0022-3018/00/1887-454
THE JOURNAL OF NERVOUS AND MENTAL DISEASE
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Vol. 188, No. 7
Printed in U.S.A.

Benzodiazepine Use in Posttraumatic Stress Disorder among Veterans with Substance Abuse

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Veterans with posttraumatic stress disorder (PTSD) and substance abuse may abuse benzodiazepines and develop violent dyscontrol when using them. A total of 370 veterans were compared by substance abuse diagnosis (50%), benzodiazepine use (36%), and their interaction on 1-year outcomes after inpatient discharge. Substance abusers were less likely to be prescribed benzodiazepines (26% *vs.* 45%). No outcome showed a differential worsening by substance abuse or benzodiazepines, although some baseline differences were noted. Outpatient health care utilization was lower in benzodiazepine users (47 *vs.* 33 visits). Among PTSD patients with comorbid substance abuse, benzodiazepine treatment was not associated with adverse effects on outcome, but it may reduce health care utilization.

— *J Nerv Ment Dis* 188:454–459, 2000

Benzodiazepine treatment of substance abusers with anxiety disorders is usually discouraged, because of the abuse potential of these medications, as well as specific complications of these medications such as violent dyscontrol syndromes (American Psychiatric Association, 1990; Barlow, 1997; Cole and Kando, 1993; Michelini et al., 1996; Mueller et al., 1996; Rickels and Downing, 1974; Risse et al., 1990; Rosenbaum et al., 1984; Salzman, 1997). Although substance abuse is one of the most common comorbid disorders in posttraumatic stress disorder (PTSD), these medications have been frequently used in treating PTSD (Chilcoat and Breslau, 1998; Cottler et al., 1992; Kessler et al., 1995; Kulka et al., 1990, 1998; Laufer et al., 1981; Najavits et al., 1998; Orsillo et al., 1996). The relative prohibition in using benzodiazepines among substance abusers (except for acute detoxification) has been well disseminated clinically, with the Veterans Administration Healthcare System (VA) specifically alerting clinicians to this potential problem in treating PTSD during the early 1990s (Ashton, 1994; Fontana and Rosenheck, 1996; Uhlenhuth et al., 1995). Thus, a large 1-year follow-up study of PTSD outpatient care that was conducted in the 2 years after this VA alert offered an opportunity to examine this issue from several perspectives (Fontana and Rosenheck, 1997). These perspectives include whether such an administrative alert would sufficiently impact clinical practice to virtually eliminate all benzodiazepine prescribing to substance abusers with PTSD, or whether substance abusers might be more carefully selected by clinicians following this alert to minimize complications in these patients.

An initial question in this study of veterans who were followed after short-term hospitalization for PTSD was whether benzodiazepine pharmacotherapy after discharge was less frequently prescribed for substance abusers with PTSD. For comparison, we also examined antidepressants, which have been the most common pharmacotherapy for PTSD to determine whether substance abusers were simply less likely to get pharmacotherapy for their PTSD (Frank et al., 1988; Friedman, 1988). Although many characteristics of the outpatient care besides the pharmacotherapy might contribute to differences in outcome, a second question was whether those substance abusers given benzodiazepines had a worse outcome than either the non-substance abusers or than the substance abusers that were not given benzodiazepines. The specific outcomes that might be worse for the substance abusers who were given these medications include alcohol and drug abuse itself, particularly sedative abuse and violence, because recent work has indicated that substance abusers are at higher risk of violence associated with benzodiazepine use (Rickels and Downing, 1974; Risse et al., 1990; Salzman, 1997).

A third question was whether benzodiazepines would increase the need and costs for outpatient or

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This work was supported by National Institute on Drug Abuse Grants P50–DA04060 and P50–09250, and the Veterans Administration Healthcare System.

inpatient care among those substance abusers given benzodiazepines. Substance abusers might have greater health service utilization not only for detoxification but also due to disinhibition of violence by benzodiazepines (Bremmer et al., 1996; Cole and Kando, 1993; Michelini et al., 1996). Moreover, because benzodiazepines relieve anxiety, this relief could reduce the number of emergency room visits and hospitalizations due to crises associated with the PTSD and amplify the difference between the abusers and nonabusers given benzodiazepines. Thus, we also compared substance abusers to nonabusers on outpatient and subsequent inpatient care utilization during the 1-year follow-up.

Methods

This study was a quasi-experimental design comparing specialized to nonspecialized short-term inpatient care for PTSD at nine different sites within the VA, as described elsewhere (Fontana and Rosenheck, 1997). Five units were a general psychiatry type (GEN), the other four were specialized 1-month inpatient programs for PTSD (EBPTU). These inpatient programs represented substantial geographic diversity across the United States as described elsewhere and were chosen to represent the diversity of veterans with PTSD treated within the Department of Veterans Affairs (Fontana and Rosenheck, 1997). In the original study, a third treatment setting—long-term inpatient care—was also examined, but the veterans in that program were unlikely to get any medications at follow-up. For example, less than 4% of those leaving the long-term inpatient care were prescribed benzodiazepines making any comparison between users and nonusers uninformative due to the small number of subjects.

