Do Benzodiazepines Reduce the Effectiveness of Exposure Therapy for Posttraumatic Stress Disorder?

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ABSTRACT

Objective: Benzodiazepines, other anxiolytics, or sedative hypnotics are prescribed for 30%–50% of posttraumatic stress disorder (PTSD) patients. Prior data and theory suggest that these medications may inhibit response to exposure therapy, one of the most effective PTSD treatments. The present post hoc study reanalyzed results from a psychotherapy trial to assess whether benzodiazepine use was associated with reduced response to exposure therapy.

Method: Between August 2002 and October 2005, 283 female veterans and soldiers meeting *DSM-IV* criteria for PTSD were randomly assigned to 10 weekly 90-minute sessions of either prolonged exposure (n = 140) or present-centered psychotherapy (n = 143). Benzodiazepine use (n = 57) or non-use (n = 226) at intake was not randomly assigned. Multilevel modeling was used to assess the effects of benzodiazepine status, psychotherapy condition, and their interaction on changes on the Clinician-Administered PTSD Scale and the PTSD Checklist during the treatment and 6-month follow-up periods.

Results: Consistent with prior reports from these data, prolonged exposure psychotherapy produced greater reductions per week in PTSD symptoms than did present-centered psychotherapy ($b = -0.48$, $P = .02$). Patients prescribed benzodiazepines did not have weaker response to prolonged exposure, but demonstrated poorer posttreatment maintenance of gains from present-centered psychotherapy ($b = -0.78$, $P < .001$).

Conclusions: Prolonged exposure is a sufficiently robust treatment that patients who are taking benzodiazepines can benefit from it. It is unclear whether benzodiazepine use or other patient factors accounted for benzodiazepine recipients' poorer maintenance of gains in present-centered psychotherapy.

Trial Registration: ClinicalTrials.gov identifier: NCT00032617

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About 8% of the US population and 13% of military personnel returning from deployment in Iraq or Afghanistan are affected by posttraumatic stress disorder (PTSD).[1,2] In the US population 18 to 64 years of age, lifetime prevalence of PTSD is substantially higher among women (11.4%) than men (4.0%).[1,3] PTSD often has a chronic course and is associated with greater risk for substance misuse, smoking, cardiovascular disease, violence, divorce, impaired vocational functioning, and suicide.[4–6]

The most efficacious treatments for PTSD are trauma-focused psychotherapies that involve reprocessing of trauma-related memories

or cognitions.[7,8] One of the most extensively studied trauma-focused psychotherapies, prolonged exposure psychotherapy,[9] has consistently been shown to be more effective than wait list or non–trauma-focused treatments.[10] However, not all patients who receive trauma-focused treatments experience full and sustained remission of PTSD symptoms.[11–13]

There has been relatively little research examining how commonly prescribed medications affect response to exposure therapy. Between 30% and 50% of Veteran and civilian patients diagnosed with PTSD are prescribed benzodiazepines, other anxiolytics, or sedative hypnotics.[14–16] Although benzodiazepines are not effective for treating reexperiencing, avoidance, or most arousal symptoms of PTSD,[17] they are often prescribed to PTSD patients with disturbed sleep or other anxiety disorders.[18]

Prior research suggests several ways in which benzodiazepines might interfere with exposure therapy.[19,20] In humans, benzodiazepine use is associated with decreased attention and deficits in several memory domains.[21,22] Animal research shows that extinction of fear responses is blocked by administration of GABAergic agents (including benzodiazepines) before or immediately after extinction training.[20] These extinction trials in animal models are analogous to prolonged exposure psychotherapy. Benzodiazepines may also interfere with extinction through dose-response suppression of cortisol, which plays a critical role in habituation and extinction of fear.[19,23] Finally, people using benzodiazepines during exposure may attribute their reduction in anxiety to the medication, which may reduce generalization of the effects of exposure.[24]

