprazolam were administered a small battery of psychomotor tests and mood scales at three time periods. These tests are described briefly below in the order of their administration. These behavioral tests were selected because they were reported to be sensitive to the effects of BZs in normal volunteers and were also used by our research group previously when comparing the responses of long-term BZ users with those of normal and untreated anxious patients. [15]

Subjective mood scales. The subjective report of mood was measured using 100-mm lines that separated 12 pairs of items describing opposite feeling states, as described by Norris. [19] Scales of mental sedation (MS) (alert/drowsy, clearheaded/fuzzy, quick-witted/mentally slow, attentive/dreamy), physical sedation (PS) (strong/feeble, well-coordinated/fuzzy, energetic/lazy, capable/incompetent), and tranquilization (TR) (calm/excited, contented/discontented, peaceful/agitated, relaxed/tense) were constructed by grouping the scores from four similar items. A larger score indicated a report of more intense feelings of MS, PS, or TR.

DSST. A code of nine matched digits and symbols was presented at the top of the test form. The DSST required subjects to record the appropriate symbol below the sample digits that were matched by a code appearing at the top of the form. The test was scored using the number of correct items completed in 90 seconds. Different forms and codes were used each time that the test was administered to prevent subjects from improving their performance by memorizing a single code. This test was similar to one of the subtests of the Wechsler Adult Intelligence Scale, Revised. [20]

SC. The SC test required subjects to draw symbols immediately below a sample. The nine same symbols that were used in the DSST were represented in a random order on each test form. Different test forms were used each time that the test was given. The test was scored using the number of items completed in 90 seconds. This test has been used in combination with the DSST as a motor control for physical writing speed. [11,15]

CFF. The CFF threshold was included in the test battery because it has been shown to be sensitive to the effects of psychoactive medications including BZs, [21] although its significance is not completely understood. The CFF was measured using the Leeds psychomotor tester apparatus. Subjects examined an illuminated display of four red light-emitting diodes with a continuously changing frequency placed 1 meter away approximately at eye level. The subjects pressed an indicator button when they observed the display of flickering lights change to appear continuously illuminated (trials of ascending frequency) or when the continuously illuminated disk plate changed to appear to flicker (trials of descending frequency). Trials of ascending and descending frequency were presented alternately, with the first two trials administered for practice but not scored. The score was a combined average frequency of five trials of ascending frequency and five trials of descending frequency.

Symptomatology assessment

The Hamilton Rating Scale for Anxiety (HAM-A) and for Depression (HAM-D) were used to assess anxiety and depressive symptomatology.

Testing procedure

The initial psychomotor evaluation occurred at baseline after patients were accepted into the BZ discontinuation program but had not yet started their taper (N = 113). Patients were seen at various times of the day without regard to the time of the previous dose of medication. Patients were told, however, not to take their medication within 4 hours before arrival at the clinic so that the behavior tests were conducted approximately 4 to 14 hours after the previous BZ dose. The same holds true for unsuccessful taper patients 5 and 12 weeks post taper. Thus, this evaluation might be regarded as representing the status of these patients as they ordinarily appeared in their daily activities.

Patients were again evaluated 5 weeks (N = 96) and 12 weeks (N = 77) after they had either successfully or unsuccessfully tapered their BZ dose to zero BZ intake. Seventeen patients completed the test series only at baseline and therefore were not included in this report. It should be mentioned that these patients did not differ

from the 96 patients who had at least the first posttaper visit on any of the demographic and illness variables reported for the study.

Data analyses

Data were entered into a computer database, and all statistical analyses were conducted using the Statistical Analysis Package, microcomputer version 6.02 and macrocomputer version 5.0. [22] Data for each individual test were analyzed by analysis of covariance (ANCOVA) using scores at baseline as covariates, and data are presented as adjusted posttaper 5-week and 12-week scores. Patients were divided into those who successfully and those who unsuccessfully tapered from their BZ. Because age and education are known to be highly positively correlated with at least the SC and DSST tests, all analyses for CFF, SC, and DSST were conducted by adjusting not only for baseline of the test in question but also for age and education. Zero order correlations between psychomotor measures and age and education were run for the 113 patients with baseline data. These correlations were statistically significant, ranging from 0.42 to 0.51 ($p < 0.0001$) for SC and DSST but not for CFF. Correlations between age and education and the three mood scales were much smaller, ranging from 0.26 to 0.02, with age and education correlating significantly ($p < 0.05$) with MS and age correlating ($p < 0.01$) with TR. Finally, a multiple regression analysis was conducted for SC, DSST, and CFF 5 weeks post taper, using age, sex, duration of BZ use, mean diazepam equivalent dose per day (5 mg of diazepam was considered equivalent to 1 mg of lorazepam and 0.5 mg of alprazolam), caffeine intake in cups of coffee or its equivalents, baseline score of the psychomotor outcome variable, and baseline HAM-A score as potential predictors.

