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Benzodiazepines for PTSD: A Systematic Review and Meta-Analysis

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Objective: **Although benzodiazepines (BZDs) are commonly used in the treatment of posttraumatic stress disorder (PTSD), no systematic review or meta-analysis has specifically examined this treatment. The goal of this study was to analyze and summarize evidence concerning the efficacy of BZDs in treating PTSD.**
Methods: **The review protocol was undertaken according to the principles recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and is registered with the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO, registration number CRD42014009318). Two authors independently conducted a search of all relevant articles using multiple electronic databases and independently abstracted information from studies measuring PTSD outcomes in patients using BZDs. Eighteen clinical trials and observational studies were identified, with a total of 5236 participants. Outcomes were assessed using qualitative and quantitative syntheses, including meta-analysis.**
Results: **BZDs are ineffective for PTSD treatment and prevention, and risks associated with their use tend to outweigh potential short-term benefits. In addition to adverse effects in general populations, BZDs are associated with specific problems in patients with PTSD: worse overall severity, significantly increased risk of developing PTSD with use after recent trauma, worse psychotherapy outcomes, aggression, depression, and substance use. Potential biopsychosocial explanations for these results are proposed based on studies that have investigated BZDs, PTSD, and relevant animal models.**
Conclusions: **The results of this systematic review suggest that BZDs should be considered relatively contraindicated for patients with PTSD or recent trauma. Evidence-based treatments for PTSD should be favored over BZDs.**
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Key Words: benzodiazepine, sedative, trauma, stress disorder, posttraumatic stress disorder, psychopharmacology

The use of benzodiazepines (BZDs) in the treatment of posttraumatic stress disorder (PTSD) is both common and controversial. Although BZDs are prescribed to 30% to 74% of patients with PTSD,[1–2] there is little literature—and no reviews before this article—focusing exclusively on the use of BZDs to prevent or treat PTSD. Considering all the service members returning from Afghanistan and Iraq with combat-related PTSD, there is no better time to evaluate this topic than now.

Some argue that BZDs are effective symptomatic treatments for the anxiety, insomnia, and irritability associated with PTSD, and they defend the prescription of BZDs for PTSD as necessary for treatment-resistant patients with severe symptoms. Others contend that BZDs may diminish subjective anxiety in the short term at the cost of worsening other features of PTSD, such as promoting avoidance, in the long term. They explain the correlation between BZDs and increased symptom severity as the result of BZDs actually prolonging and worsening PTSD.

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Most PTSD practice guidelines pay little attention to BZDs or caution against their use, citing weak evidence, risks that outweigh benefits, and contraindication for conditions that are commonly comorbid with PTSD such as traumatic brain injury (TBI) and substance use disorder (SUD). Some guidelines go further, declaring BZDs contraindicated for combat-related PTSD (Veterans Affairs and Department of Defense),[3] traumatic grief (British National Formulary),[4] and all PTSD (International Society for Traumatic Stress Studies).[5]

Despite the abundance of articles about PTSD and the frequent prescription of BZDs, little research has evaluated the use of BZDs for PTSD. In our literature review, we attempted to capture every available study about BZDs in PTSD to examine 3 questions:

(1) What are the effects of BZDs on the development of PTSD in trauma patients?
(2) What are the effects of BZDs on PTSD-associated outcomes in patients with PTSD?
(3) What are the effects of BZDs on PTSD-associated outcomes in trauma patients with and without PTSD?

METHODS

Study Selection

Studies were included for review using the following eligibility criteria:

(1) Study design: clinical trials or observational studies.
(2) Participants: any patient with a history of trauma assessed for PTSD.
(3) Intervention: any dose, duration, or type of BZD.
(4) Outcomes measured: PTSD-associated symptoms.

Studies were excluded if they were reviews or anecdotal or if BZDs were not distinguished from other medications.

The authors conducted electronic searches using PubMed, PsycINFO, MEDLINE, Cochrane Library, and Google Scholar (all the studies eventually selected are available in PubMed). Search parameters included all English-language articles published until June 30, 2014. Search terms included *PTSD*, *stress disorder*, *benzodiazepine*, and the generic names of the different BZDs. For example, the following search was used in PubMed:

((PTSD) OR (stress disorder)) AND ((benzodiazepine) OR (alprazolam) OR (chlordiazepoxide) OR (clonazepam) OR (clorazepate) OR (diazepam) OR (flurazepam) OR (lorazepam) OR (midazolam) OR (oxazepam) OR (temazepam) OR (triazolam)).

References in retrieved articles were further scanned for additional relevant articles. Duplicate articles were not counted in the total sample of identified records. Abstracts were screened for relevance. Full-text articles were retrieved to determine eligibility. Two authors independently determined eligibility, for which interobserver agreement was calculated using percent agreement and kappa statistics. Disagreements regarding eligibility were resolved by consensus among the authors. For each eligible study, 2 authors independently abstracted information concerning study characteristics.

Data Synthesis

The findings of the selected articles were categorized according to levels of scientific evidence based on clinical practice guidelines from the US Department of Health and Human Services[6]:

A. Multiple double-blind placebo-controlled trials and a confirmatory meta-analysis (in addition to level B of evidence).
B. At least 1 double-blind placebo-controlled trial (in addition to level C of evidence).
C. Anecdotal reports, case series, and open trials, in addition to expert endorsement or consensus.
D. Few case reports without any expert panel endorsement.

To evaluate evidence for an association between BZDs and PTSD, the following 3 null hypotheses were tested:

H_1: BZDs are not associated with the development of PTSD in trauma patients.
H_2: BZDs are not associated with PTSD-associated symptoms in patients with PTSD.
H_3: BZDs are not associated with PTSD-associated symptoms in trauma patients with and without PTSD.

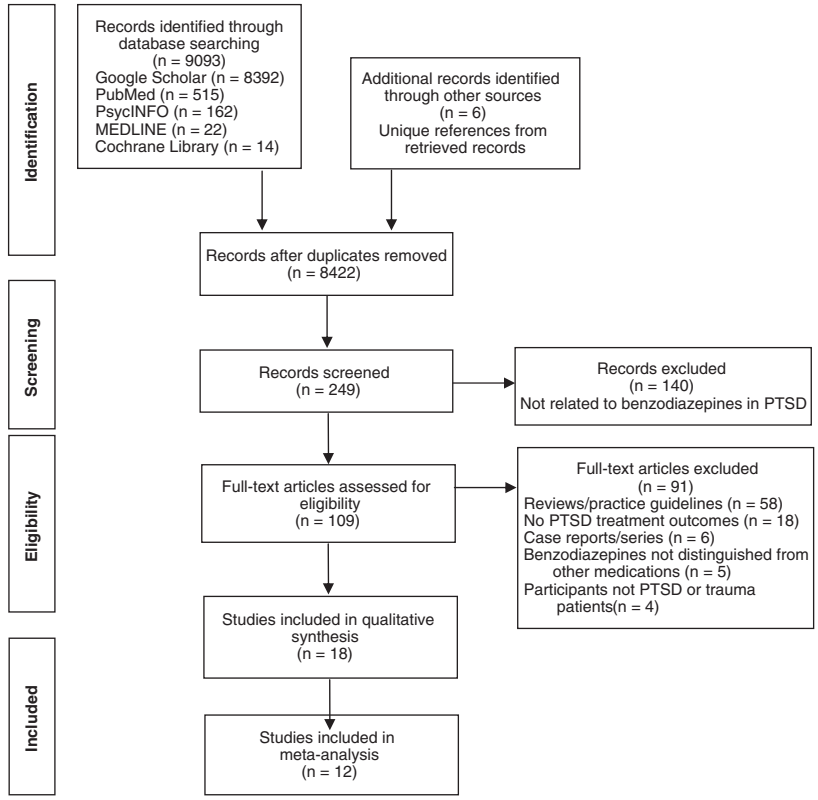
In each case, the hypothesis was tested using a meta-analysis carried out in the MetaEasy Excel add-in (http://www.statanalysis.co.uk/meta-analysis.html). Studies included in the meta-analysis were those that compared outcomes between a group of patients given BZDs and a control group. An estimate and 95% confidence interval (CI) for the standardized effect size (ES) was computed for each outcome in a study. To compute a single effect estimate for each study, MetaEasy uses the within-study median ES and confidence limits. Finally, a meta-analysis was used to test each hypothesis after pooling information over all of the relevant studies. Note that the meta-analysis for H_3 is not simply pooling the other 2 meta-analyses, but includes all PTSD-related outcomes in addition to "PTSD diagnosis," which was the only outcome measured in H_1. Using a random-effects model (to account for the heterogeneity between studies), we estimated the ES and 95% CI associated with each hypothesis. All tests were 2 sided and at the 0.05 level of significance.

RESULTS

Study Characteristics

The authors reviewed 8422 citations, 249 abstracts, and 109 full-text articles. The selection process is illustrated in Figure 1 using the PRISMA flow diagram[7] with reasons for exclusion. The percent agreement (kappa statistic) for eligibility was as follows: full-text review, 89.9% (κ=0.63); randomized-controlled trials (RCTs), 99.1%

FIGURE 1. Flow diagram of literature search results from identification to inclusion of studies.



PTSD indicates posttraumatic stress disorder.