Little research has examined how benzodiazepines influence response to exposure therapy for PTSD. Research on combined cognitive-behavioral therapy and pharmacotherapy for PTSD has largely been limited to selective serotonin reuptake inhibitors.[25] One study of people receiving exposure therapy for PTSD found that taking benzodiazepines at intake was associated with less improvement in symptoms at 1-month follow-up.[26] Because that study did not include a comparison condition of people receiving non–trauma-focused psychotherapy, it is uncertain whether benzodiazepine use interfered with psychotherapy in general or specifically blunted the effects of exposure. A review[27] of studies for panic disorder concluded that receiving cognitive-behavioral therapy plus benzodiazepines might produce better results than receiving cognitive-behavioral therapy alone immediately after treatment, yet contribute to deterioration in the 6 months after treatment, especially if benzodiazepines are not continued. It is unclear whether these findings would generalize to PTSD.

The present post hoc study reanalyzed data from a randomized controlled trial[11] designed to estimate the effectiveness of prolonged exposure relative to present-centered therapy among female veterans and active duty soldiers diagnosed with PTSD. The study showed that PTSD symptoms improved more among women who received

- Prolonged exposure psychotherapy is one of the most effective posttraumatic stress disorder (PTSD) treatments.
- Prolonged exposure psychotherapy is robust enough that even PTSD patients who are taking benzodiazepines can often benefit from it.
- Clinicians should avoid prescribing benzodiazepines to PTSD patients who are prescribed opiates or who misuse substances.

Clinical Points

prolonged exposure than among women who received present-centered therapy. We focus here on whether benzodiazepine use at baseline moderated the effects of psychotherapy condition, especially prolonged exposure therapy, on patients' PTSD symptoms during psychotherapy and in the 6 months after psychotherapy was completed.

Exposure therapy is posited to work through learning of new responses to fear-invoking cues. On the basis of previous research findings on the effects of benzodiazepines on memory and extinction, we hypothesized that the effects of prolonged exposure therapy would be blunted by benzodiazepine use. We hypothesized that present-centered therapy, which is not based on an exposure/extinction paradigm, would be less affected by benzodiazepine use. This difference in effect between treatments would be reflected in a significant interaction of psychotherapy condition by benzodiazepine use on both clinician-assessed and self-reported PTSD symptoms. Although we expected prolonged exposure therapy to produce more improvement in PTSD symptoms than would present-centered therapy, we also anticipated that the effect of psychotherapy condition on outcomes would be smaller among people taking benzodiazepines than among those not taking benzodiazepines.

METHOD

Participants

A total of 284 female veterans and active duty soldiers meeting *DSM-IV* criteria for PTSD were recruited between August 2002 and October 2005, from 9 Veterans Affairs (VA) Medical Centers, 2 VA Readjustment Counseling Centers, and 1 military hospital. Eligibility criteria included being female, having a current diagnosis of PTSD based on the Clinician-Administered PTSD Scale (CAPS)[28] and a CAPS score of 45 or higher, receiving no other concurrent PTSD psychotherapy other than brief visits with an existing therapist or participation in self-help groups, and having no change in psychoactive medications for at least 2 months prior to study recruitment. Exclusion criteria were substance dependence not in remission for at least 3 months; current psychotic symptoms, mania, or bipolar disorder; prominent current suicidal or homicidal ideation; cognitive impairment indicated by chart diagnosis or observable cognitive difficulties; current involvement in a violent relationship; or self-mutilation within the past 6 months. The study is registered at ClinicalTrials.gov (identifier: NCT00032617).

Medication use at intake was decided by patients and their prescribers and was not randomly assigned. One participant who did not report medication status at intake was excluded from the present analyses, leaving 283 participants. Of those, 213 participants (75%) were receiving psychoactive medications at the start of the trial, including 57 (20%) who were prescribed benzodiazepines. Patients using benzodiazepines were evenly split between the prolonged exposure (n = 28) and present-centered (n = 29) psychotherapy conditions. Forty-eight (84%) of the participants who were prescribed benzodiazepines reported their medication use at the end of the study. Of those, 40 participants (83%) maintained the same dose, 2 (4%) increased their dose, 1 (2%) decreased her dose, and 5 (10%) discontinued benzodiazepines.

