Borrower: NHUDAR $11A

Lending String:

Patron: Hermann, Barbara - TN;491882

Journal Title: The Journal of clinical psychiatry

Volume: [Epub ahead of print]
Article **Issue:** Print
Month/Year: 2011 **Pages:** Electronic format

Article Author: Lund BC;Bernardy NC;Alexander B;Friedman MJ

Article Title: Declining benzodiazepine use in veterans with post

Imprint:

ILL Number: 32310658

Call #: EFTS

Location: ONLINE

ARIEL
We send our documents electronically using Odyssey. ILLiad libraries can enable Odyssey for receiving documents seamlessly. Non-ILLiad libraries can download Odyssey stand alone for FREE. Check it out at: http://www.atlas-sys.com/Odyssey.html

Charge
Maxcost: $25.00

Shipping Address:
Dartmouth College
Biomedical Libraries Document Delivery
6168 Dana Biomedical Library
Hanover, NH 03755-3880

Fax: 1.603.650-1354
Ariel: 129.170.124.3

Declining Benzodiazepine Use in Veterans With Posttraumatic Stress Disorder

Brian C. Lund, PharmD, MS; Nancy C. Bernardy, PhD; Bruce Alexander, PharmD; and Matthew J. Friedman, MD, PhD

ABSTRACT

Objective: Clinical practice guidelines issued by the US Department of Veterans Affairs (VA) and the Department of Defense caution against benzodiazepine use among veterans with posttraumatic stress disorder (PTSD) because of insufficient evidence for efficacy and emerging safety concerns. We examined recent trends in benzodiazepine prescribing among veterans with PTSD in terms of frequency of use, duration of use, and dose.

Method: Administrative VA data from fiscal years 1999 through 2009 were used to identify veterans with PTSD according to *ICD-9* codes extracted from inpatient discharges and outpatient encounters. Benzodiazepine use among these individuals was determined for each fiscal year by using prescription drug files. Modal daily doses were examined by using standard daily dosage units.

Results: The number of veterans receiving care for PTSD in the VA increased from 170,685 in 1999 to 498,081 in 2009. The proportion of individuals receiving a benzodiazepine decreased during this time period from 36.7% to 30.6%. In addition, the proportion of long-term users (> 90 days) decreased from 69.2% to 64.1%, and daily dose decreased from 2.1 to 1.8 standard daily dosage units.

Conclusions: Decreasing benzodiazepine use among veterans with PTSD is encouraging. However, the frequency of use remains above 30%, and focused interventions may be required to achieve further reductions. Given the growing number of veterans being diagnosed and treated for PTSD, minimizing benzodiazepine exposure will remain a vital policy issue for the VA.

J Clin Psychiatry

Submitted: *December 8, 2010; accepted March 4, 2011.*
Online ahead of print: *November 29, 2011 (doi:10.4088/JCP.10m06775).*
Corresponding author: *Brian C. Lund, PharmD, Iowa City VA Medical Center (Mailstop 152), 601 Hwy 6 West, Iowa City, IA 52246 (Brian.Lund@va.gov).*

The safe and effective treatment of posttraumatic stress disorder (PTSD) is a vital issue for the US Department of Veterans Affairs (VA). The number of veterans seeking care for PTSD has increased dramatically in the past decade.[1] Given US involvement in recent wars and other military conflicts, PTSD will remain a major focus for VA research and clinical management. In addition to several evidenced-based psychotherapy options, the 2004 clinical practice guideline issued jointly by the VA and the US Department of Defense (DoD),[2] as well as guidelines from the American Psychiatric Association,[3] recommended selective serotonin reuptake inhibitors as first-line pharmacologic monotherapy. Second-line treatment options included tricyclic antidepressants and monoamine oxidase inhibitors, and many other medications are commonly prescribed in clinical care. Unfortunately, clinical trial data concerning the efficacy of these treatments are sparse, and information concerning real-world comparative effectiveness is nonexistent.