TABLE 1. Summary of Clinical and Observational Studies of Benzodiazepines in Posttraumatic Stress Disorder (PTSD)

References	*Study Design*	*Participants (N)*	*Benzodiazepine*	*Follow-up*	*Assessment*	*Outcomes*
Rothbaum et al[8]	Randomized-controlled trial	103 patients with PTSD in virtual reality exposure therapy (sufficient data for meta-analysis was available only for 69 patients)	Alprazolam (0.25 mg per session for 5 sessions)	12 mo	CAPS	Those taking BZDs significantly more likely to have PTSD at 3 mo posttreatment than those taking placebo (83% compared with 48%). No significant difference between BZDs and placebo in PTSD symptoms at any other time
					PCL	No significant difference between BZDs and placebo in the change in PTSD symptoms
					Orbicularis oculi EMG	No significant difference between BZDs and placebo in startle response
					Salivary cortisol	No significant difference between BZDs and placebo in cortisol levels
Mellman et al[9]	Randomized-controlled trial	22 recent physical trauma patients with insomnia	Temazepam (30 mg for 5 nights then 15 mg for 2 nights)	6 wk or before starting nonstudy medication	CAPS	Those taking BZDs more likely to develop PTSD than those taking placebo (55% compared with 27%), but difference was not significant
					Sleep diary	Those taking BZDs had significantly increased sleep duration on the first night compared with those taking placebo. No significant difference between BZDs and placebo on any sleep measure at any other time
Braun et al[10]	Randomized-controlled trial	10 patients with PTSD	Alprazolam (1.5-6 mg/d for 5 wk, then 2 wk taper)	12 wk	PTSD Scale	No significant difference between BZDs and placebo in PTSD symptoms
					IES	No significant difference between BZDs and placebo in PTSD symptoms
					HAM-A	Those taking BZDs had significantly decreased anxiety compared with those taking placebo
					HAM-D	No significant difference between BZDs and placebo in depression
					VAS	No significant difference between BZDs and placebo in overall well-being
Cates et al[11]	Randomized-controlled trial	6 patients with PTSD	Clonazepam (1 mg for 7 nights, then 2 mg for 7 nights, then 1 wk taper)	5 wk	CAPS-adapted sleep diary	No significant difference between BZDs and placebo on any sleep measure or in nightmares
Gelpin et al[12]	Nonrandomized-controlled trial	26 recent physical trauma patients	Alprazolam (2.5 mg/d) or clonazepam (2.7±0.8 mg/d) for 1-6 mo	6 mo	CAPS	Those taking BZDs significantly more likely to develop PTSD than those not taking BZDs (69% vs. 15%)

TABLE 1. Summary of Clinical and Observational Studies of Benzodiazepines in Posttraumatic Stress Disorder (PTSD) *(continued)*

References	*Study Design*	*Participants (N)*	*Benzodiazepine*	*Follow-up*	*Assessment*	*Outcomes*
					IES	No significant difference between BZDs and no BZDs in PTSD symptoms
					MISS	No significant difference between BZDs and no BZDs in PTSD symptoms
					SCID	Those taking BZDs significantly more likely to develop major depressive disorder than those not taking BZDs (54% vs. 0%). No significant difference between BZDs and no BZDs in development of phobias, alcohol abuse, panic disorder, or dysthymia
					STAI	No significant difference between BZDs and no BZDs in anxiety
					BDI	No significant difference between BZDs and no BZDs in depression
					Heart rate	Those taking BZDs had decreased heart rate in the first week compared with those not taking BZDs, but this difference was not significant. No significant difference between BZDs and no BZDs in heart rate at any other time
Shalev et al[13]	Nonrandomized comparison trial	18 patients (9 with PTSD, 9 with panic disorder)	Alprazolam (2.05± 0.69 mg/d)	2 wk	HAM-A	No significant difference between PTSD and panic disorder in prestimulation anxiety
					Orbicularis oculi EMG, skin conductance, heart rate	No significant difference between patients with PTSD and panic disorder in physiological measures before BZDs. Acoustic startle responses in PTSD were not statistically different before and after BZDs, but they were significantly decreased in patients with panic disorder after BZDs
Zatzick et al[14]	Prospective cohort	2931 physical trauma patients	Any agent, dose, and duration	12 mo	PCL	Those receiving BZDs before injury significantly more likely to have PTSD symptoms than those not taking BZDs

TABLE 1. Summary of Clinical and Observational Studies of Benzodiazepines in Posttraumatic Stress Disorder (PTSD) *(continued)*

References	*Study Design*	*Participants (N)*	*Benzodiazepine*	*Follow-up*	*Assessment*	*Outcomes*
Shin et al[15]	Prospective cohort	376 patients with PTSD	Any agent, dose, and duration	5-12 mo	CTS	Those with a history of aggression taking BZDs had significantly increased aggression compared with those not taking BZDs and those without a history of aggression
Kosten et al[16]	Prospective cohort	370 patients with PTSD in mental health treatment	Any agent, dose, and duration	12 mo	MISS	Those taking BZDs had significantly increased PTSD symptoms at baseline compared with those not taking BZDs
					BSI	Those taking BZDs had significantly increased anxiety at baseline compared with those not taking BZDs. No significant difference between BZDs and no BZDs in change in anxiety
					NVVRS-derived instrument	No significant difference between BZDs and no BZDs in violence at baseline. Those with comorbid SUD taking BZDs had less improvement in violence compared with those with comorbid SUD not taking BZDs, but this difference was not significant
					ASI	Those taking BZDs had significantly increased alcohol use at baseline compared with those not taking BZDs. No significant difference between BZDs and no BZDs in change in substance use or social functioning. Those with comorbid SUD taking BZDs had less improvement in substance use compared with those with comorbid SUD not taking BZDs, but this difference was not significant
Rosen et al[17]	Prospective cohort	283 patients with PTSD (140 in prolonged exposure, 143 in present-centered psychotherapy; sufficient data for meta-analysis was only available for 143 patients)	Any agent, dose, and duration	6 mo	CAPS	No significance difference between BZDs with prolonged exposure and no BZDs with either therapy in PTSD symptoms. Those taking BZDs in present-centered psychotherapy had significantly worse posttreatment maintenance of improvements in PTSD symptoms compared with other groups
					PCL	In present-centered therapy, those taking BZDs had significantly less improvement in PTSD symptoms during psychotherapy compared with those not taking BZDs. Significance of results for prolonged exposure were not determinable due to presence of an interaction term and the way the results were presented

TABLE 1. Summary of Clinical and Observational Studies of Benzodiazepines in Posttraumatic Stress Disorder (PTSD) *(continued)*

References	*Study Design*	*Participants (N)*	*Benzodiazepine*	*Follow-up*	*Assessment*	*Outcomes*
Jones et al[18]	Prospective cohort	238 recent trauma patients (ICU)	Any agent, dose, and duration	3 mo	PTSS-14	Higher BZD doses in the ICU associated with significantly increased PTSD symptoms
Samuelson et al[19]	Prospective cohort	226 recent trauma patients (ICU)	Midazolam (any dose or duration)	2 mo	IES-R	Those receiving BZDs significantly more likely to develop PTSD than those not taking BZDs (68% vs. 30%)
Bienvenu et al[20]	Prospective cohort	186 recent trauma patients (ICU)	Any agent, dose, and duration	3-24 mo	IES-R	Higher BZD doses in the ICU not associated with significant changes in the risk of developing PTSD
Baranyi et al[21]	Prospective cohort	126 trauma patients (solid-organ transplants)	Any agent, dose, and duration	Mean of 24.9 mo	PTSS-10	Chronic BZD use, either before or after surgery, associated with significantly increased risk of PTSD symptoms
Girard et al[22]	Prospective cohort	43 recent trauma patients (ICU)	Any agent, dose, and duration	6 mo	PTSS-10	Greater BZD administration in the ICU associated with significantly increased risk of developing PTSD
Van Minnen et al[23]	Prospective cohort	43 patients with PTSD in prolonged exposure	Daily use of any agent or dose	3 mo	PSS-SR	Those taking BZDs had significantly less improvement in PTSD symptoms and more dropouts compared with those not taking BZDs
McGhee et al[24]	Retrospective cohort	211 trauma patients (burns requiring surgery)	Midazolam (any dose, intraoperative)	Any up to 4 y	PCL	No significant difference between BZDs and no BZDs in risk of developing PTSD
Shalev and Rogel-Fuchs[25]	Cross-sectional	18 patients with PTSD	Clonazepam (2.7±1.1 mg/d)	Not applicable	Orbicularis oculi EMG, skin conductance, heart rate	No significant difference between BZDs and no BZDs in magnitude or habituation rate of acoustic startle responses

ASI indicates Addiction Severity Index; BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory; BZD, benzodiazepine; CAPS, Clinician-administered PTSD Scale; CTS, Conflicts Tactics Scale; EMG, electromyography; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression; ICU, intensive care unit; IES, Impact of Event Scale; MISS, Mississippi Rating Scale for PTSD; NVVRS, National Vietnam Veterans Readjustment Study; PCL, PTSD Checklist; PSS-SR, PTSD Symptom Scale Self-report; PTSS, Posttraumatic Stress Syndrome Scale; PTSD, posttraumatic stress disorder; SCID, Structured Clinical Interview for the DSM; STAI, State-Trait Anxiety Inventory; SUD: substance use disorder; VAS, visual analog scale.