Measures

PTSD symptom severity was assessed with the CAPS (by clinicians who were blind to participants' psychotherapy condition) and by self-report using the PTSD Checklist (PCL).[29] Both measures were administered at baseline, posttreatment, and 3 and 6 months posttreatment. The PCL was also completed every other session during the treatment phase.

Several possible confounders in the relationships between benzodiazepine use and PTSD symptoms were also assessed. Depressive symptoms were measured with the Beck Depression Inventory,[30] and overall mental and health functioning was assessed with the Medical Outcomes Study 36-item Short Form Health Survey (SF-36).[31] Trauma exposure was assessed with the Life Events Checklist.[32] Current psychoactive prescriptions, prior engagement in psychotherapy, and PTSD disability pension status were assessed by self-report. We classified participants' benzodiazepine use on the basis of their self-reports (0 = no, 1 = yes) of medication use at baseline assessment and follow-up. Additional details of the study design have been published previously.[11,33]

Procedure

Study procedures were overseen by institutional review boards at each of the study sites. Participants who gave consent were randomly assigned to receive either prolonged exposure psychotherapy or present-centered psychotherapy. Both psychotherapies were delivered in 10 weekly 90-minute sessions using manualized protocols. Prolonged exposure includes psychoeducation about common reactions to trauma, breathing retraining, repeated recounting of trauma memories during sessions, and exposure homework (for example, listening to a recording of the recounting during the therapy session and in vivo exposure to safe situations that the person has been avoiding because of the trauma).[9,11] The study protocol did not provide specific instructions regarding benzodiazepine use during exposure exercises. Rather than focusing on past traumatic events, present-centered therapy focuses on current life problems as manifestations of PTSD. Therapists helped patients identify and review daily stressors and discussed them in a nondirective mode, but did not teach cognitive restructuring or assign exposure exercises.

As has been previously reported,[11] dropout from psychotherapy was significantly higher among participants in the prolonged exposure condition (n = 53, 38%) than among those in the present-centered therapy condition (n = 30, 21%; odds ratio = 2.3; 95% CI, 1.2–4.5; $P < .05$). Dropout rates did not vary by either benzodiazepine status or the interaction of benzodiazepine status and psychotherapy condition.

Analysis Plan

Baseline characteristics of participants in the 4 treatment groups (2 psychotherapy conditions × benzodiazepine use or non-use) were compared using analysis of variance and logistic regression with 3 planned contrasts (benzodiazepine status, psychotherapy condition, benzodiazepine status × psychotherapy condition). Race/ethnicity, previous psychotherapy, psychoactive medication use, PTSD symptoms, and SF-36 mental health component score varied by treatment group (Table 1).

Outcome analyses were performed on an intent-to-treat basis. As in the original trial, we estimated participants' missing outcome values with SAS PROC MI and SAS PROC MI ANALYZE (SAS Institute Inc; Cary, North Carolina) multiple imputation procedures using Markov chain Monte Carlo methods initiated using estimates from an expectation-maximization algorithm.[34,35] Due to the large number of covariates in the multiple-imputation model, the quantity of initial burn-in iterations (ie, NBITER) and the number of iterations between imputations (ie, NITER) were each set at 5,000. We used 30 imputations for the CAPS and 40 for the PCL to minimize between-imputation variance and maximize relative efficiency. Trace plots of coefficient means and autocorrelation plots were consistent with good mixing and convergence at the target distribution. Multilevel regression analyses (SAS 9.0, Proc GLIMMIX) were conducted to assess the effects of psychotherapy condition (coded +0.5 for prolonged exposure psychotherapy, –0.5 for present-centered psychotherapy), benzodiazepine status (coded +0.5 for benzodiazepines, –0.5 for none), and their interaction on initial status and rate of change in PTSD symptoms.[36] One analysis predicted changes in clinician-assessed PTSD symptoms using the CAPS; a second predicted changes in the self-report PCL. Both analyses covaried clinical factors associated with benzodiazepine use: prior receipt of psychotherapy, use of psychoactive medications, PTSD symptoms, depression symptoms, and SF-36 mental health scores, as well the interaction of initial severity × time (the latter controls for initial severity influencing the slope of treatment response). As in the original trial,[11] baseline PTSD symptom severity, psychotherapy condition, and site were controlled as fixed effects, and random intercepts were employed for participant and for therapist to account for possible clustering of repeated measures within participants and of participants within therapists, respectively.