Among all treatment options, the role of benzodiazepines in PTSD management is particularly contentious. Currently, no data support the efficacy of benzodiazepines for the treatment of core PTSD symptoms,[4] and the 2004 VA/DoD Clinical Practice Guideline for Management of Post-Traumatic Stress[2] specifically recommended against long-term use of these drugs. While benzodiazepines are ineffective for core PTSD symptoms like avoidance or dissociation,[5,6] these agents are commonly prescribed to manage secondary symptoms such as insomnia and anxiety. Clinicians and patients will attest that benzodiazepines can bring about rapid, short-term symptomatic relief. When faced with a patient suffering from significant PTSD symptoms, the desire to provide immediate relief is understandable. However, mounting evidence suggests that the long-term harms imposed by benzodiazepine use may outweigh the short-term benefits.

Two common and frequently underrecognized comorbidities among veterans with PTSD include substance use disorders and traumatic brain injury, both of which are contraindications to benzodiazepine use.[3] Benzodiazepine tolerance and physiological dependence occur with long-term use, and severe withdrawal symptoms as well as dramatic rebound anxiety symptoms can occur upon discontinuation.[7] Finally, growing evidence from animal research has shown that benzodiazepines interfere with the extinction of conditioned fear.[8,9] Since extinction of conditioned fear is a critical element of prolonged exposure therapy, there is concern that this cornerstone of PTSD treatment may be affected by benzodiazepine use. While this relationship has not been conclusively demonstrated in real-world patients, there is some clinical evidence that benzodiazepines can reduce the effectiveness of prolonged exposure therapy.[10]

With an updated Clinical Practice Guideline[11] released in early 2011, there is renewed interest in national policy regarding benzodiazepine use in the VA. Documenting recent prescribing trends is essential to determine whether interventions to curtail benzodiazepine use are necessary and to suggest how successful interventions could be developed and disseminated. One prior national study reported that 31% of veterans with PTSD received a benzodiazepine in 2004.[1] This cross-sectional view of prescribing suggests that benzodiazepine use is common but does not demonstrate the trajectory of use over time. Therefore, we sought to build upon this work and

Clinical Points

- The frequency of benzodiazepine use among veterans with posttraumatic stress disorder declined substantially over the past decade, from 36.7% in 1999 to 30.6% in 2009.
- Benzodiazepine dose and duration of use also decreased during this period.
- Benzodiazepine use among veterans with posttraumatic stress disorder remains above 30% and presents an opportunity for further improvement in prescribing quality.

examine the trends in benzodiazepine prescribing among veterans with PTSD over the past decade. We hypothesized that benzodiazepine use would decrease across 3 different aspects of utilization: frequency of use, duration of use, and dose.

METHOD

Data Sources

This analysis used national administrative VA datasets over an 11-year time period, from fiscal years 1999 through 2009 (October 1, 1998 to September 30, 2009). Inpatient discharge datasets and outpatient encounter datasets were obtained from the Austin Information Technology Center (Austin, Texas). Prescription drug records were obtained from the VA Pharmacy Benefits Management Services (Hines, Illinois). Records from these separate data sources were linked using a scrambled patient identification number. This study was approved by the University of Iowa Institutional Review Board and the Iowa City Veterans Administration Research and Development Committee.

Patients

For each individual year, all veterans with at least 1 inpatient or outpatient encounter containing a diagnostic code for PTSD during that year were selected. Posttraumatic stress disorder was identified from these records using the *International Classification of Diseases, Ninth Revision* (*ICD-9*) code of 309.81 listed as either a primary or a secondary diagnosis. This algorithm has been used in prior research examining drug utilization patterns among veterans with PTSD.[1,12]

For several analyses, it was important to determine the length of time that veterans had been receiving care for PTSD within the VA system. Of primary interest were treatment patterns among patients who received their first PTSD diagnosis within the VA system. Veterans seen for PTSD in a given fiscal year were considered to be newly diagnosed in the system if no inpatient discharges or outpatient encounters coded for PTSD were observed during the prior 3 fiscal years. This definition was chosen to balance data availability and the likelihood of falsely identifying a preexisting patient as a new patient. For example, among veterans seen for PTSD in 2009 who had only 1 year of PTSD absence (during 2008), 17.9% had a code for PTSD during the prior year (2007). In contrast, requiring 5 years of prior absence reduced this false-positive frequency to only 1.8%. However, this stringent requirement reduced the range of years for which benzodiazepine use could be described to 2004 through 2009. We therefore selected 3 years of prior PTSD absence, which reduced the false-positive rate to 4.8% and allowed for benzodiazepine frequencies to be calculated for fiscal years 2002 through 2009. It should be noted that this definition was not meant to define a new onset of PTSD illness or even the initial recognition and diagnosis of PTSD. The onset of illness could have been many years prior to diagnosis, or the individual could have received prior treatment for PTSD outside the VA system. The remaining veterans were classified as having received treatment for 1 to 2 years or 3 or more years.