TABLE 2. Summary of Participant Characteristics in Reviewed Studies of Benzodiazepines in PTSD

References	*Inclusion (I) and Exclusion (E) Criteria*	*Mean Age (y)*	*Female (%)*	*Race (%)*	*Trauma Type (%)*
Rothbaum et al[8]	I: Iraq and/or Afghanistan veterans, DSM-IV criteria for PTSD due to military trauma verified through discharge papers, discontinued taking long-acting BZDs for 1 mo and short-acting BZDs for 2 wk before screening, stable doses of other psychotropic medications for at least 2 wk before the study, written informed consent E: Medically unstable, psychosis, bipolar disorder, current suicidal risk, current alcohol or drug dependence, pregnancy, glucocorticoids, BZDs, chronically used opioids	35	4%	Black: 50% White: 42% Hispanic: 5% Other: 3%	Combat: 100%
Mellman et al[9]	I: Admitted to level I trauma center, recall of trauma, at least moderate impairment of sleep initiation or maintenance, meet full criteria for at least 2 PTSD symptom clusters in DSM-IV, willing and able to provide written informed consent E: Intoxication at time of trauma, brain injury, preexisting psychiatric disorders	36	36%	Hispanic: 82% White: 9% Black: 9%	MVC: 68% Assault: 23% Accident: 9%
Braun et al[10]	I: DSM-III criteria for PTSD, willing and able to provide written informed consent, free of psychotropic medications at least 2 wk before study E: Physically unhealthy, significant head injury	38			Combat: 40% MVC: 30% Accident: 20% Terrorism: 10%
Cates et al[11]	I: DSM-IV criteria for PTSD, at least thrice weekly problems with sleep and nightmares, willing and able to provide written informed consent E: <18 y old, unstable medical conditions, sensitivity to BZDs, current BZD use, substance abuse or dependence in past 4 wk, inability to attend regular follow-up visits, women who were either pregnant or of child-bearing potential and not using contraceptives, dementia, cognitive disorder	52	0%		Combat: 100%
Gelpin et al[12]	I: Emergency room admissions with a trauma E: Taking psychotropic medications before the trauma, coma, head injury, loss of consciousness	29	46%		MVCs: 77% Terrorism: 19% Accident: 4%
Shalev et al[13]	I: DSM-III-R criteria for PTSD or panic disorder, medication free E: Psychosis, major depression, current or past substance or alcohol use, patients with PTSD with spontaneous panic attacks, patients with panic disorder with a history of trauma	34	39%		

TABLE 2. Summary of Participant Characteristics in Reviewed Studies of Benzodiazepines in PTSD *(continued)*

References	*Inclusion (I) and Exclusion (E) Criteria*	*Mean Age (y)*	*Female (%)*	*Race (%)*	*Trauma Type (%)*
Zatzick et al[14]	I: 18-84 y old, English-speaking or Spanish-speaking patients, arrived alive at hospital, moderate to severe injuries E: greater than or equal to ≥65 y old with a first listed diagnosis of hip fracture, major burns, treatment delays >24 h, incarcerated at time of injury	41	35%	White: 67% Black: 16% Hispanic: 13% Other: 3%	Injury: 100%
Shin et al[15]	I: 18-69 y old, military veterans serving in Vietnam era or later, at least one outpatient VA visit with a PTSD diagnosis E: No PTSD diagnosis in the prior 2 y	42	50%	White: 65% Black: 17% Hispanic: 10% Other: 3%	
Kosten et al[16]	I: DSM-III criteria for PTSD, military veterans	45	0%	White: 75%	
Rosen et al[17]	I: female veteran or active duty soldier, DSM-IV criteria for PTSD, CAPS score >45 E: Concurrent PTSD psychotherapy other than brief visits with an existing therapist or participation in self-help groups, change in psychoactive medications during the 2 mo before study recruitment, substance dependence not in remission for at least 3 mo, current psychotic symptoms or mania, bipolar disorder, prominent current suicidal or homicidal ideation, cognitive impairment, current involvement in violent relationship, self-mutilation within the past 6 mo		100%	White: 55% Black: 33% Hispanic 6% Other: 7%	Sexual: 93% Accident: 82% Disaster: 72% Combat: 25%
Jones et al[18]	I: >18 y old, mechanically ventilated, ICU length of stay at least 48 h E: Prior PTSD, admitted after suicide attempt, preexisting or concomitant psychotic illness, resides >30 km from hospital, unresolved confusion, enrolled in another research study	61	38%		Life-threatening medical condition: 100%
Samuelson et al[19]	I: >18 y old, mechanically ventilated, general ICU length of stay at least 24 h E: Head injury, psychotic illness, mental retardation, intoxication, admitted after suicide attempt, hearing/speech disability, non-Swedish speaking, transferred to another hospital, mechanically ventilated at discharge, mechanically ventilated >24 h preadmission	63	48%		Life-threatening medical condition: 100%
Bienvenu et al[20]	I: Mechanically ventilated with acute lung injury E: Neurological specialty ICU, preexisting illness with a life expectancy <6 mo, preexisting cognitive impairment or communication/language barriers, no fixed address, transfer to a study site ICU with preexisting acute lung injury >24 h,		45%		Life-threatening medical condition: 100%

TABLE 2. Summary of Participant Characteristics in Reviewed Studies of Benzodiazepines in PTSD *(continued)*

References	*Inclusion (I) and Exclusion (E) Criteria*	*Mean Age (y)*	*Female (%)*	*Race (%)*	*Trauma Type (%)*
	>5 d of mechanical ventilation before acute lung injury, a physician order for no escalation of ICU care at the time of study eligibility				
Baranyi et al[21]	I: Patients receiving solid-organ transplants and ICU treatment	52	31%	White: 100%	Life-threatening medical condition: 100%
Girard et al[22]	I: In medical or coronary ICU, mechanically ventilated E: Neurological disease impairing cognitive function, mental retardation, non–English speaking, sensory deficits impairing communication	52	53%	Black: 16%	Life-threatening medical condition: 100%
Van Minnen et al[23]	I: DSM-III-R criteria for PTSD for 3 mo or more	37	74%		Sexual: 22% Violence: 21% Battering: 19% Accident: 14% MVC: 13% Other: 11%
McGhee et al[24]	I: Thermal injuries during military deployments, surgery within 30 d of injury between 2004 and 2008, PCL between 2004 and 2008				Combat: 100%
Shalev and Rogel-Fuchs[25]	I: DSM-III-R criteria for PTSD, receiving clonazepam or medication free E: Panic disorder, substance dependence	35	11%		

BZD indicates benzodiazepine; CAPS, Clinician-administered PTSD Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICU, intensive care unit; MVC, motor vehicle collision; PCL, PTSD Checklist; PTSD, posttraumatic stress disorder; VA, Veterans Affairs.

TABLE 3. Summary of Outcomes of Reviewed Studies of Benzodiazepines in PTSD

	Randomized-controlled Trials				
	Double-blind	***Other***	***Nonrandomized Clinical Trials***	***Observational Studies***	***Level of Evidence***
Efficacy	**1**	**1**	**0**	**0**	**D***
Anxiety, short term	1	0	0	0	D*
Sleep, short term	0	1	0	0	D*
PTSD core symptoms	0	0	0	0	D†
Long term	0	0	0	0	D†
Inefficacy	**2**	**2**	**2**	**12**	**A‡**
Overall severity	2	1	1	10	A‡
Startle reflex	1	0	1	1	B
Psychotherapy outcomes	1	0	0	2	B
Depression	1	0	1	0	B
Overall well-being	1	0	0	0	B
Sleep	0	2	0	0	C
Nightmares	0	1	0	0	C
Anxiety	0	0	1	1	C
Aggression	0	0	0	2	C
Substance use	0	0	0	1	C
Social functioning	0	0	0	1	C
Worsened outcomes	**1**	**1**	**1**	**10**	**B**
Overall severity	1	1	1	9	B
Psychotherapy outcomes	1	0	0	2	B
Depression	0	0	1	0	C
Aggression	0	0	0	2	C
Substance use	0	0	0	1	C
Anxiety	0	0	0	1	C

Note that studies with multiple measures or mixed results are counted more than once, and bolded rows summarize the studies in the areas listed below.

The findings of the selected articles were categorized according to levels of scientific evidence based on clinical practice guidelines from the US Department of Health and Human Services[6]:

A. Multiple double-blind placebo-controlled trials and a confirmatory meta-analysis (in addition to level B of evidence).

B. At least 1 double-blind placebo-controlled trial (in addition to level C of evidence).

C. Anecdotal reports, case series, and open trials, in addition to expert endorsement or consensus.

D. Few case reports without any expert panel endorsement.

**No expert consensus supports this finding.*

†Nothing but case reports supports this finding.

‡Supported by meta-analysis.

PTSD indicates posttraumatic stress disorder.

(κ=0.89); nonrandomized clinical trials, 100% (κ=1.00); observational studies, 97.7% (κ=0.63). The percent agreement for data abstraction was 76.1%.