Table 1. Characteristics of Participants by Psychotherapy Condition and Benzodiazepine Use Status*

Characteristic	Total (n=283) n	%	BZD–/PE (n=112) n	%	BZD–/PCT (n=114) n	%	BZD+/PE (n=28) n	%	BZD+/PCT (n=29) n	%
Post–high school	252	89	102	91	98	86	26	93	26	90
Unemployed	108	38	43	38	46	40	9	32	10	35
Married/cohabitating	89	31	36	32	36	32	8	29	9	31
Race/ethnicity										
White	155	55	60	54[A]	57	50[A]	19	68[B]	19	66[B]
Black	92	33	40	36[A]	41	36[A]	6	21[B]	5	17[B]
Hispanic	17	6	6	5	7	6	2	7	2	7
Other	19	7	6	5	9	8	1	4	3	10
Any sexual trauma	263	93	105	94	106	93	25	89	27	93
Military sexual trauma	207	73	76	68	85	75	22	79	24	83
Physical trauma type	248	88	102	91	95	83	26	93	25	86
Combat	70	25	28	25	29	25	6	21	7	24
Disaster	204	72	84	75	75	66	21	75	24	83
Accident	231	82	92	82	87	76	24	86	28	97
Other life-threatening trauma	123	44	48	43	42	37	17	61	16	55
Other trauma	251	89	100	89	100	88	24	86	27	93
PTSD disability claim status										
Approved	63	23	23	21	24	22	5	19	11	38
Pending	66	24	21	19	32	29	7	26	6	21
Denied	21	8	11	10	5	5	3	11	2	7
Never applied	126	46	55	50	49	45	12	44	10	35
Received prior psychotherapy	176	62	69	62[A]	64	56[A]	25	89[B]	18	62[A]
Psychiatric medications (other than benzodiazepines)	206	73	80	71[A]	74	65[A]	26	93[B]	26	90[B]
SSRI or SNRI	159	56	60	54[A]	58	51[A]	18	64[A,B]	23	79[B]
Other antidepressant	67	24	28	25	20	18	9	32	10	35
Trazodone	55	19	24	21	21	18	4	14	6	21
Second-generation antipsychotic	26	9	8	7[A]	7	6[A]	4	14[B]	7	24[B]
Mood stabilizer	38	13	16	14[A]	7	6[A]	7	25[B]	8	28[B]
Co-occurring psychiatric diagnoses	221	78	81	72	93	82	25	89	22	76
Mood disorder	181	64	66	59	75	66	21	75	19	66
Anxiety disorder other than PTSD	136	48	55	49	55	48	14	50	12	41
Substance use disorder	6	2	2	2	2	2	1	4	1	3
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
No. of psychiatric medications other than benzodiazepines	1.2	0.1	1.2[A]	0.1	1.0[A]	0.1	1.5[B]	0.1	1.9[C]	0.2
Clinician-Administered PTSD Scale	77.8	1.0	76.4[A]	1.7	76.7[A]	1.5	82.5[B]	2.8	82.4[B]	3.4
PTSD Checklist	57.6	0.7	57.3[A]	1.2	56.2[A]	1.1	61.8[B]	2.3	60.7[B]	2.4
Beck Depression Inventory	24.6	0.6	24.6[A]	0.9	23.1[A]	0.9	28.3[B]	1.5	27.1[B]	1.9
SF-36 v2 mental health component†	30.3	0.6	30.9[A]	0.9	31.5[A]	1.1	26.8[B]	1.9	26.7[B]	2.1
SF-36 v2 physical health component†	39.0	0.7	38.8	1.1	40.3	1.2	35.9	2.1	37.1	2.4