Results

Population

Demographic and baseline data were compared for the three BZ groups. Only age was differentially distributed among the groups, with alprazolam patients being younger (42 years) than lorazepam (52 years) and diazepam (52 years) patients ($p < 0.001$). All results are therefore given for the total group of 96 patients who had tested both at baseline and at 5-week follow-up. Forty-nine percent of the patients were female, 66% were employed, and 53% had more than a high school education. The mean +/- SD age was 47 +/- 15 years, with a range of 22 to 75 years. Forty-one percent received a diagnosis of GAD; 33%, panic disorder; 11%, major depressive disorder; and 15% had no current psychiatric diagnosis. Fifty-eight percent of patients either drank no coffee or just one or two cups per day, whereas 42% drank three or more cups a day. Sixty-two percent of the patients were nonsmokers; 37% never drank any alcohol, 40% drank alcohol only once or twice weekly, and 23% had more than four drinks weekly. Mean (+/- SD) duration of BZ intake was 90 +/- 87 months (range, 11-348 months; modal value, 36 months), and mean (+/- SD) BZ intake, expressed as diazepam equivalents, was 15.6 mg +/- 12.5 mg/day (range, 2-60 mg).

Daily BZ dose and BZ plasma levels at baseline are given in Table 1. The mean +/- SD HAM-A score at baseline was 13.2 +/- 7.5 (range, 0-32), and the mean HAM-D score at baseline was 12.2 +/- 7.4 (range, 0-34). The mean +/- SD CFF, SC, and DSST scores at baseline, respectively, were 28.06 +/- 3.51, 104.4 +/- 32.7, and 52.38 +/- 14.0 ($N = 96$) and did not differ significantly ($p < 0.05$) between the three BZ groups taken at baseline (diazepam, lorazepam, and alprazolam) even when BZ intake, age, and education were used as covariates. It

should be noted that our sample had an age range of 22 to 75 years, and this age distribution may possibly have contributed to the slightly lower baseline scores found in this study compared with scores reported by Lucki and associates. [15]

Table 1. Benzodiazepine daily dose and plasma levels

Taper success versus taper failure groups

Of 96 patients entering taper, 66 (69%) successfully tapered off their BZ dose and remained BZ-free for at least 5 weeks. BZ-free status was confirmed by BZ plasma level determinations. [23-25] Compared with taper failures, the taper success group (off BZ >or=to5 weeks) included fewer panic disorder patients ([chi squared] = 7.78; df = 3; p < 0.05), fewer smokers ([chi squared] = 4.03; df = 1; p < 0.05), and older patients (49 vs. 42 years, t = 2.03; p < 0.05), and they had a lower mean +/- SD BZ diazepam equivalent dose at baseline (12.5 +/- 9.3 vs. 22.7 +/- 15.8; t = 3.93; p < 0.001) and lower baseline HAM-A scores (11.1 +/- 9.3 vs. 17.7 +/- 7.7; t = 4.52; p < 0.001). It is interesting to note that the taper success group had lower SC (100.2 +/- 33.6 vs. 113.7 +/- 29.3) and DSST scores (51.5 +/- 15.1 vs. 54.3 +/- 11.1) than the taper failure group; this difference, however, was not statistically significant.

The thirty patients who failed taper, however, had their BZ intake reduced, which was assessed in diazepam equivalents (mg +/- SD), from 22.7 +/- 15.8 mg/day to 15.3 +/- 12.1 mg/day (p < 0.001). A decrease in BZ plasma levels paralleled this decrease in BZ intake (diazepam + desmethyldiazepam [N = 8]: 1,102 ng/mL at baseline, 593 ng/mL at week 5; lorazepam [N = 3]: 39 ng/mL at baseline, 12 ng/mL at week 5; and alprazolam [N = 16]: 42 ng/mL at baseline, 25 ng/mL at week 5). However, HAM-A scores (mean +/- SD) remained unchanged from baseline (17.7 +/- 7.7) to 5 weeks post taper (17.5 +/- 10.1). This is in contrast to the taper success group whose HAM-A baseline scores (11.06 +/- 6.5), although lower than that of the taper failure group, nevertheless were reduced at 5 weeks (7.78 +/- 6.7) (ANCOVA: F = 14.6; df = 1.94; p < 0.001).

Psychomotor and mood scale data

(Figure 1) shows the results for the SC test, adjusted for baseline and age. As can be seen both at 5 weeks and 12 weeks post taper, patients who successfully tapered off their BZ dose copied symbols significantly faster than those who were unsuccessful in their taper attempt and who remained on BZ. The addition of education as a second covariate to the Equation didnot alter the results.

Figure 1. SC adjusted for baseline and age, for successful (off BZ) ([square]) and unsuccessful (on BZ) ([black square]) taper patients at two time periods (adjusted mean +/- SE). Statistically significant differences at 5 weeks post taper (F = 12.87; N = 96; p < 0.001) and at 12-week follow-up (F = 6.54; N = 77; p < 0.013).

(Figure 2) shows the results for the DSST, again adjusted for DSST baseline score and age. Patients who successfully tapered off their BZ had higher scores, i.e., conducted their tasks faster than did unsuccessful taper patients who remained on BZ. However, this difference was statistically significant only at 5 weeks post taper.