After excluding ineligible articles, 18 studies were selected for review and are summarized in Table 1. Sample sizes varied from 6 to 2931, with a total of 5236 completers. Because not every study reported the same characteristics, the following numbers were calculated using available data for participants as summarized in Table 2. Participants

TABLE 4. Summary of Effect Sizes (ES) and Confidence Intervals (CI) by Study and Outcome Measure

References	*Hypotheses (H_1, H_2, H_3)*	*Outcome Measure*	*Sample Size (n)*		*ES*	*95% CI*
			BZD	*Control*		
Rothbaum et al[8]	2, 3	CAPS posttreatment	35	34	−0.0214	−0.4934, 0.4505
	2, 3	CAPS 3 mo	29	23	−0.5297	−1.0770, 0.0176
	2, 3	CAPS 6 mo	25	23	−0.5787	−1.1450, −0.0124
	2, 3	CAPS 12 mo	22	20	−0.2217	−0.8273, 0.3838
	2, 3	PCL posttreatment	35	34	−0.1370	−0.6089, 0.3350
	2, 3	PCL 3 mo	29	23	−0.5031	−1.0503, 0.0442
	2, 3	PCL 6 mo	25	23	−0.6787	−1.2450, −0.1124
	2, 3	PCL 12 mo	22	20	−0.3191	−0.9247, 0.2864
	2, 3	PTSD posttreatment	35	34	−0.0172	−0.4892, 0.4547
	2, 3	PTSD 3 mo	29	23	−0.7767	−1.3240, −0.2295
	2, 3	PTSD 6 mo	25	23	−0.7007	−1.2670, −0.1344
	2, 3	PTSD 12 mo	22	20	−0.1763	−0.7819, 0.4292
	2, 3	CAPS posttreatment change	35	34	−0.1851	−0.6571, 0.2869
	2, 3	PCL posttreatment change	35	34	−0.2041	−0.6761, 0.2679
	2, 3	CAPS 12 mo change	22	20	−0.0277	−0.6332, 0.5779
	2, 3	PCL 12 mo change	22	20	−0.0320	−0.6376, 0.5735
	2, 3	Pooled study (median ES and CI by hypothesis)			−0.2129	−0.7697, 0.3439
Mellman et al[9]	1, 3	PTSD diagnosis	11	11	−0.5774	−1.4131, 0.2584
	1	Pooled study (median ES and CI by hypothesis)			−0.5774	−1.4131, 0.2584
	3	CAPS	11	11	−0.2876	−1.1234, 0.5481
	3	Pooled study (median ES and CI by hypothesis)			−0.4325	−1.2682, 0.4033
Braun et al[10]	2, 3	PTSD Scale Intrusion	10	10	0.5433	−0.3332, 1.4199
	2, 3	PTSD Scale Avoidance	10	10	0.1632	−0.7133, 1.0398
	2, 3	HAM-D	10	10	0.0281	−0.8484, 0.9047
	2, 3	HAM-A	10	10	0.6808	−0.1958, 1.5573
	2, 3	IES Intrusion	10	10	0.5241	−0.3525, 1.4006
	2, 3	IES Avoidance	10	10	0.1103	−0.7663, 0.9868
	2, 3	VAS	10	10	0.5217	−0.3548, 1.3982
	2, 3	Pooled study (median ES and CI by hypothesis)			0.5217	−0.3548, 1.3982
Cates et al[11]	2, 3	Sleep onset problems	6	6	1.1303	−0.0013, 2.2619
	2, 3	Mid-sleep awakening	6	6	0.2196	−0.9120, 1.3512
	2, 3	Early-morning awakening	6	6	0.7458	−0.3858, 1.8774
	2, 3	Difficulty falling asleep	6	6	0.5021	−0.6295, 1.6337

TABLE 4. Summary of Effect Sizes (ES) and Confidence Intervals (CI) by Study and Outcome Measure *(continued)*

References	*Hypotheses (H_1, H_2, H_3)*	*Outcome Measure*	*Sample Size (n)*		*ES*	*95% CI*
			BZD	*Control*		
	2, 3	Sleep quantity	6	6	0.3016	−0.8300, 1.4332
	2, 3	Sleep quality	6	6	0.4110	−0.7206, 1.5426
	2, 3	Distressing dreams frequency	6	6	−0.1851	−1.3167, 0.9465
	2, 3	Distressing dreams intensity	6	6	−0.1381	−1.2697, 0.9936
	2, 3	Pooled study (median ES and CI by hypothesis)			0.3563	−0.7753, 1.4879
Gelpin et al[12]	1, 3	PTSD diagnosis	13	13	−1.2999	−2.0686, −0.5311
	1	Pooled study (median ES and CI by hypothesis)			−1.2999	−2.0686, −0.5311
	3	Major depression diagnosis	13	13	−1.5275	−2.2963, −0.7587
	3	Simple phobia diagnosis	13	13	0.4364	−0.3323, 1.2052
	3	Social phobia diagnosis	13	13	0.2425	−0.5262, 1.0113
	3	Alcohol abuse diagnosis	13	13	−0.4082	−1.1770, 0.3605
	3	Panic disorder diagnosis	13	13	−0.4082	−1.1770, 0.3605
	3	Dysthymia	13	13	0.4082	−0.3605, 1.1770
	3	STAI-State	13	13	−0.1511	−0.9199, 0.6176
	3	STAI-Trait	13	13	−0.1743	−0.9431, 0.5945
	3	IES Intrusion	13	13	−0.2933	−1.0620, 0.4755
	3	IES Avoidance	13	13	0.2780	−0.4908, 1.0468
	3	BDI	13	13	−0.3691	−1.1379, 0.3996
	3	MISS	13	13	−0.4628	−1.2315, 0.3060
	3	HR	13	13	0.3729	−0.3959, 1.1417
	3	Pooled study (median ES and CI by hypothesis)			−0.2338	−1.0026, 0.5350
Shalev et al[13]	2, 3	HAM-A	9	9	1.4430	0.5191, 2.3670
	2, 3	Resting EMG	9	9	−0.0974	−1.0213, 0.8266
	2, 3	Base EMG	9	9	0.4704	−0.4535, 1.3944
	2, 3	EMG 1st tone response	9	9	0.4304	−0.4935, 1.3544
	2, 3	EMG 15th tone response	9	9	−0.2495	−1.1734, 0.6745
	2, 3	Mean EMG response	9	9	0.2952	−0.6288, 1.2191
	2, 3	EMG response-TTC	9	9	−0.0371	−0.9611, 0.8868
	2, 3	Resting SC	9	9	0.3722	−0.5518, 1.2961
	2, 3	Base SC	9	9	−0.9585	−1.8825, −0.0346
	2, 3	SC 1st tone response	9	9	−0.9737	−1.8976, −0.0497

TABLE 4. Summary of Effect Sizes (ES) and Confidence Intervals (CI) by Study and Outcome Measure *(continued)*

References	*Hypotheses (H_1, H_2, H_3)*	*Outcome Measure*	*Sample Size (n)*		*ES*	*95% CI*
			BZD	*Control*		
	2, 3	SC 15th tone response	9	9	0.0789	−0.8451, 1.0028
	2, 3	Mean SC response	9	9	−0.1390	−1.0630, 0.7849
	2, 3	SC response-TTC	9	9	−0.2220	−1.1459, 0.7020
	2, 3	Resting HR	9	9	0.1113	−0.8127, 1.0352
	2, 3	Base HR	9	9	−0.4793	−1.4032, 0.4447
	2, 3	Mean HR response	9	9	−0.3632	−1.2871, 0.5608
	2, 3	Pooled study (median ES and CI by hypothesis)			−0.0673	−0.9912, 0.8567
Zatzick et al[14]	1, 3	PCL	99	2832	−0.3711	−0.5715, −0.1707
Rosen et al[17]	2, 3	CAPS psychotherapy	29	114	0.0193	−0.3883, 0.4270
	2, 3	CAPS follow-up	29	114	−0.1944	−0.6020, 0.2133
	2, 3	PCL psychotherapy	29	114	−0.4728	−0.8805, −0.0652
	2, 3	PCL follow-up	29	114	−0.1096	−0.5173, 0.2980
	2, 3	Pooled study (median ES and CI by hypothesis)			−0.1520	−0.5596, 0.2556
Samuelson et al[19]	1, 3	IES-R	75	151	−0.4058	−0.6827, −0.1289
Baranyi et al[21]	1, 3	PTSS-10	22	104	−0.4570	−0.9170, 0.0029
McGhee et al[24]	1, 3	PCL	142	69	−0.0966	−0.3843, 0.1910
Shalev and Rogel-Fuchs[25]	2, 3	STAI	9	9	−0.1592	−1.0832, 0.7647
	2, 3	MISS	9	9	−0.6777	−1.6016, 0.2463
	2, 3	IES	9	9	−0.6884	−1.6124, 0.2355
	2, 3	HR baseline	9	9	−0.2558	−1.1798, 0.6681
	2, 3	HR 1st tone response	9	9	−0.7462	−1.6701, 0.1778
	2, 3	HR 15th tone response	9	9	−0.0404	−0.9644, 0.8835
	2, 3	SC 1st tone response	9	9	−0.0443	−0.9683, 0.8796
	2, 3	SC 15th tone response	9	9	−0.3431	−1.2670, 0.5809
	2, 3	SC response-TTC	9	9	−0.3809	−1.3048, 0.5431
	2, 3	EMG 1st tone response	9	9	−0.7093	−1.6333, 0.2146
	2, 3	EMG 15th tone response	9	9	−0.2636	−1.1876, 0.6603
	2, 3	EMG response-TTC	9	9	−0.6023	−1.5263, 0.3217
	2, 3	Pooled study (median ES and CI by hypothesis)			−0.3620	−1.2859, 0.5620

BDI indicates Beck Depression Inventory; BZD, benzodiazepine; CAPS, Clinician-administered PTSD Scale; EMG, electromyography; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression; HR, heart rate; IES, Impact of Event Scale; MISS, Mississippi Rating Scale for PTSD; PCL, PTSD Checklist; PTSD, posttraumatic stress disorder; PTSS, Posttraumatic Stress Syndrome Scale; SC, skin conductance; STAI, State-Trait Anxiety Inventory; TTC, trials to habituation criterion; VAS, visual analog scale.

survived 1 or more of the following: physical injuries (n=2979), life-threatening medical conditions (n=841), combat-related trauma (n=431), sexual trauma (n=277), disaster exposure (n=203), and other traumas (n=47). The majority of the participants (approximately 67%) survived a physical injury. The mean age was approximately 44 years and approximately 38% were women.