*Different superscripted uppercase letters indicate groups are significantly different (*P*<.05).
†Higher scores indicate better functioning.
Abbreviations: BZD–=not prescribed benzodiazepines at intake, BZD+=prescribed benzodiazepines at intake, PCT=present-centered psychotherapy, PE=prolonged exposure, PTSD=posttraumatic stress disorder, SF-36=Medical Outcomes Study 36-item Short Form Health Survey, SNRI=serotonin-norepinephrine reuptake inhibitor, SSRI=selective serotonin reuptake inhibitor.

In addition to controlling for additional covariates, we modified the analysis plan from the original study[11] in 3 ways. First, we added benzodiazepine status and a benzodiazepine×psychotherapy interaction term as fixed effects. Second, in the analysis with PCL as the outcome, we included PCL scores obtained during treatment, as well as those obtained at baseline, posttreatment, and the 2 follow-up assessments. Third, parameter estimates of interest were rates of change in PTSD symptoms, rather than mean outcome symptom scores at individual time points. This allowed us to maximize statistical power by using all available symptom assessments rather than fitting a separate model for each assessment. Because some prior research suggests that the moderating effects of benzodiazepines might be different during and after completion of psychotherapy,[27] we fit our data using piecewise-linear regression, which allowed rate of change over time in the average participant's PTSD symptoms to differ between psychotherapy (weeks 0–16) and the 6-month posttreatment period (weeks 16–42).

## RESULTS
Clinician-Assessed PTSD Symptoms

Changes in clinician-assessed PTSD symptoms are shown in Figure 1. In Table 2, *b* weights indicate mean change in symptoms per week associated with each increment of the predictors in the model. Clinician-assessed PTSD symptoms declined over the course of psychotherapy (*b*=−1.20, *P*<.001) and declined more rapidly among participants who received prolonged exposure rather than present-centered psychotherapy (*b*=−0.48, *P*=.02). More severe symptoms at intake were associated with less improvement, regardless of therapy type (*b*=0.24, *P*=.03). Baseline use of benzodiazepines, the interaction of psychotherapy type with benzodiazepines, and the interaction of symptom severity at intake and therapy type had no significant effect on rate

Table 2. Effects of Prolonged Exposure, Benzodiazepine Status, and Their Interaction on PTSD Symptom Change During Psychotherapy and Postpsychotherapy Follow-Up[a]

Predictor	Clinician-Assessed PTSD Symptoms (CAPS)			Self-Reported PTSD Symptoms (PCL)		
	b	95% CI	P	b	95% CI	P
Symptom change per week during psychotherapy						
Overall mean change	−1.20	−1.41 to −0.99	<.001	−0.72	−0.82 to −0.62	<.001
Prolonged exposure (vs present-centered therapy)	−0.48	−0.85 to −0.10	.02	−0.60	−0.77 to −0.42	<.001
Benzodiazepines (vs not taking benzodiazepines)	−0.02	−0.44 to 0.41	NS	0.23	0.03 to 0.43	.03
Benzodiazepines × prolonged exposure	0.01	−0.75 to 0.76	NS	−0.13	−0.48 to 0.22	NS
Symptom severity at intake	0.24	0.04 to 0.45	.03	−0.11	−0.21 to −0.01	.03
Symptom severity at intake × prolonged exposure	0.25	−0.18 to 0.67	NS	−0.08	−0.27 to 0.10	NS
Symptom change per week during follow-up						
Overall mean change	−0.08	−0.22 to 0.05	NS	0.10	0.03 to 0.17	<.01
Prolonged exposure (vs present-centered therapy)	−0.07	−0.33 to 0.19	NS	0.12	−0.02 to 0.27	NS
Benzodiazepines (vs not taking benzodiazepines)	0.13	−0.14 to 0.41	NS	0.04	−0.11 to 0.19	NS
Benzodiazepines × prolonged exposure	−0.78	−1.31 to −0.25	<.001	−0.25	−0.54 to 0.04	NS
Symptom severity at intake	−0.02	−0.15 to 0.11	NS	0.01	−0.05 to 0.07	NS
Symptom severity at intake × prolonged exposure	−0.10	−0.37 to 0.18	NS	−0.04	−0.16 to 0.09	NS