Benzodiazepine Use

Veterans were considered a benzodiazepine user during a given fiscal year if they received at least 1 outpatient prescription fill, regardless of quantity, days' supply, or dosage form, for any of the following medications during that year: alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, oxazepam, prazepam, quazepam, temazepam, triazolam. This definition of any benzodiazepine use was intentionally inclusive. However, short-term use of benzodiazepines may be more clinically justifiable than chronic use, and it was important to understand what proportion of any benzodiazepine use was for relatively short duration versus chronic management. Therefore, duration of use was examined in a subanalysis by classifying veterans as short-term versus long-term benzodiazepine users. Veterans who received greater than 90 days of continuous benzodiazepine treatment at any point during the fiscal year were considered long-term users. This definition was selected because short-term use of benzodiazepines for acute symptom management (eg, insomnia) is generally limited to 3 months or less. Moreover, veterans can receive up to a 90-day supply of medication at a time, and this definition thus required all long-term users to have received at least 2 fills.

Change in benzodiazepine dosing was also examined over time. Benzodiazepine dose was first determined for each fill by dividing the product of the unit drug strength and quantity dispensed fields by the days' supply field. Patient-level doses were then determined by the modal dose across all individual fills in that fiscal year. Patient-level doses were then converted to standard daily dosage units, which represent the typical minimum effective daily dose.[13-21] Standard daily dosage units conversion was used to facilitate dosing comparisons between drugs and allow aggregation across the various benzodiazepines to examine system-level dosing trends over time.

Analysis

Inferential statistics were not used in this analysis since complete data for the study population, veterans receiving

Table 1. Frequency of Benzodiazepine Use Overall and by Time Since Diagnosis of Posttraumatic Stress Disorder (PTSD) by Department of Veterans Affairs

			Time Since PTSD Diagnosis[a]					
			New Diagnosis		1–2 Years		≥ 3 Years	
Fiscal Year	PTSD, N	Benzodiazepine, n (%)	PTSD, n	Benzodiazepine, n (%)	PTSD, n	Benzodiazepine, n (%)	PTSD, n	Benzodiazepine, n (%)
1999	170,685	62,578 (36.7)	...	...	...	...	...	...
2000	181,745	65,412 (36.0)	...	...	...	...	...	...
2001	197,544	69,964 (35.4)	...	...	...	...	...	...
2002	219,141	76,933 (35.1)	58,700	13,607 (23.2)	53,658	17,355 (32.3)	106,783	45,971 (43.1)
2003	243,767	82,478 (33.8)	63,584	14,261 (22.4)	57,007	17,427 (30.6)	123,176	50,790 (41.2)
2004	270,025	88,838 (32.9)	70,703	15,636 (22.1)	63,266	18,574 (29.4)	136,056	54,628 (40.2)
2005	317,644	102,337 (32.2)	85,377	18,209 (21.3)	75,924	22,252 (29.3)	156,343	61,876 (39.6)
2006	331,674	106,879 (32.2)	78,878	16,684 (21.2)	85,261	24,581 (28.8)	167,535	65,614 (39.2)
2007	393,815	126,223 (32.1)	98,032	20,922 (21.3)	92,712	26,432 (28.5)	203,071	78,869 (38.8)
2008	437,861	136,389 (31.1)	100,426	20,595 (20.5)	101,415	27,793 (27.4)	236,020	88,001 (37.3)
2009	498,081	152,547 (30.6)	109,804	22,506 (20.5)	115,947	31,537 (27.2)	272,330	98,504 (36.2)

[a]Frequency of benzodiazepine use could not be determined for subgroups prior to fiscal year 2002.

care within the VA health care system, were observed. The clinical significance of differences in benzodiazepine frequencies across time, or between certain subgroups, is discussed.