Qualitative Synthesis

Table 3 compares study designs, outcomes, and levels of evidence.

The studies supporting BZD efficacy for PTSD demonstrate short-term improvement in sleep[9] and anxiety.[10]

The studies demonstrating BZD inefficacy for PTSD demonstrate no significant improvement compared with controls for overall severity of PTSD symptoms,[8–10,12,14,16–24] startle reflex,[8,13,25] psychotherapy outcomes,[8,17,23] depression,[10,12] overall well-being,[10] sleep,[9,11] nightmares,[11] anxiety,[12,16] aggression,[15–16] substance use,[16] and social functioning.[16]

The studies showing BZDs being associated with worsened PTSD outcomes demonstrate worsened overall severity of PTSD symptoms,[8–9,12,14,16–23] psychotherapy outcomes,[8,17,23] depression,[12] aggression,[15–16] substance use,[16] and anxiety.[16]

Meta-analysis

Twelve studies (4 RCTs, 2 nonrandomized, 6 observational) obtained data sufficient for estimating ESs for PTSD-associated symptoms. Individual outcome measures and their associated ESs and 95% CIs are shown in Table 4. Figure 2 summarizes the ESs and CIs in forest plots by study for hypotheses H_1, H_2, and H_3. Results are presented so that a positive ES corresponds to BZDs improving PTSD-associated outcomes and a negative ES corresponds to BZDs worsening PTSD-associated outcomes. The row labeled "POOLED" contains the estimated ES and 95% CI for the meta-analysis. The row labeled "RCTs only" illustrates the results when restricted to only the 4 RCTs (denoted by "RCT" to the right of the corresponding CI).

The estimated ES of BZDs on the development of PTSD in trauma patients was −0.3974, with a 95% CI of (−0.6057, −0.1891). Thus, we reject H_1 and conclude that BZDs increase the likelihood of developing PTSD when taken by trauma patients.

The estimated ES of BZDs on PTSD-associated symptoms in PTSD patients was −0.0839, with a 95% CI of (−0.3544, 0.1866). Thus, we have insufficient evidence to reject H_2. That is, we have insufficient evidence to conclude that BZDs alleviate PTSD-associated symptoms when taken by patients who already have PTSD.

The estimated ES of BZDs on PTSD-associated symptoms in trauma patients with and without PTSD (here, "symptoms" includes all PTSD-related outcomes including PTSD diagnosis for trauma patients who were not previously diagnosed with PTSD) was −0.2798, with a 95% CI of (−0.3981, −0.1616). Thus, we reject H_3 and conclude that BZDs have an overall adverse impact in the prevention and treatment of PTSD. When the analysis was restricted only to the 4 RCTs, the estimated ES of BZDs on PTSD-associated symptoms in trauma patients with and without PTSD was −0.0422, with a 95% CI of (−0.4505, 0.3661). Thus, the RCTs alone do not provide sufficient evidence to reject H_3. On the basis of the RCTs alone, we conclude that there is no evidence that BZDs alleviate PTSD-associated symptoms in PTSD patients or prevent the development of PTSD in trauma patients.

DISCUSSION

Inefficacy (Level of Evidence A)

Before our study, the ceiling for the level of evidence for inefficacy was at B due to the lack of a confirmatory meta-analysis. However, this meta-analysis and at least 1 measure in every study that was reviewed, including all 4 RCTs of BZDs in PTSD,[8–11] suggest a lack of efficacy of BZDs for PTSD. All PTSD-specific measures that were used, such as the Clinician-administered PTSD Scale (CAPS) and the PTSD Checklist, demonstrated that BZDs are, at best, not significantly different from placebo or no BZD for PTSD. BZD inefficacy is also endorsed by every available PTSD practice guideline. These findings are likely explained in part by the tolerance and cognitive effects associated with BZDs and also indicate that BZDs appear to inadequately target PTSD pathophysiology.

A major disadvantage of BZDs is that tolerance develops to hypnotic and myorelexant effects within days to weeks, and to anticonvulsant and anxiolytic effects within weeks to months.[26–28] Therefore, BZDs are unlikely to be effective long-term hypnotics or anxiolytics, which is confirmed by several general studies of BZDs for sleep and anxiety.[27,28] Tolerance to BZDs is a distinct problem in PTSD because most patients have symptoms that persist for longer than 3 months.[29]

BZDs may be ineffective for PTSD because of amnestic effects that unintentionally target learning how to cope with PTSD symptoms rather than traumatic memories. Although therapeutic effects decrease with tolerance, cognitive effects (ie, BZD-induced neurocognitive disorder) usually persist for attention, memory, and learning.[28] Cognitive impairments are more common with long-term use and high doses, but they can also occur with short-term use and low doses.[28,29] Unfortunately, PTSD is a risk factor for BZD-induced neurocognitive disorder, as are conditions that are often comorbid with PTSD such as SUD, neurocognitive disorders (including TBI), and psychotic, bipolar, and depressive disorders.[29]

BZDs may be ineffective for PTSD because the pathophysiology of PTSD differs from that of the anxiety disorders for which BZDs have some efficacy. Studies of flumazenil, which have demonstrated that GABA-receptor antagonism induces panic in patients with panic disorder but not in healthy controls or patients with PTSD,[30,31] suggest that the pathophysiology underlying anxiety in PTSD is different from that in panic disorder despite experiential similarities. Researchers in 2 of the studies that were reviewed[13,25] concluded that, while locus ceruleus dysregulation is implicated in both panic disorder and PTSD, the amygdala and hippocampus are also implicated in PTSD anxiety. Shalev et al[13] speculated that these structures may be less responsive to BZDs than the locus ceruleus. In addition, rather than targeting specific implicated structures, BZDs indiscriminately depress global brain function (including structures such as the prefrontal cortex that are already hypoactive in PTSD and which, when functioning adequately, allow for various cognitive processes and modulation of the amygdala). Therefore, anxiety in PTSD may be different than anxiety in other disorders and may require different treatments.

Worsened Outcomes (Level of Evidence B)

Thirteen of the studies that were reviewed (including 2 RCTs), several practice guidelines, and some case reports suggest that BZDs have the risk of worsening the severity and prognosis of PTSD. All but 2[10,24] of the 13 studies that used PTSD-specific measures (eg, CAPS, PTSD Checklist) demonstrated that BZDs are associated with worse overall severity of symptoms when compared with placebo or no BZD. Potential biopsychosocial explanations for BZDs worsening PTSD outcomes include discontinuation symptoms, disruption of normal stress responses, avoidance of cognitive and emotional processing of trauma, and worsening of underlying PTSD pathophysiology (eg, effects on the hypothalamic-pituitary-adrenal [HPA] axis and on gamma-aminobutyric acid [GABA], glutamate, and serotonin systems).

Discontinuation symptoms provide a model for how BZDs may worsen PTSD. Chronic BZD use leads to GABA-receptor desensitization and glutamate receptor sensitization.[26,32] When BZDs are suddenly discontinued in tolerant patients, the patients experience decreased inhibition from GABA and hyperactive excitation from glutamate, causing withdrawal symptoms that can mimic and worsen PTSD symptoms (eg, anxiety, insomnia, agitation, autonomic hyperactivity, perceptual disturbances). Although less severe than withdrawal, rebound symptoms, which are the inverse of the therapeutic effects of BZDs and include worsened anxiety, insomnia, and irritability, can occur shortly after discontinuation, including between doses (especially with BZDs that have a short half-life). Discontinuation symptoms are commonly misinterpreted as a worsening of underlying conditions while the iatrogenic contribution of BZDs is overlooked.[27,28,33] Although anxiety, insomnia, and irritability may be temporarily exacerbated during withdrawal, general studies of BZDs have demonstrated that these symptoms are usually less severe after discontinuation than while taking BZDs.[27,28] Both PTSD and BZD use have been associated with decreased GABA-receptor sensitivity and hyperactive glutamatergic activity.[34] Because BZDs can synergistically worsen underlying PTSD pathophysiology, BZDs may actually exacerbate PTSD symptoms rather than improve them.

One of the most consistent findings in this review, which was supported by an RCT,[9] a nonrandomized-

controlled trial,[12] 6 observational studies, and a systematic review of PTSD risk factors in patients on an intensive care unit,[35] is that BZD use after trauma increases the risk of developing PTSD. Only 2 studies of trauma patients receiving BZDs[20,24] did not find an increased risk for PTSD, although both suggested inefficacy for PTSD prevention. Those studies providing sufficient data[9,12,19] suggest that the risk of developing PTSD is 2 to 5 times higher in groups receiving BZDs than in control groups. BZDs likely disrupt normal HPA axis stress responses and memory-related processes. Interfering with normal evolutionarily advantageous physiological responses seems to increase vulnerability to subsequent stress and worsen outcomes in PTSD.[36] Three animal studies[4,33,37] have demonstrated that BZDs increase posttraumatic behaviors upon subsequent exposure to stress, suggesting that the fear-sensitizing effects of BZDs may act synergistically with trauma-related fear, creating a generalized fear response to subsequent stressors (eg, trauma-related cues). Despite theoretical predictions that BZDs might prevent the development of PTSD after trauma (eg, by inhibiting memory consolidation and preventing stress-induced changes in the noradrenergic system),[12] no studies support BZDs for PTSD prevention, and this review suggests that the short-term antistress effects of BZDs may actually increase the long-term risk of PTSD. In hindsight, Gelpin et al[12] acknowledged:

> The inhibitory effect of benzodiazepines on memory acquisition is mostly anterograde. Hence, benzodiazepines do not alter memory for prior episodes and, therefore, should not have affected traumatic memories when administered several days after the trauma. Moreover, recovery from trauma should not be equated with forgetting, but rather adaptation, reappraisal, and learning. Administered during the recovery phase, benzodiazepines may, in fact, interfere with such relearning … it may be argued that early treatment with benzodiazepines negatively affected survivors who might have otherwise recovered (p. 393).