[a]Prolonged exposure = effect of prolonged exposure vs present-centered therapy. Benzodiazepines = effect of benzodiazepines prescribed at intake vs not prescribed at intake. Symptom severity at intake = average of standardized scores on the PTSD symptom measure (either CAPS or PCL), Beck Depression Inventory, and (reverse-coded) Medical Outcomes Study 36-item Short Form Health Survey mental health aggregate. Mean change in symptoms per week associated with each variable is indicated by b weights, with negative values corresponding to reductions in symptoms. Estimates of effects on intercept are not shown. Model intercepts are adjusted for fixed effects of site, baseline scores on the PTSD symptom measure, baseline scores on Beck Depression Inventory, baseline scores of Medical Outcomes Study 36-item Short Form Health Survey mental health aggregate, number of nonbenzodiazepine psychiatric medications taken, and whether the participant had received prior psychotherapy and for random effect of therapist.
Abbreviations: CAPS = Clinician-Administered PTSD Scale, NS = nonsignificant, PCL = PTSD Checklist, PTSD = posttraumatic stress disorder.

Figure 1. Clinician-Administered PTSD Scale (CAPS) Scores by Time, Psychotherapy Condition, and Benzodiazepine Status
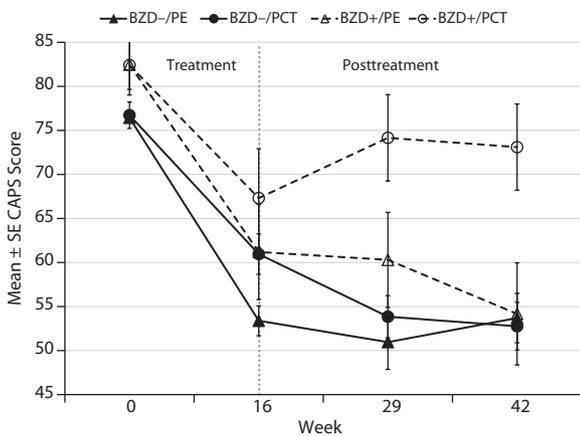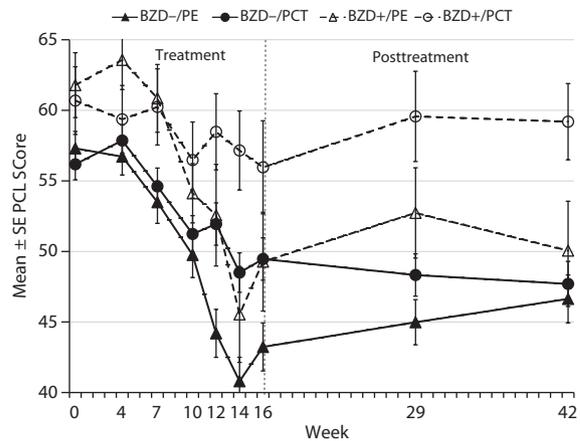

Abbreviations: BZD− = not prescribed benzodiazepines at intake, BZD+ = prescribed benzodiazepines at intake, PCT = present-centered therapy, PE = prolonged exposure.

Figure 2. PTSD Checklist (PCL) Scores by Time, Psychotherapy Condition, and Benzodiazepine Status

Abbreviations: BZD− = not prescribed benzodiazepines at intake, BZD+ = prescribed benzodiazepines at intake, PCT = present-centered therapy, PE = prolonged exposure.

of change in clinician-assessed PTSD symptoms during the course of treatment (see weeks 0–16 in Figure 1).