Within these two short-term programs 541 veterans were examined at baseline, but during a 1-year follow-up, only 370 (68%) were available. All had a diagnosis of PTSD, and about half had substance use disorders that were diagnosed using a clinical interview with DSM-III criteria. All were men and the average age was 45 years old. Most veterans were white (75%). Only 6% were never married, but over half of those married had been divorced. Although only 5% were employed full-time, this low rate reflects their status upon entry into the inpatient treatment program, not their employment status during the one-year follow-up. However, about half were service-connected for PTSD and 20% were service-connected for some other disorder and not considered currently employable. The EBPTU program treated about half of the veterans, and most had had previous inpatient care (85%). Medication was used in over 80%, as ascertained by self-report, which specified medication type, but not medication dosage or brand name. Participation in these assessments followed written informed consent.

At baseline and during the 1-year follow-up at 4, 8, and 12 months after discharge, outcome measures included inpatient and outpatient health services utilization, severity of alcohol and illicit drug use, anxiety and PTSD symptoms, psychosocial functioning, and violence. Substance abuse and psychosocial outcome were assessed using the Addiction Severity Index (ASI; McLellan et al., 1985). Anxiety was assessed using the Brief Symptom Inventory (BSI), violent actions were assessed using a self-report instrument derived from the National Vietnam Veterans Readjustment Study (NVVRS), and PTSD specific symptoms were assessed using the Mississippi Scale for PTSD (Derogatis and Melisaratos, 1983; Keane et al., 1988; Kulka et al., 1990).

Baseline comparisons between benzodiazepine treated and untreated veterans were conducted using chi-squared and simple *t*-tests. The characteristics showing a difference were then entered into a stepwise discriminant function to select those characteristics that independently contributed at least 2% to the overall variance of being treated with benzodiazepines. These characteristics then were used as covariates for further analyses of outcome. The outcome measures such as violence, the ASI and the other psychological scales were analyzed using a random regression model (RRM) from SAS 6.12 (PROC Mixed). Our model was based on an autoregressive order one covariance structure, with linear time interactions (Gibbons et al., 1993; Jenrich and Schluchter, 1986). With this RRM approach, we had 370 of 541 potential subjects (68% follow-up) for the comparisons of the aftercare following the two short-term inpatient programs (EBPTU and GEN).

The first set of analyses examined the impact of benzodiazepines on time trends for each of the outcomes. In addition to the covariates mentioned previously, each model included terms representing main effects of time and benzodiazepine use and the interaction of benzodiazepine use and time. A significant time by benzodiazepine interaction was taken as evidence of an effect of benzodiazepine use on outcomes. A second set of analyses then examined whether time trends with benzodiazepines differed among patients with current substance abuse and those without such problems. These analyses included terms representing main effects for benzodiazepine use, time and substance abuse; two-way interaction terms between each of the three pairs of these factors; and a three-way interaction of time,

benzodiazepine use, and substance abuse. The three-way interaction term was used to identify any difference in benzodiazepine effect associated with substance abuse.

Results

Pharmacotherapy was used commonly with both substance abusers and nonabusers during the outpatient care of these veterans. The most common medications used were antidepressants and benzodiazepines with 90% of the treated patients given either one or both of these medications. Other medications such as antipsychotic agents and lithium were infrequently used. One or both of these medications were used by 72% of the EBPTU and 85% of the GEN veterans, but benzodiazepines were used less often by the EBPTU than by the GEN veterans (25% *vs.* 47%) ($\chi^2 = 14$; $p < .001$). Antidepressants were prescribed to 71% of the substance abusers and 66% of the nonabusers. In comparison, only 26% of the substance abusers and 45% of the nonabusers were given benzodiazepines ($\chi^2 = 14$; $p < .001$).

Prescription of benzodiazepines showed no interaction between program type and substance abuse. The rates of prescription for substance abusers were about half the rate of the non-substance abusers in both types of programs (18% *vs.* 31% for EBPTU and 34% *vs.* 59% for GEN; for the interaction: $F = 1.5$; $df = 1{,}369$; $p < .3$). Among the substance abusers, 63 (17% of all subjects) had a history of sedative abuse, but the rates of benzodiazepine prescribing did not differ between these abusers and nonabusers (36% *vs.* 38%).