Three studies examined the effects of BZDs in patients receiving psychotherapy: Van Minnen et al[23] found that daily BZD use was associated with worse outcomes, and Rosen et al[17] and Rothbaum et al[8] had mixed results (ie, inefficacy or worsening, depending on whether measures were rated by observers or patients). Rather than augmenting psychotherapy, BZDs seem to do nothing or to inhibit recovery. Evidence-based trauma-focused psychotherapies (eg, prolonged exposure, cognitive processing therapy) require that patients experience and then master anxiety. BZDs can impair that experience by numbing emotions, decreasing learning efficiency, and inhibiting memory processing of material learned in therapy.[17,38] BZD-induced "emotional anesthesia"[26] directly interferes with the therapeutic effects of exposure to anxiety-provoking stimuli (in psychotherapy or the natural environment) by inhibiting fear activation, a "necessary condition for effective exposure therapy."[23] Several animal and human studies have demonstrated that BZDs interfere with fear extinction, which is critical to exposure therapy.[2,39,40] For fear extinction to occur, patients must emotionally and cognitively process the experience of anxiety, but BZDs allow patients to avoid these processes. Some patients with PTSD use distraction techniques to avoid internal reminders of trauma, some rarely leave places of comfort to avoid external reminders, and others engage in reckless behaviors to "escape."[29] BZDs may provide another form of avoidance, an attempt to self-medicate hyperarousal, numb feelings, suppress memories, and escape thoughts. Overcoming avoidance behaviors is essential for successful treatment, but it is often the patient's largest obstacle for recovery. As Herman[41] explains:

> The helpless person escapes from her situation not by action in the real world but rather by altering her state of consciousness …. Traumatized people who cannot spontaneously dissociate may attempt to produce similar numbing effects by using alcohol or narcotics …. Although dissociative alterations in consciousness, or even intoxication, may be adaptive at the moment of total helplessness, they become maladaptive once the danger is past. Because these altered states keep the traumatic experience walled off from ordinary consciousness, they prevent the integration necessary for healing …. They narrow and deplete the quality of life and ultimately perpetuate the effects of the traumatic event (p. 44).

Because an avoidant coping style is a poor prognostic factor for trauma-related disorders[29] and BZDs are inherently avoidant (eg, they inhibit cognitive processing and induce emotional numbing), BZDs may prolong and worsen PTSD.

Two studies that were reviewed measured aggression, both of which found that BZDs were associated with aggression in some patients with PTSD.[15,16] In general, BZDs have been known to cause "paradoxical reactions" (eg, behavioral disinhibition, impulsivity, irritability, aggression) in which patients may engage in uncharacteristic behaviors such as assaults, theft, or sexual indiscretions without any history of similar behaviors before use or after discontinuation.[26,32,42,43] This is troublesome for patients with PTSD who often already display irritability, aggression, and reckless behavior. Proposed mechanisms for paradoxical reactions include rebound irritability, inhibition of serotonin regulation, inhibition of emotional reactivity to aversive events that deters behavioral activation, and inhibition of cognitive processing in which causal associations are formed between behaviors and their consequences.[32,42] Risk factors for paradoxical reactions include several conditions common in PTSD: SUD (especially alcohol use disorder), neurocognitive disorders (especially TBI), anxiety disorders (comorbid to and including PTSD), previous impulsivity, and previous aggression.[2,15,16,40] Unfortunately, factors such as SUD, TBI, and comorbid anxiety disorders are also correlated with increased prescription of BZDs for PTSD.[1,2,39]

Two of the studies that were reviewed measured depression: Braun et al[10] found that BZDs were ineffective for depression in PTSD and Gelpin et al[12] found that BZD use after trauma increased the risk of developing major depressive disorder. In general, BZDs have been known to cause or worsen dysphoria and suicidality (ie, BZD-induced depressive disorder) even in individuals without a history of depression.[5,39,43,44] Unfortunately, although the therapeutic effects of BZDs decrease with tolerance, depression and impulsivity with high suicidal risk commonly persist.[27] The mechanisms responsible for BZD-induced depression are a matter of speculation but they may be similar to those causing paradoxical reactions (eg, inhibition of serotonin regulation, impulsivity). Regardless of the explanation, the prospect of BZDs worsening depression is of concern for patients with PTSD, who commonly have negative moods and cognitions, anhedonia, suicidality, and comorbid depressive disorders.

One study[16] that was reviewed measured substance use, and the findings suggested that BZDs are associated with substance use in some patients with PTSD. Although BZDs are some of the more commonly misused substances following trauma, data about BZDs and SUD specific to patients with PTSD are limited. In general, 58% to 100% of those prescribed chronic BZDs become physically dependent (especially with high doses and short-acting BZDs).[28,45] Risk factors for developing BZD use disorder include preexisting or active SUD, family history, early onset of use, medical availability, chronic medical conditions, chronic pain, chronic anxiety, chronic insomnia, chronic dysphoria, previous impulsivity, and personality disorders.[2,27–29,45] Unfortunately, SUD and chronic anxiety are also correlated with increased prescriptions for BZDs for PTSD.[1,2,39] Because BZD use disorder develops in at least 50% of patients with a history of SUD who are prescribed BZDs, many authors and organizations have declared BZDs contraindicated in all patients with histories of SUD, except during withdrawal.[26,40] Although a previous SUD may be the predominant risk factor, when BZDs are continuously available, drug reinforcement can lead to misuse by patients without any history of substance misuse.[46] "Their greatest asset is also their greatest liability: drugs that work immediately tend to be addictive."[26] SUD occurs in 21% to 43% of patients with PTSD[47] and in as many as 50% of veterans with PTSD.[3] This high comorbidity suggests that PTSD and SUD are functionally related, a concept supported by several studies that indicate a pathway related to corticotropin-releasing hormone and norepinephrine whereby PTSD precedes SUD.[47] The high risk of SUD in patients with PTSD is one reason why so many authors and organizations recommend against treating PTSD with BZDs.

Efficacy (Level of Evidence D)

A few anecdotal reports and parts of 2 RCTs support short-term symptomatic treatment, but there is no available expert consensus endorsing BZDs for PTSD treatment, so the ceiling for the level of evidence is D.

Although both the studies supporting efficacy are RCTs,[9,10] they had mixed findings (ie, they also demonstrated inefficacy or worsening of PTSD) and, at best, they only supported short-term use for some PTSD-associated symptoms. For example, Mellman et al[9] found that temazepam initially improved sleep but that it was not significantly different from placebo after the first night and worsened overall PTSD severity in the long term. Braun et al[10] found short-term improvement in anxiety (described as a "slight reduction," "modest," and "disappointing"), but no significant difference from placebo in any other measure (overall severity of PTSD symptoms, depression, overall well-being). Other studies that were reviewed demonstrated inefficacy for sleep[11] and anxiety.[12,16] Only 1 other nonanecdotal study supported efficacy: Lee et al[48] found that lorazepam improved intrusive symptoms, but the RCT was excluded from this review because the participants experienced an artificial "trauma" by video and were assessed only 1 day later (less than the 1 month threshold for PTSD). The study by Lee and colleagues also found no significant improvement in anxiety, depression, or arousal. The authors suggested that lorazepam is "atypical" and differs from other BZDs such as diazepam that can trigger intrusion. Even if BZDs improve PTSD-associated symptoms on a short-term basis, the benefits are unlikely to last due to tolerance.

There is no evidence besides anecdotal reports that supports the use of BZDs for the treatment of PTSD core symptoms (ie, intrusion, avoidance, hyperarousal) or for long-term symptomatic treatment of PTSD. Many researchers have criticized the frequent citation of case reports to justify the use of BZDs to treat patients with PTSD, "despite risks and lack of studies."[11] These case reports are mostly retrospective and based on subjective reports. Patients' reports of their experiences while taking BZDs are inherently unreliable, as 1 case series[49] concedes:

> It is possible that patients' memories of subjective sensations while intoxicated do not correspond to their actual affective state. For instance, many people report euphoria after the fact with alcohol intoxication, even though at the time of intoxication they were tearful and agitated (p. 374).

In the case of sleep, BZDs are often credited (like alcohol) for improving sleep quality, but they actually promote sleep induction while inhibiting the deepest, most restorative stages of sleep.[28,45] At times, subjective reports of improvement with BZDs may reflect distortions due to cognitive impairments or they may be due to patients mistaking the temporary relief of discontinuation symptoms for improvement of baseline symptoms or mistaking sedation for genuine improvement of their condition.