After psychotherapy was completed, type of psychotherapy, benzodiazepine use, and initial symptom severity did not have a statistically significant main effect on change in clinician-assessed symptoms during the 6-month follow-up period (see Table 2). However, benzodiazepine use interacted with type of psychotherapy to predict the rate of change in symptoms—but in the opposite direction than predicted (b = −0.78, P < .001). Benzodiazepine use was not associated with change in symptoms after the end of prolonged exposure therapy, but it was associated with worsening PTSD symptoms

after the end of present-centered therapy (see weeks 16–42 in Figure 1). The mean improvement in CAPS scores from pretreatment to 6-month follow-up among benzodiazepine users who received present-centered therapy was less than half as large as the improvement among veterans in the other 3 groups (see Figure 1).

Self-Reported PTSD Symptoms

As shown in Figure 2 and Table 2, participants' self-reported PTSD symptoms improved over the course of treatment (b = −0.72, P < .001) and improved more rapidly among those who received prolonged exposure than among

those who obtained present-centered therapy ($b = -0.60$, $P < .001$). Benzodiazepine use was associated with less improvement ($b = 0.23$, $P = .03$), whereas greater initial symptom severity (controlling for benzodiazepine use) was associated with slightly more improvement ($b = -0.11$, $P = .03$). However, the interaction of benzodiazepine use and psychotherapy condition had no effect on symptom course during treatment (see Table 2 and weeks 0–16 in Figure 2). Participants' self-reported symptoms tended to increase slightly ($b = 0.10$, $P < .01$) during the posttreatment follow-up period. However, neither the main effects of psychotherapy condition, benzodiazepine, and initial symptom severity nor their interactions predicted symptom course after the end of treatment (see Table 2 and Figure 2).

DISCUSSION

The present study reanalyzed data from a randomized clinical trial to determine whether benzodiazepine use might impede response to exposure therapy. Contrary to our hypotheses, benzodiazepine use was not associated with weaker response to exposure therapy during either treatment or the follow-up period. This was particularly striking because patients who were prescribed benzodiazepines tended to have other clinical characteristics (more severe PTSD symptoms, worse SF-36 mental health functioning scores, more prior sessions of psychotherapy, and more use of psychotropic medications) that could indicate failure to respond to prior treatments. Yet, prolonged exposure was a sufficiently robust treatment that these patients were able to benefit.

Unexpectedly, benzodiazepine use was associated with poorer maintenance of clinician-rated PTSD symptom improvements by participants who received present-centered psychotherapy. Our findings are not accounted for by discontinuation of benzodiazepines, because most participants using benzodiazepines at the beginning of the study also reported using them at the end of the study.

Benzodiazepines may have made it more difficult to attend to and retain information from present-centered psychotherapy. Beyond their effects on fear extinction, benzodiazepines have broader effects on memory and attention that may have interfered with retention of psychotherapy content.[21,22]

It is also possible that present-centered therapy may not be sufficiently powerful to produce lasting changes in patients with a history of poor response to other mental health treatments. As noted above, variables associated with benzodiazepine use suggest that these patients may have been hard to treat. An American Psychological Association workgroup concluded that trials in which present-centered therapy was used as a comparator condition suggest that present-centered therapy is efficacious,[37] but the efficacy of present-centered therapy has not been tested relative to placebo.

Our findings contrast with those of van Minnen and colleagues,[26] who found that benzodiazepine use was associated with poorer outcomes 1 month after completion of prolonged exposure therapy for PTSD. The measure of benzodiazepine use differed in the 2 studies: our sample of benzodiazepine users included anyone with a benzodiazepine prescription, whereas the van Minnen et al study defined benzodiazepine use as daily use. Van Minnen et al also analyzed outcomes among treatment completers only; this may have biased their findings toward poorer outcomes for the benzodiazepine group because dropout was much higher among benzodiazepine non-users than among benzodiazepine users in their sample.