RESULTS

The number of veterans receiving care for PTSD in the VA health care system increased nearly 3-fold during the study time frame, from 170,685 in 1999 to 498,081 in 2009 (Table 1). The mean age of veterans with PTSD increased from 52.8 (SD = 11.2) years in 1999 to a peak of 56.0 (SD = 11.0) years in 2004, then steadily decreased to 53.8 (SD = 14.6) years in 2009. When restricted to veterans given their first PTSD diagnosis within the VA system, the mean age remained flat from 2002 through 2004 at approximately 54 years, but then dropped steadily to 47.2 (SD = 16.4) years in 2009. Furthermore, the proportion of first PTSD diagnosis veterans ≤ 25 years of age was 0.9% in 2002, but increased to 13.0% in 2009. The proportion of female veterans also increased steadily over this period. Women comprised 6.2% of veterans receiving care for PTSD in the VA in 1999 and steadily increased to 7.5% in 2009.

The overall frequency of benzodiazepine use in veterans with PTSD decreased steadily from 36.7% in 1999 to 30.6% in 2009 (Table 1). The likelihood of receiving benzodiazepines was very clearly influenced by time since first VA PTSD diagnosis (Table 1). In 2009, new patients were the least likely to receive a benzodiazepine (20.5%), followed by patients 1–2 years following first VA diagnosis (27.2%) and by patients 3 or more years after diagnosis (36.2%). Most notably, benzodiazepine use decreased over time in all 3 groups. The proportion of long-term users also decreased slightly over time, from a peak of 69.2% in 2000 to a low of 64.1% in 2009.

The distribution of individual benzodiazepine agents for selected fiscal years is found in Table 2. Clonazepam was the most commonly prescribed benzodiazepine across all years, accounting for more than one-quarter of benzodiazepine utilization. Other commonly prescribed agents included diazepam, lorazepam, alprazolam, and temazepam. Together these 5 drugs comprised over 85% of benzodiazepine use in 1999 and nearly 98% of use in 2009.

Patient-level modal daily doses were converted to standard daily dosage units by using the conversion ratios found in Table 2. For example, a 1-mg daily dose of clonazepam was converted to 1 standard daily dosage units, and a 20-mg daily dose of diazepam was converted to 2 standard daily dosage units. The actual observed study-level modal daily dose (mg) for each drug is also reported in Table 2. For example, the most commonly prescribed daily dose of clonazepam was 1 mg. Importantly, the observed modal daily dose was equal the standard daily dosage units value for the 4 most commonly prescribed benzodiazepines. Because the standard daily dosage unit value represents the minimum effective dose typically used in practice, it is notable that the most commonly prescribed dose given to veterans with PTSD was this minimum effective dose. Mean daily doses for the individual benzodiazepine agents are presented in Table 2. Overall benzodiazepine doses steadily declined over the study period from 2.1 standard daily dosage units in 1999 to 1.8 standard daily dosage units in 2009. While dosing remained flat or even increased for some agents, the 4 most commonly prescribed benzodiazepines (clonazepam, diazepam, lorazepam, alprazolam) demonstrated the same consistent decrease in dose of approximately 10%–15%, from approximately 2 standard daily dosage units to 1.8 standard daily dosage units.

DISCUSSION

The appropriateness of benzodiazepine use among veterans with PTSD is controversial and was specifically discouraged in the 2004 VA/DoD Clinical Practice Guideline.[2] The recommendation against benzodiazepine use in PTSD was maintained in the recently updated VA/DoD Clinical Practice Guideline,[11] officially released in early 2011. Commensurate with this philosophy, we documented decreased benzodiazepine use in this population over the past decade, across multiple measures of utilization. The overall proportion of veterans receiving a benzodiazepine decreased from 36.7% in 1999 to 30.6% in 2009. In addition, the proportion of long-term users decreased modestly from 69.2% to 64.1%, and the mean daily dose declined nearly 15%. These data