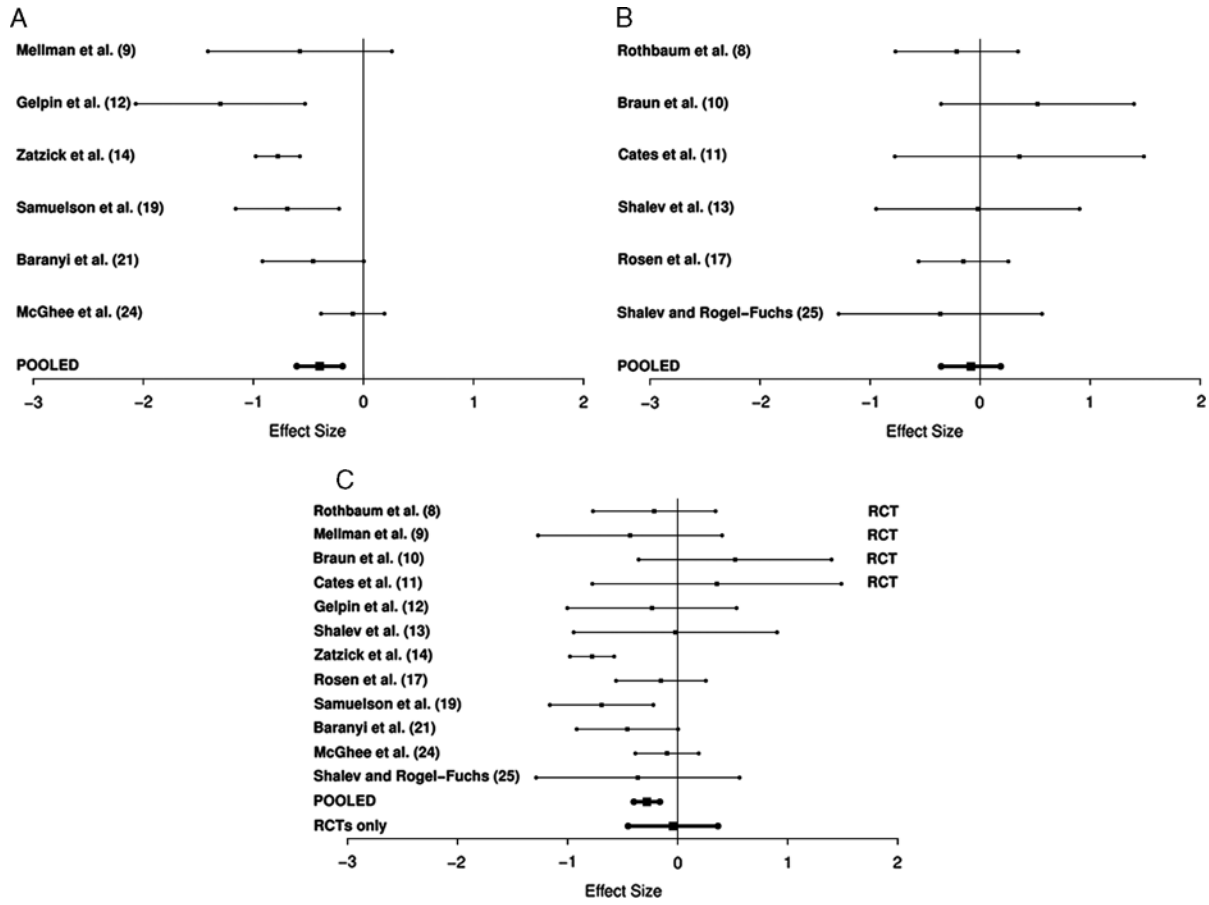
The findings of Mellman et al[50] highlight the importance of caution when extrapolating the results of anecdotal evidence to clinical practice. In this prospective case series of 4 recent trauma patients with insomnia, the researchers found that short-term temazepam was associated with improved PTSD symptoms; however, this was a pilot study for Mellman et al,[9] the RCT that found that short-term temazepam increases the risk of developing PTSD. In addition, "because benzodiazepines reduce anxiety without addressing the underlying PTSD, clinicians may incorrectly believe the patient has improved, thus delaying definitive PTSD care."[40] BZDs "need to be carefully considered, taking into account their potential harm to the spontaneous recovery process, and the trajectory of PTSD, and not only judging them according to their immediate (comforting) effects."[36]

Limitations

There was little consistency in participants, diagnostic method, trauma type, recency, severity, intervention, follow-up, or outcome measures among the studies selected for review. For example, the studies conducted in intensive care units examined only life-threatening medical conditions,[18–20,22] whereas McGhee et al[24] examined only combat-related PTSD. Nine articles studied the use of any BZD, whereas others studied specific agents. Follow-up ranged from 2 weeks to 4 years. Seven studies used multiple assessment instruments and no instrument was used in more than 4 studies. These inconsistencies resulted in heterogeneity among the studies. However, random-effects models were used in the meta-analyses to account for this heterogeneity, resulting in wider CIs for ESs than would have resulted if a fixed-effects approach had been used.

Our meta-analytic approach also had some limitations. In particular, publication bias, if present, would result in an underreporting of nonsignificant studies. However, in the present context, there is

FIGURE 2. A–C, Summary of effect sizes (boxes) and confidence intervals (horizontal lines) of reviewed studies of benzodiazepines (BZDs) in posttraumatic stress disorder (PTSD).



A, H_1: BZDs are not associated with the development of PTSD in trauma patients. B, H_2: BZDs are not associated with PTSD-associated symptoms in patients with PTSD. C, H_3: BZDs are not associated with PTSD-associated symptoms in trauma patients with and without PTSD.

less reason for studies with nonsignificant results not to have been published, as they would have supported the view that BZDs are not harmful. An additional potential limitation is that the meta-analytic method chosen implicitly assumes that there is no systematic bias across these studies favoring positive associations.

Although there is evidence that BZDs can worsen PTSD-associated symptoms, the authors cannot exclude the likelihood that those patients who were treated with BZDs in the observational studies that were reviewed were more severely affected and had worse prognoses. For example, the results of the intensive care unit studies were likely confounded by indication (eg, patients who are more delirious, agitated, or anxious in the ICU may be more likely to receive higher BZD doses). Therefore, BZD use may be an indicator, rather than a cause, of poorer prognosis. However, such confounding factors were eliminated in a study by Treggiari et al,[51] a RCT that found that lower sedation in critically ill patients is associated with fewer PTSD symptoms (this study was excluded from this review because it did not distinguish BZDs from other sedatives). Likewise, similar confounding factors were eliminated in the reviewed RCTs that demonstrated worsening of PTSD.[8,9]

The greatest limitation of this review was the limited number of RCTs available. Of the 4 placebo-controlled trials, only 2 were double-blind,[8,10] whereas 1[11] was single-blind and another was open-label.[9] Nevertheless, the authors believed it was worthwhile to compile the data from all of the available studies given the widespread use of BZDs for PTSD and disagreements and misconceptions among clinicians about this practice. When the meta-analysis was limited only to the RCTs, the results were inconclusive due to the small sample sizes of those RCTs and the great amount of heterogeneity among the studies with 2 showing non-significant negative effects and 2 showing non-significant positive effects. Although one might argue that only RCTs should be considered for inclusion in a rigorous review, in light of the limited number of studies of BZDs in PTSD, we elected to use more expansive inclusion criteria to create a comprehensive review of the available literature, and to stimulate clinical thought and further research. Further studies are recommended, especially randomized placebo-controlled trials with extended follow-up.

CONCLUSIONS

Although BZDs have been in use since 1960 and trauma survivors have always existed, hard knowledge is scanty. Nevertheless, based on our meta-analysis and qualitative synthesis, we can conclude that BZDs are more likely to be ineffective than effective for the treatment or prevention of PTSD and that risks tend to outweigh potential short-term benefits. Consistent evidence supports a lack of efficacy, especially for PTSD core symptoms, psychotherapy augmentation, and depression. There is also suggestive evidence that BZDs may worsen outcomes, with BZDs being correlated with worse overall severity of PTSD symptoms, increased risk of trauma patients developing PTSD, and worse psychotherapy outcomes. However, more double-blind placebo-controlled trials are needed before it can be concluded that BZDs consistently worsen PTSD. There is little evidence for anything except the most transient efficacy, which is limited to a few symptoms, and this is outweighed by better evidence for inefficacy and potential risks. For these reasons and others, BZDs should be considered relatively contraindicated in trauma patients.

Most studies specific to BZDs in PTSD are small and few are RCTs. However, taken together and in combination with general BZD studies, they raise enough questions about potential harms that providers should use considerable caution when continuing BZD prescriptions and would be safer to avoid starting them altogether in PTSD patients. Some of these potential problems are general concerns about the medication class (eg, cognitive effects, dependence, misuse), and others are specific to the diagnosis (eg, adverse effects synergistically worsening PTSD symptoms, inhibiting psychotherapy, promoting avoidance). Although BZDs might be effective if they were to selectively inhibit the stress and anxiety centers of the brain that are often hyperactive in PTSD (eg, amygdala, HPA axis), they indiscriminately target the entire brain, including those areas that are already hypoactive in PTSD, including the cognitive and memory centers (eg, prefrontal cortex, hippocampus), and serotonergic circuits (implicated in PTSD, anxiety, depression, suicidality, impulsivity, aggression). Although it may be tempting to treat PTSD-associated symptoms with BZDs, they are best avoided due to evidence of long-term risks outweighing evidence of any short-term benefits, and the difficulty of discontinuing BZDs once started. When patients with PTSD are already taking BZDs, providers should evaluate whether the treatment is actually improving the patients' functioning or if there are any—often subtle—iatrogenic effects on the course of their condition. After weighing risks and benefits, some providers will choose to continue BZDs, some will unilaterally discontinue or change medications, and some will work through the stages of change to help patients transition toward evidence-based treatments. Regardless, recovery from PTSD should denote improved functioning (eg, healthy relationships, employment), not simply sedation.