As shown in Table 1, independent of substance abuse, benzodiazepine-treated veterans were more likely to have been previously hospitalized, had more severe PTSD symptoms, and had more anxiety and overall psychiatric symptoms on the BSI. They were more likely to be also prescribed antidepressants and less likely to have an alcohol or drug abuse diagnosis. Independent of benzodiazepine use, the substance abusers had higher Helzer scores, more severe drug abuse severity, and more family instability. For age, alcohol problems and receipt of VA disability benefits, the veterans differed on both benzodiazepine use and substance abuse. All of these distinguishing characteristics were entered into a stepwise discriminant function and four were selected as making at least a 2% contribution to the variance in being prescribed benzodiazepines: age, ASI alcohol problems, PTSD symptoms, and service connection. When separated into substance abusers and nonabusers, two discriminating characteristics for benzodiazepine prescription were the same for abusers or nonabusers: age and receipt of VA disability benefits. Two other characteristics distinguished benzodiazepine prescribing for only substance abusers or nonabusers, but not both: BSI anxiety discriminated only among the substance abusers and PTSD severity discriminated only among the nonabusers. Finally, a more complex four-group discrimination yielded similar discriminators: age, service connection, anxiety, and prior hospitalization.

Table 2 provides the mean change from baseline to 1 year follow-up for 10 outcomes as well as outpatient and inpatient service utilization (days/year). As shown, benzodiazepine use had no significant impact on clinical outcome in either substance abusers or nonabusers, but substance abusers had significant reductions in both alcohol problems and violence. Although violence did not differ at baseline, as shown in Table 1, it was significantly higher in the benzodiazepine treated veterans at the 4-, 8-, and 12-month follow-up using simple *t*-tests (data not shown). By using a random regression model to examine changes over time, however, violence showed no significant time interactions with benzodiazepine use. Thus, benzodiazepine use did not make either violence or substance abuse worse for the substance abusers, although substance abusing veterans treated with benzodiazepines showed less improvement on both outcomes than those not given benzodiazepines.

For healthcare utilization the veterans treated with benzodiazepines had fewer outpatient visits per year (OPV; 64 *vs.* 32 visits, $t = 3.4$; $df = 364$; $p < .001$) but no significant difference in inpatient days (22 *vs.* 29 days). Furthermore, among the substance abusers inpatient days were the same whether or not treated with benzodiazepines (29 days). The outpatient difference was greatest for the first 4 months (27 *vs.* 17 visits, $t = 3.7$; $p < .001$) and was not significant for the last 4-month block between months 8 and 12 (19 *vs.* 16 visits). Covariance adjustments for program type, baseline differences, and alcohol abuse had little effect on this difference in OPV.

Discussion

The veterans treated with benzodiazepines after a brief hospitalization for PTSD had more severe PTSD symptoms and less severe alcohol problems as well as being slightly younger. The substance abusers treated with benzodiazepines did not have worse outcomes. A surprising finding was the reduction in outpatient healthcare utilization with benzodiazepine treatment of the substance abusers. This difference in 32 compared with 64 visits per

TABLE 1

Baseline Comparison: Veterans with vs. *without Substance Abuse (SA) and Benzodiazepine Treated* vs. *Nontreated (N = 370)*

	Substance Abuse		No Substance Abuse		Significance[a]	
Characteristic	Benzodiazepines	No Benzodiazepines	Benzodiazepines	No Benzodiazepines	Benzodiazepines	SA
N	46	88	129	107		
Age (yr)	44	45	45	46	.0002	.02
Times married	1.8	1.8	1.7	1.7	NS	NS
Combat Score	11.1	11.8	11.1	11.3	NS	NS
Mississippi Score	137	140	133	134	.001	NS
Peri guilt	3.8	3.4	3.3	3.7	NS	NS
Helzer	2.1	1.4	2.0	1.2	NS	.001
ASI Alcohol	12	6	22	6	.05	.0001
ASI Drug	6	2	4	2	NS	.0001
ASI Family	34	31	28	26	NS	NS
ASI Legal	3	5	6	4	NS	NS
ASI Medical	62	52	55	54	NS	NS
ASI Work	56	54	59	54	NS	NS
ASI Psych	73	77	68	69	.0001	NS
Family instability	3.7	2.7	3.4	3.0	NS	.02
BSI total	26	26	24	25	.01	NS
BSI Anxiety	30	30	27	28	.002	NS
Violence	11.3	12.0	11.4	10.0	NS	NS
Black	11%	13%	19%	19%	NS	NS
Never married	9%	7%	5%	5%	NS	NS
Service connect	57%	75%	37%	51%	.001	.001
Working now	7%	8%	15%	18%	NS	NS
Ever hospitalized	88%	96%	73%	85%	.002	NS
Taking antidepressants	70%	74	72	60%	0.01	NS
Alcoholism	83%	0%	86%	0%	0.01	NS
Drug Dependence	39%	0%	48%	0%	0.01	NS

[a]Significance levels for benzodiazepine user *vs.* nonuser and for substance abuser *vs.* nonabuser.