Table 2. Distribution and Dosing of Individual Benzodiazepines

Drug	Fiscal Year 1999 n (%)	Fiscal Year 1999 Standard Daily Dosage Units	Fiscal Year 2004 n (%)	Fiscal Year 2004 Standard Daily Dosage Units	Fiscal Year 2009 n (%)	Fiscal Year 2009 Standard Daily Dosage Units	Standard Daily Dosage Units Ratio, mg	Modal Daily Dose, mg
Clonazepam	15,446 (25.8)	2.0	25,756 (29.8)	1.9	48,422 (32.6)	1.8	1	1
Diazepam	11,023 (18.4)	1.9	13,336 (15.5)	1.8	19,138 (12.9)	1.6	10	10
Lorazepam	9,570 (16.0)	2.3	18,473 (21.4)	2.1	33,973 (22.9)	2.0	1	1
Alprazolam	8,708 (14.6)	2.0	12,231 (14.2)	1.9	22,290 (15.0)	1.8	1	1
Temazepam	6,594 (11.0)	1.7	12,362 (14.3)	1.7	21,315 (14.4)	1.6	15	30
Oxazepam	5,466 (9.1)	3.7	1,800 (2.1)	3.6	943 (0.6)	3.9	10	30
Chlordiazepoxide	1,990 (3.3)	2.0	1,604 (1.9)	2.1	1,664 (1.1)	2.3	25	30
Clorazepate	565 (0.9)	1.4	400 (0.5)	1.4	283 (0.2)	1.4	15	15
Triazolam	220 (0.4)	0.6	190 (0.2)	0.6	218 (0.1)	0.6	0.5	0.25
Flurazepam	222 (0.4)	1.9	156 (0.2)	1.9	140 (0.1)	1.9	15	30
Overall	59,804 (100)	2.1	86,308 (100)	1.9	148,386 (100)	1.8		

suggest that, when benzodiazepine use was deemed necessary, prescribers attempted to constrain potential harms by minimizing dose and duration. Decreasing benzodiazepine exposure is encouraging and represents a significant advance toward the safe and effective management of PTSD in the VA. The extent to which these trends were driven by the publication and dissemination of the VA/DoD Clinical Practice Guideline[11] is unknown. While determining the impact of the Guideline publication was not an objective of our analysis, it is important to acknowledge the potential influence on our findings.

While benzodiazepine use in the VA is on the decline, our findings raise the perennial question, as most notably asked by Wennberg, "Which rate is right?"[22] Setting a target goal of zero benzodiazepine use is probably not realistic nor consistent with the individual circumstances that drive patient-centered care. On the other hand, the current rate of 30.6% undoubtedly leaves room for improvement. This is particularly important when shifting the scope from patient-level treatment decisions to national policy. The number of veterans receiving care for PTSD in the VA increased nearly 3-fold from 1999 to 2009. Thus, despite decreasing frequency of use, the absolute number of veterans with PTSD receiving benzodiazepines increased almost 250%. Given the rapidly increasing number of veterans affected by PTSD, the detrimental effects of benzodiazepine use will continue to be a major health concern to not only the VA but also the many other health care systems involved in the care of returning veterans. In addition, rapidly changing demographics, such as increasing numbers of female veterans and a major downward shift in age distribution, are creating significant new challenges in all areas of VA health care.

One particular subgroup of interest includes veterans first receiving treatment for PTSD through the VA. Shifts in prescribing behavior over time are often first observed in patients newly treated for a particular disorder, and new user subgroups are becoming a more common focal point of pharmacoepidemiology research.[23] Because benzodiazepine discontinuation is often challenging,[7] the least problematic means to curtail use is to avoid these drugs in newly treated, benzodiazepine-naive patients. Our findings were consistent with this notion, with only 20.5% of newly treated veterans receiving a benzodiazepine compared to 36.2% among veterans with a history of 3 or more years of treatment. However, the decline in benzodiazepine use was not limited to new patients but was similar across all treatment-duration groups. It is noteworthy that duration of treatment did not seem to be a significant barrier to benzodiazepine discontinuation. These findings also highlight the need to understand benzodiazepine prescribing prior to entrance into VA health care. This could include veterans transferring care from community providers or recently discharged veterans transferring care from the DoD. These individuals may enter VA care with preexisting benzodiazepine use, but ongoing management becomes the responsibility of their VA providers.

This analysis is subject to several limitations. First, the selection of veterans with PTSD was based exclusively on *ICD-9* codes extracted from administrative datasets. While this approach has been used by prior authors,[1,12] the accuracy of PTSD coding in the VA has not been well-characterized. A common concern with administrative diagnostic codes is low sensitivity. That is, a veteran with PTSD may not have been seen for care or was seen for other medical issues and the PTSD diagnosis may have gone unrecorded during a particular fiscal year. These veterans may have less severe PTSD symptoms and may be at lower risk to receive a benzodiazepine. Thus, their absence from our study sample may have slightly inflated benzodiazepine use rates, though this effect was likely consistent over time and unlikely to explain declining usage. A second limitation is that we could observe care provided only by VA. It is possible that veterans received PTSD treatment and benzodiazepine medications outside the VA system. While information concerning non-VA care would provide a more complete picture of benzodiazepine use, it is unlikely to explain declining utilization rates. It is worth noting that understanding the nature and extent of PTSD treatment received by veterans outside the VA system will become even more vital in coming years. As increasing numbers of recently discharged veterans return to civilian jobs and have access to private insurance, the extent to which veterans will seek PTSD care in community setting is unknown, and it is unclear whether non-VA providers are properly equipped to appropriately identify and manage PTSD on a large scale.