Neither our study nor van Minnen and colleagues' study controlled dosage or timing of benzodiazepine use. Because the effects of benzodiazepines on learning are dose dependent, effects might be different for people taking different doses.[19] Although dosage was not assessed in this study, the average dose of benzodiazepines prescribed for VA PTSD patients at the time of the study was 1.9 standard daily dosage units, comparable to 1.9 mg/d of clonazepam or 19.0 mg/d of diazepam.[14] Timing may also be a factor. Benzodiazepines have been shown to interfere with extinction of conditioned fear responses if they are used during or shortly after the time of exposure to fear-inducing conditions.[19,20,24] If many veterans were primarily taking benzodiazepines at bedtime to help them sleep,[18] this would be unlikely to interfere with exposure exercises conducted during waking hours.

Aside from the issue of whether benzodiazepines can interfere with psychotherapy, many veterans with PTSD have comorbid conditions for which benzodiazepines are contraindicated. Substance misuse[38] and prescribing of opiates for pain[39] are both common in the PTSD patient population. For patients with these comorbidities, there are efficacious and safer alternatives to benzodiazepines for managing anxiety or insomnia.[17,40]

The present study has several limitations. Our sample was limited to treatment-seeking female veterans and military personnel. Benzodiazepine use was not randomly assigned, and we did not control for benzodiazepine half-life, dosage, or timing. Moreover, benzodiazepine users were a relatively small subsample of our patients. Further research using larger samples of benzodiazepine users might provide more definitive information about the influence of benzodiazepines on psychotherapies to alleviate PTSD symptoms. Further information is also needed about specific patient characteristics associated with benzodiazepine use that account for its influence on psychotherapy outcomes.

Notwithstanding these limitations, findings from this investigation add to previous research by demonstrating that veterans who are prescribed benzodiazepines can benefit from prolonged exposure therapy and thus do not necessarily need to discontinue benzodiazepines before undergoing this efficacious psychotherapy. More research is needed on the efficacy of present-centered therapy for PTSD. Further investigation is also needed on whether cognitive effects of benzodiazepines may impede retention of material taught in psychotherapy.

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For the CME Posttest, see next page.

CME INSTITUTE™   **POSTTEST**

1. **About ___% of the United States population and ___% of military personnel who were deployed in Iraq or Afghanistan have posttraumatic stress disorder (PTSD).**

   a. 1; 7

   b. 3; 25

   c. 8; 13

   d. 25; 7

2. **The most efficacious treatments for PTSD are ___.**

   a. Trauma-focused psychotherapies

   b. Benzodiazepines

   c. Selective serotonin reuptake inhibitors (SSRIs)

   d. Other anxiolytics

3. **Your patient, Ms A, was diagnosed with PTSD by a previous physician. She had refused to begin prolonged exposure therapy. Ms A was given an SSRI that she quit taking after a year because of weight gain and sexual dysfunction. She saw a new doctor when she became unable to sleep because of anxiety and nightmares. She was given a benzodiazepine. Because Ms A's PTSD symptoms are bothering her, she has come to you and says she is now ready to try exposure therapy. Which of the following statements accurately describes the *best* option?**

   a. Begin exposure therapy only if she first discontinues the benzodiazepine, because the benzodiazepine will lessen the efficacy of exposure therapy

   b. Proceed with exposure therapy regardless of whether she agrees to discontinue the benzodiazepine

   c. Continue the benzodiazepine and begin a present-centered psychotherapy that does not involve exposure

   d. Begin exposure therapy and continue the benzodiazepine because it will enhance the efficacy of the exposure therapy

4. **Mr B is a veteran who has come to you for help with symptoms that you diagnose as PTSD. He had previously received a benzodiazepine prescription at a minor medical clinic when he complained of anxiety and trouble sleeping. Mr B also takes an opioid for pain from an injury. Which of the following strategies is *better*?**

   a. Discontinue the benzodiazepine because of the concomitant opioid and have Mr B begin prolonged exposure therapy for his PTSD

   b. Continue the benzodiazepine and have Mr B begin prolonged exposure therapy for his PTSD