TABLE 2

One-Year Outcome: Veterans with vs. *without Substance Abuse (SA) and Benzodiazepine Treated* vs. *Nontreated*

	Substance Abuse		No Substance Abuse		Significance[a]		
Outcome[b,c]	Benzodiazepines	No Benzodiazepines	Benzodiazepines	No Benzodiazepines	Benzodiazepines	SA	× Time
N	46	129	88	107	—	—	—
Violence	−4.0	−4.3	−2.1	−2.8	—	.05	—
ASI Alcohol	−4	−8	−1	−1	—	.05	—
ASI Drug	−1	−0.2	−0.7	−0.7	—	—	—
ASI Family	−10	−4	3	−1	—	—	—
ASI Legal	3.1	−1.0	−1.1	−0.4	—	—	—
ASI Medical	−10	5	10	3	—	—	—
ASI Work	5	2	1	−2	—	—	—
ASI Psych Work	−8	−7	−7	−8	—	—	—
BSI Anxiety	1	3	11	−10	—	—	—
BSI Total SX	2	22	5	9	—	—	—
Outpatient days	35	47	32	46	.001	—	—
Inpatient days	29	29	29	15	—	—	—

[a]Not significant. Significance levels reflect two- and three-way interactions of benzodiazepines with time (benzodiazepine), substance abuse with time (SA), benzodiazepines, and substance abuse with time (× time); (three-way interaction).

[b]Addiction Severity Index and Brief Symptom Inventory change scores for composite scales have been multiplied by 100 for presentation; negative scores indicate worsening during follow-up.

[c]Outpatient and inpatient days reflect average total days for whole year.

year represents savings of $600 to $1200 per patient, per year, in outpatient care. Although it might be argued that more outpatient care is superior, the average number of outpatient treatments was substantial for the benzodiazepine treated patients with over 30 visits/year. The contribution of benzodiazepines to this lower utilization cannot be separated from differences in practice patterns among the practitioners included in this follow-up, however. Only future placebo controlled studies using randomization and perhaps stratification of providers by those who focus more on psychotherapies

versus those who rely more on medications and perhaps less frequent outpatient visits.

Previous alcohol abuse has been considered a risk factor for developing increased violence as well as worsening substance abuse while taking benzodiazepines, but benzodiazepine-treated veterans with alcohol abuse showed no differences from untreated veterans during the follow-up (American Psychiatric Association, 1990; Barlow, 1997; Michelini et al., 1996; Nunes et al., 1995; Rickels and Downing, 1974; Salzman, 1997). Because no previous large scale study has examined this clinical assertion of alcoholism as a risk factor for violence, this assertion may be incorrect. Alternatively, the treating clinicians appeared to be aware of this potential risk factor, because the severity of alcohol problems was significantly lower in the benzodiazepine treated compared with untreated veterans at hospital entry. These findings suggest that clinicians may have been able to select their substance abuse patients for benzodiazepine use in order to minimize the potential for violence. However, these selection factors for benzodiazepine use in substance abusers were not obvious in this study, and their identification remains a goal for future studies.

Besides alcohol problem severity, the other two clinical factors uniquely contributing to a decision for benzodiazepine treatment were severity of PTSD as assessed by the Mississippi Scale and receipt of VA disability benefits for PTSD. These two measures reflect not only the severity of PTSD symptoms, but also the disability associated with PTSD in these veterans. Interestingly, however, benzodiazepine treatment did not improve either the anxiety symptoms of these veterans nor their social functioning in employment, legal or family areas. Thus, the therapeutic role of chronic benzodiazepines in PTSD is not clear.

This study has several limitations in its nonrandom allocation to medications and reliance on self-reports rather than toxicology verified substance abuse outcomes. Because of nonrandom allocation, we checked for demographic or clinical differences between the medication groups at baseline. We adjusted for these differences, and we added covariates for baseline PTSD and general symptom levels without effecting the main findings. Self-report limitations may have biased the reporting of adverse events by the veterans given benzodiazepines, but serious complications leading to hospitalization including the need for detoxification were not evident. Self-reports in this PTSD population have also shown excellent validity compared with urine toxicology (Weiss et al., 1998). Other limitations are the pooling of various medications into two broad classes and the lack of dosing information or compliance measures. Although these can be serious limitations due to potential under-dosing for many medications, benzodiazepines tend to be requested by patients and compliance is good. If these medications were under-dosed, this would bias against their potential efficacy and suggests that our effect sizes may be minimal estimates of the efficacy for their addition to PTSD treatment. In conclusion, benzodiazepines may put some veterans with PTSD at risk for violence, but neither alcoholism nor relatively lower levels of outpatient care appear to identify a high-risk group for violence or other psychosocial complications or poor treatment outcomes.

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