Our findings highlight the need for additional research in several areas. A more detailed description of patient-level

longitudinal treatment histories would be very informative, particularly among veterans receiving a new diagnosis of PTSD in the VA. This would reveal the time course leading to first use of benzodiazepines and the various pharmacologic options that were attempted prior to benzodiazepine initiation. Benzodiazepine use may be more easily justified among individuals who first received guideline-adherent medication and psychotherapy trials. While we found that the likelihood of receiving a benzodiazepine increased substantially with duration of PTSD treatment, patient-level analyses would be required to thoroughly examine this issue. A second issue concerns trends in alternative medication use. Ideally, benzodiazepine use has decreased because veterans with PTSD are receiving higher rates of evidence-based treatments for core symptoms, including cognitive-behavioral therapy and adequate trials of first-line medications, thereby minimizing residual symptoms and eliminating the need for adjunctive benzodiazepines. The emergence of prazosin during this time period as an effective treatment alternative for reducing nightmares and improving sleep may also have played a role.[24] However, it is possible that benzodiazepine use decreased simply through direct substitution with other drugs, such as nonbenzodiazepine hypnotics (eg, zolpidem) or atypical antipsychotics (eg, quetiapine). While these agents are possibly safer, their effectiveness for PTSD is unknown, and it is unclear that direct substitution should be considered an important improvement in the quality of PTSD care.

Decreasing benzodiazepine prescribing among veterans with PTSD is encouraging, but the frequency of use remains above 30%. Simply advocating against benzodiazepine use without understanding current practice patterns and providing practical alternative strategies would be justifiably ignored by clinicians or could change prescribing practices in unexpected and equally harmful ways. A thorough understanding of the issues surrounding benzodiazepine prescribing is vital for the development of effective intervention strategies aimed at further reducing benzodiazepine use. Given the growing number of veterans being diagnosed and treated for PTSD, minimizing benzodiazepine exposure will remain a vital policy issue for the VA.

Drug names: alprazolam (Xanax, Niravam, and others), chlordiazepoxide (Librium and others), clonazepam (Klonopin and others), clorazepate (Gen-Xene, Tranxene, and others), diazepam (Diastat, Valium, and others), flurazepam (Dalmane and others), lorazepam (Ativan and others), prazosin (Minipress and others), quazepam (Doral), quetiapine (Seroquel), temazepam (Restoril and others), triazolam (Halcion and others), zolpidem (Ambien, Edluar, and others).

Author affiliations: Center for Comprehensive Access and Delivery Research and Evaluation, Veterans Affairs Medical Center (Dr Lund); VISN 23 Mental Health Pharmacoepidemiology, Iowa City Veterans Affairs Health System (Dr Alexander), Iowa City, Iowa; and National Center for PTSD, Veterans Affairs Medical Center, White River Junction, Vermont (Drs Bernardy and Friedman).

Potential conflicts of interest: None reported.

Funding/support: This project was supported by the Health Services Research and Development Service, Department of Veterans Affairs (VA), through the Center for Comprehensive Access & Delivery Research and Evaluation (RE A 09-220) at the Iowa City VA Medical Center (Dr Lund) and by the National Center for PTSD at the White River Junction VA Medical Center (Drs Bernardy and Friedman).