Figure 2. DSST adjusted for baseline and age, for successful (off BZ) ([square]) and unsuccessful (on BZ) ([black square]) taper patients at two time periods (adjusted mean +/- SE). Differences at 5 weeks post taper are statistically significant (F = 3.98; N = 96; p < 0.05) but not at 12-week follow-up (F = 1.55; N = 77; p = NS).

No results are given for CFF because no statistically significant difference was found between successful and unsuccessful taper patients at the 5- or 12-week posttaper period. The respective scores (mean +/- SE) for the successful and unsuccessful taper patients were 28.6 +/- 0.31 and 28.7 +/- 0.46 (F = 0.03; p = not significant [NS]) for the 5-week posttaper period and 28.6 +/- 0.33 and 29.2 +/- 0.42 (F = 0.10; p = NS) for the 12-week posttaper period.

(Figure 3) shows the results obtained with the subjective mood scales, adjusted for their baseline scores, for the 5- and 12-week posttaper periods. At the 5-week follow-up, patients off BZ reported less MS and PS and more TR than patients on BZ. These differences, although still present, were less marked at the 12-week follow-up.

Figure 3. Alteration in mood state assessed by MS, PS, and TR (baseline adjusted mood +/- SE) is given as a function of being off ([square]) or on ([black square]) BZ 5 weeks (N = 96) and 12 weeks (N = 77) after participation in a BZ taper program. Patients off BZ had lower MS and PS and higher TR scores (#p < 0.06; *p < 0.05; **p < 0.01).

Independent predictors of psychomotor test results

(Table 2) gives the results of three multiple regression analyses conducted for CFF, SC, and DSST for the 5-week posttaper assessment period, using nine variables as potential predictors including BZ status at the assessment period (on/off BZ). The overall multiple regression equations were highly significant for CFF, SC, and DSST; the significance was contributed to primarily by the baseline scores of the psychomotor test and by age. However, for SC and DSST, status at 5 weeks post taper (successful vs. unsuccessful) also significantly predicted SC and DSST responses. Patients off BZ had higher SC and DSST scores than did patients on BZ. All other variables included in the regression analyses, such as education, sex, months on BZ, caffeine intake, HAM-A score at baseline, and higher BZ dose at baseline, had no additional significant contribution to the prediction of 5-week, posttaper CFF, SC, and DSST scores. Results for the multiple regression analyses conducted for MS, PS, and TR are not given because only mood scale baseline and baseline HAM-A scores, but not BZ taper status, contributed significantly to the regression equation.

Table 2. Independent predictors of Critical Flicker Fusion (CFF), symbol copying (SC), and digital symbol substitution test (DSST) scores at 5 weeks after successful or unsuccessful taper: multiple regression analyses (N = 96)[a]

Discussion

Compared with unsuccessful taper patients (on BZ), successful taper patients (off BZ) experienced more cognitive improvement in the SC and DSST tests. These findings are in agreement with those reported by Sakol and Power [16] and Golombok and associates. [17] CFF, SC, and DSST scores correlated positively and significantly with age and baseline test scores, but not with education, sex, months on BZ, caffeine intake, HAM-A baseline score, or

daily BZ dose. The differences in cognitive test scores between taper successes and taper failures were more marked at 5 weeks than at 12 weeks post taper. Similarly, successful taper patients (off BZ) reported less MS and PS, more TR, and a higher reduction in anxiety levels assessed with the HAM-A scale than did unsuccessful taper patients (on BZ), clearly supporting earlier findings. [26] Again, these differences were less marked at 12 weeks post taper.

The observation that the differences between study groups in our test battery at 12 weeks were less marked than the ones obtained at 5 weeks post taper may be partially related to patient dropout (N = 96 vs. N = 77) and to a switch of nine patients with three patients on BZ at 5 weeks being off BZ at 12 weeks, and six patients off BZ at 5 weeks being back on BZ at 12 weeks. It should be noted that all tests were administered at a time when patients were not in BZ withdrawal. Patients were either BZ-free at a stage post taper or had resumed BZ intake, albeit at a lower dose level than at baseline.

In conclusion, our data seem to suggest that short-term [5] but not necessarily long-term BZ therapy is beneficial for many patients and, in fact, that with long-term BZ exposure, patients may be worse off receiving than discontinuing BZ. Our data also suggest that at least some patients may have been in a constant mild withdrawal state while still on their low daily BZ intake. In either case, many long-term BZ users continue treatment long past the time period such treatment is needed. Regretfully, no data are available on the cognitive status of our two taper outcome groups at baseline, before initiation of BZ therapy. What we can say, however, is that those patients who had evidence of impaired cognitive functions while on long-term BZ therapy did improve in these functions when BZ therapy was discontinued. We can further say that compared with unsuccessful taper patients, patients who were able to discontinue their BZ intake after many years of BZ use became more alert, more relaxed, and less anxious, and that this change was accompanied by improved psychomotor functions.

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- Table 1
- Figure 1
- Figure 2
- Figure 3
- Table 2

Back to Top