Although there is little evidence of benefits associated with BZDs in PTSD, substantial evidence supports the benefits associated with other treatments. A myriad of evidence-based treatments for PTSD exist (eg, psychotherapy, serotonergic antidepressants, adrenergic inhibitors),[3,38,40] all of which should be exhausted before BZDs are considered. For years, sedatives were the only thing we had in our armamentarium for PTSD. Now, we have many more tools and our patients—whether survivors of assault, combat, or any other trauma—deserve those treatments that have been proven to be safer and more effective than BZDs.

REFERENCES

1. Harpaz-Rotem I, Rosenheck RA, Mohamed S, et al. Pharmacologic treatment of posttraumatic stress disorder among privately insured Americans. Psychiatr Serv. 2008;58:1184–1190.
2. Lund BC, Bernardy NC, Vaughan-Sarrazin M, et al. Patient and facility characteristics associated with benzodiazepine prescribing for veterans with PTSD. Psychiatr Serv. 2013;64:149–155.
3. Veterans Affairs and Department of Defense. VA/DoD clinical practice guideline for management of post-traumatic stress, 2010. Available at: http://www.healthquality.va.gov/guidelines/MH/ptsd/cpg_PTSD-FULL-201011612.pdf. Accessed April 8, 2013.
4. Matar MA, Zohar J, Kaplan Z, et al. Alprazolam treatment immediately after stress exposure interferes with the normal HPA-stress response and increases vulnerability to subsequent stress in an animal model of PTSD. Eur Neuropsychopharmacol. 2009;19:283–295.
5. Foa EB, Keane TM, Friedman MJ, et al. Effective Treatments for PTSD: Practice Guidelines From the International Society for Traumatic Stress Studies, 2nd ed. New York, NY: Guilford; 2009:566.
6. US Department of Health and Human Services. Clinical Practice Guideline No 5: Depression in Primary Care, Vol 2: Treatment of Major Depression. Rockville, MD: AHCPR Publications; 1993:71–123.
7. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
8. Rothbaum OR, Price M, Jovanovic T, et al. A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan war veterans. Am J Psychiatry. 2014;171:640–648.
9. Mellman TA, Bustamante V, David D, et al. Hypnotic medication in the aftermath of trauma. J Clin Psychiatry. 2002;63:1183–1184.
10. Braun P, Greenberg D, Dasberg H, et al. Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. J Clin Psychiatry. 1990;51:236–238.
11. Cates ME, Bishop MH, Davis LL, et al. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. Ann Pharmacother. 2004;38:1395–1399.
12. Gelpin E, Bonne O, Peri T, et al. Treatment of recent trauma survivors with benzodiazepines: a prospective study. J Clin Psychiatry. 1996;57:390–394.
13. Shalev AY, Bloch M, Peri T, et al. Alprazolam reduces response to loud tones in panic disorder but not in posttraumatic stress disorder. Biol Psychiatry. 1998;44:64–68.
14. Zatzick DF, Rivara FP, Nathens AB, et al. A nationwide US study of post-traumatic stress after hospitalization for physical injury. Psychol Med. 2007;37:1469–1480.
15. Shin HJ, Rosen CS, Greenbaum MA, et al. Longitudinal correlates of aggressive behavior in help-seeking US veterans with PTSD. J Trauma Stress. 2012;25:649–656.
16. Kosten TR, Fontana A, Sernyak MJ, et al. Benzodiazepine use in posttraumatic stress disorder among veterans with substance abuse. J Nerv Ment Dis. 2000;188:454–459.
17. Rosen CS, Greenbaum MA, Schnurr PP, et al. Do benzodiazepines reduce the effectiveness of exposure therapy for posttraumatic stress disorder? J Clin Psychiatry. 2013;74:1241–1248.
18. Jones C, Backman C, Capuzzo M, et al. Precipitants of post-traumatic stress disorder following intensive care: a hypothesis generating study of diversity in care. Intensive Care Med. 2007;33:978–985.
19. Samuelson KAM, Lundberg D, Fridlund B. Stressful memories and psychological distress in adult mechanically ventilated intensive care patients—a 2 month follow-up study. Acta Anaesthesiol Scand. 2007;51:671–678.
20. Bienvenu OJ, Gellar J, Althouse BM, et al. Post-traumatic stress disorders symptoms after acute lung injury: a 2-year prospective longitudinal study. Psychol Med. 2013;43:2657–2671.
21. Baranyi A, Krauseneck T, Rothenhausler HB. Posttraumatic stress symptoms after solid-organ transplantation: preoperative risk factors and the impact on health-related quality of life and life satisfaction. Health Qual Life Outcomes. 2013;11:111.
22. Girard TD, Shintani AK, Jackson JC, et al. Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. Crit Care. 2007;11:R28.
23. Van Minnen A, Arntz A, Keijsers GPJ. Prolonged exposure in patients with chronic PTSD: predictors of treatment outcome and dropout. Behav Res Ther. 2002;40:439–457.
24. McGhee LL, Maani CV, Garza TH, et al. The relationship of intravenous midazolam and posttraumatic stress disorder development in burned soldiers. J Trauma. 2009;66(suppl):S186–S190.
25. Shalev AY, Rogel-Fuchs Y. Auditory startle reflex in posttraumatic stress disorder patients treated with clonazepam. Isr J Psychiatry Relat Sci. 1992;29:1–6.
26. Longo LP, Johnson B. Addiction: part I. Benzodiazepines—side effects, abuse risk and alternatives. Am Fam Physician. 2000;61:2121–2128.
27. Michelini S, Cassano GB, Frare F, et al. Long-term use of benzodiazepines: tolerance, dependence and clinical problems in anxiety and mood disorders. Pharmacopsychiatry. 1996;29:127–134.
28. Ashton H. The diagnosis and management of benzodiazepine dependence. Curr Opin Psychiatry. 2005;18:249–255.
29. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth ed. Arlington, VA: American Psychiatric Association; 2013:265–290, 550–560.
30. Coupland NJ, Lillywhite A, Bell CE, et al. A pilot controlled study of the effects of flumazenil in posttraumatic stress disorder. Biol Psychiatry. 1997;41:988–990.
31. Randall PK, Bremner JD, Krystal JH, et al. Effects of the benzodiazepine antagonist flumazenil in PTSD. Biol Psychiatry. 1995;38:319–324.
32. Tasman A, Kay J, Lieberman JA. Psychiatry, 3rd ed, Vol 1. Chichester, UK: John Wiley & Sons; 2008:1186–1200, 2603–2615.
33. Li S, Murakami Y, Wing M, et al. The effects of chronic valproate and diazepam in a mouse model of posttraumatic stress disorder. Pharmacol Biochem Behav. 2006;85:324–331.
34. Geuze E, van Berckel BNM, Lammertsma AA, et al. Reduced $GABA_A$ benzodiazepine receptor binding in veterans with post-traumatic stress disorder. Mol Psychiatry. 2008;13:74–83.
35. Davydow DS, Gifford JM, Desai SV, et al. Posttraumatic stress disorder in general intensive care unit survivors:

a systematic review. Gen Hosp Psychiatry. 2008;30: 421–434.
36. Zohar J, Juven-Wetzler A, Sonnino R, et al. New insights into secondary prevention in post-traumatic stress disorder. Dialogues Clin Neurosci. 2011;13:301–309.
37. Hebert MA, Potegal M, Moore T, et al. Diazepam enhances conditioned defeat in hamsters. Pharmacol Biochem Behav. 1996;55:405–413.
38. Berger W, Mendlowicz MV, Marques-Portella C, et al. Pharmacologic alternatives to antidepressants in post-traumatic stress disorder: a systematic review. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:169–180.
39. Hawkins EJ, Malte CA, Imel ZE, et al. Prevalence and trends of benzodiazepine use among Veterans Affairs patients with posttraumatic stress disorder, 2003–2010. Drug Alcohol Depend. 2012;124:154–161.
40. Jeffreys M, Capehart B, Friedman MJ. Pharmacotherapy for posttraumatic stress disorder: review with clinical applications. J Rehabil Res Dev. 2012;49:703–715.
41. Herman J. Trauma and Recovery: The Aftermath of Violence—From Domestic Abuse to Political Terror. New York, NY: Basic Books; 1992:44–45.
42. Bond AJ. Drug-induced behavioural disinhibition: incidence, mechanisms and therapeutic implications. CNS Drugs. 1998;9:41–57.
43. PDR Network. Physicians' Desk Reference, 2014. Available at: http://www.pdr.net. Accessed March 5, 2014).
44. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2005;19:567–596.
45. Pary R, Lewis S. Prescribing benzodiazepines in clinical practice. Resid Staff Physician. 2008;54:8–17.
46. Griffiths RR, Weerts EM. Benzodiazepine self-administration in humans and laboratory animals—implications for problems of long-term use and abuse. Psychopharmacology. 1997;134:1–37.
47. Jacobsen LK, Southwick SM, Kosten TR. Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. Am J Psychiatry. 2001;158: 1184–1190.
48. Lee HS, Lee HP, Lee SK, et al. Anti-intrusion effect of lorazepam: an experimental study. Psychiatry Investig. 2013;10:273–280.
49. Bremner JD, Southwick SM, Darnell A, et al. Chronic PTSD in Vietnam combat veterans: course of illness and substance abuse. Am J Psychiatry. 1996;153:369–375.
50. Mellman TA, Byers PM, Augenstein JS. Pilot evaluation of hypnotic medication during acute traumatic stress response. J Trauma Stress. 1998;11:563–569.
51. Treggiari MM, Romand JA, Yanez ND, et al. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med. 2009;37:2427–2534.