Role of sponsors: None of the sponsors had any role in the study's design, methods, analyses, and interpretation or in the preparation of the manuscript and the decision to submit it for publication.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

REFERENCES

1. Mohamed S, Rosenheck RA. Pharmacotherapy of PTSD in the US Department of Veterans Affairs: diagnostic- and symptom-guided drug selection. *J Clin Psychiatry*. 2008;69(6):959–965.
2. Veterans Health Administration, Department of Defense. *VA/DoD Clinical Practice Guideline for the Management of Post-Traumatic Stress. Version 1.0*. Washington, DC: Veterans Health Administration, Department of Defense; 2004.
3. Ursano RJ, Bell C, Eth S, et al; Work Group on ASD and PTSD; Steering Committee on Practice Guidelines. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. *Am J Psychiatry*. 2004;161(suppl):3–31.
4. Berg AO, Breslau N, Goodman SN, et al. *Treatment of PTSD: An Assessment of The Evidence*. Washington, DC: Institute of Medicine; 2008.
5. Viola J, Ditzler T, Batzer W, et al. Pharmacological management of post-traumatic stress disorder: clinical summary of a five-year retrospective study, 1990–1995. *Mil Med*. 1997;162(9):616–619.
6. Friedman MJ, Davidson JRT, Stein DJ. Integration and summary. In: Foa EG, Keane TM, Friedman MJ, et al, eds. *Effective Treatments for PTSD: Practice Guidelines From the International Society for Traumatic Stress Studies*. New York, NY: Guilford Press; 2009:617–642.
7. Lader M, Tylee A, Donoghue J. Withdrawing benzodiazepines in primary care. *CNS Drugs*. 2009;23(1):19–34.
8. Hart G, Harris JA, Westbrook RF. Systemic or intra-amygdala injection of a benzodiazepine (midazolam) impairs extinction but spares re-extinction of conditioned fear responses. *Learn Mem*. 2009;16(1):53–61.
9. Hart G, Harris JA, Westbrook RF. Systemic or intra-amygdala infusion of the benzodiazepine, midazolam, impairs learning, but facilitates re-learning to inhibit fear responses in extinction. *Learn Mem*. 2010;17(4):210–220.
10. 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(4):439–457.
11. VA/DoD clinical practice guideline for management of post-traumatic stress, 2010. VA/DoD clinical practice guidelines Web site. http://www.healthquality.va.gov/PTSD-FULL-2010c.pdf.Accessed October 5, 2011.
12. Harpaz-Rotem I, Rosenheck RA. Tracing the flow of knowledge: geographic variability in the diffusion of prazosin use for the treatment of posttraumatic stress disorder nationally in the Department of Veterans Affairs. *Arch Gen Psychiatry*. 2009;66(4):417–421.
13. Smith DE, Wesson DR. Benzodiazepine dependency syndromes. *J Psychoactive Drugs*. 1983;15(1–2):85–95.
14. Harrison M, Busto U, Naranjo CA, et al. Diazepam tapering in detoxification for high-dose benzodiazepine abuse. *Clin Pharmacol Ther*. 1984;36(4):527–533.
15. Harvey SC. Hypnotics and sedatives. In: Gilman AG, Goodman LS, Rall TW, et al, eds. *The Pharmacological Basis of Therapeutics*. New York, NY: Macmillan; 1985:349–354.
16. Busto U, Sellers EM, Naranjo CA, et al. Withdrawal reaction after long-term therapeutic use of benzodiazepines. *N Engl J Med*. 1986;315(14):854–859.
17. Rickels K, Case WG, Schweizer E, et al. Benzodiazepine dependence: management of discontinuation. *Psychopharmacol Bull*. 1990;26(1):63–68.
18. Sullivan JT, Sellers EM. Detoxification for triazolam physical dependence. *J Clin Psychopharmacol*. 1992;12(2):124–127.
19. Giannini AJ. An approach to drug abuse, intoxication and withdrawal. *Am Fam Physician*. 2000;61(9):2763–2774.
20. Chouinard G. Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. *J Clin Psychiatry*. 2004;65(suppl 5):7–12.
21. Smith DE, Wesson DR. Benzodiazepines and other sedative-hypnotics. In: Galanter M, Kleber HD, eds. *Textbook of Substance Abuse Treatment*. Washington, DC: American Psychiatric Publishing; 2004:235–246.
22. Wennberg J. Which rate is right? *N Engl J Med*. 1986;314(5):310–311.
23. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915–920.
24. Byers MG, Allison KM, Wendel CS, et al. Prazosin versus quetiapine for nighttime posttraumatic stress disorder symptoms in veterans: an assessment of long-term comparative effectiveness and safety. *J Clin Psychopharmacol*. 2010;30(3):225–229.