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The Role of Benzodiazepines in the Treatment of Posttraumatic Stress Disorder (PTSD)

Benzodiazepines were introduced in the 1960's to replace barbiturates, which were effective as sedatives but were dangerous in overdosage and often abused. The stress-reducing and sedating properties of benzodiazepines made them seemingly an ideal drug to manage anxiety and insomnia symptoms and they became useful in addressing other clinical states such as epilepsy, spasmodic disorders, alcohol withdrawal, and anesthesia. Benzodiazepines rapidly became the most widely used of all psychotropic drugs; during the last 25 years it has been estimated that over 500 million people have taken a course of benzodiazepine treatment. Historically benzodiazepines were the primary posttraumatic stress disorder (PTSD) treatment agent and their anxiety-reducing properties made them seem to be a model medication for the management of symptoms related to PTSD. Soon after the development of benzodiazepines, however, reports began to appear about potential withdrawal symptoms and risks of tolerance and dependence, which contributed to the continued controversy surrounding their use (for a historical review, see Lader, 2011).

Current Recommendations Regarding Benzodiazepine Use in PTSD

The 2010 revised version of the U.S. Department of Veterans Affairs (VA) and the U.S. Department of Defense (DoD) Clinical Practice Guideline (CPG) for the management of PTSD established evidence-based psychotherapy and pharmacotherapy recommendations that promote quality care for Veterans with PTSD (VA, 2010). Beyond recommended treatments, the guideline cautioned providers against the use of benzodiazepines to

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manage PTSD due to a lack of efficacy data and growing evidence for the potential risk of harm. The research, however, supporting this recommendation is sparse. Currently, no data support the efficacy of benzodiazepines for the treatment of what is considered "core" PTSD symptoms such as avoidance, hyperarousal, numbing, or dissociation. However, they have been commonly prescribed, presumably to manage secondary symptoms of PTSD such as insomnia and anxiety due to their rapid short-term symptomatic relief. Recent work suggests that despite the recommendation against their use, prescribing of benzodiazepines for Veterans with PTSD remains above 30% in the VA, suggesting a gap between guideline recommendations and actual clinical care (Lund, Bernardy, Alexander, and Friedman, 2012). Because of renewed interest in policies regarding benzodiazepine use and the growing population of Veterans with PTSD seeking treatment, the topic presents a significant opportunity for improvement in the quality of clinical care.

More recently with the development of newer and safer medications such as the serotonin-selective reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitors (SNRIs), as well as a change in treatment recommendations for anxiety disorders that promotes the use of SSRIs over benzodiazepines in conjunction with cognitive-behavioral therapy (CBT), the debate about the continued use of benzodiazepines has reopened (Cloos, 2010). In Europe the chronic use of benzodiazepines has become a public health issue and has led to numerous campaigns to decrease their use (Lader, 2011). Some clinicians think that by allowing patients to take benzodiazepines only on an

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as-needed basis, they can avoid the physiological dependence associated with them. This practice is not supported by available data and actually can lead to fluctuating blood levels that can worsen anxiety and cognitive impairment (Cloos, 2010). However, in the United States most experts agree that the risk-benefit ratio for short-term use (2 to 4 weeks) remains positive in many patients but is not supported beyond that period of time due to the risk of dependence. A series of adverse effects continue to cause concern regarding benzodiazepine use that includes cognitive effects and psychomotor impairment as well as rebound anxiety and rebound insomnia. Unfortunately data regarding the safe duration of benzodiazepine maintenance therapy are scarce. Benzodiazepines are also commonly used adjunctively with SSRIs and many clinicians believe that they provide benefits in terms of both speed of response as well as overall response (Lader, 2011). In large part, the problem is that at a 3 to 4 week point, the patient typically feels better, has improved sleep and attributes the improvement to the benzodiazepines and not the SSRI. Consequently, the patient does not want to give the benzodiazepines up.

Studies Examining Benzodiazepine Efficacy

Both animal and human work suggests that benzodiazepines may interfere with the extinction of fear conditioning or potentiate the acquisition of fear responses, actually worsening recovery from trauma and interfering with one of our first-line recommended PTSD psychotherapies, prolonged exposure therapy (VA PTSD CPG). The two clinical trials of benzodiazepines to treat PTSD had negative findings: one with alprazolam showed no benefit in alleviating PTSD symptoms compared with placebo (Braun, Greenberg, Dasberg, and Lerer, 1990). Importantly, the slight reduction in anxiety symptoms was offset by withdrawal effects after only five weeks on the medication. The other compared clonazepam with placebo for PTSD-related sleep dysfunction and found no difference between benzodiazepine and placebo treatments (Cates, Bishop, Davis, Lowe, and Woolley, 2004). Although small, this study is important because the treatment of sleep impairment in PTSD is often a reason for the use of benzodiazepines. It is estimated that approximately 64% of returning Veterans endorse insomnia (Amin, Parisi, Gold, and Gold, 2010) and efforts to address appropriate sleep care is prominent now in the VA. Although benzodiazepines are the most widely prescribed sleep medication, evidence for their effect on sleep disturbances in PTSD is generally disappointing with changes in sleep architecture noted and poor sleep overall (Lader, 2011).

There are subgroups of patients where the use of benzodiazepines is of particular concern and this suggests a potential area to target to reduce their use. Two common and frequently under-diagnosed comorbidities among Veterans with PTSD include substance use disorders and mild traumatic brain injury. Both of these are contraindications to benzodiazepine use (VA, 2010). Indeed, the CPG cautions that benzodiazepines should be used especially cautiously in combat Veterans with PTSD because of the high comorbidity of combat-related PTSD with alcohol misuse and substance use disorders (upwards of 50% of comorbidity) and potential problems with tolerance and dependence. Another vulnerable subgroup is the elderly. Benzodiazepines have been associated with increased risk of accidents, fractures and falls, and there are also concerns about the cognitive effects of benzodiazepines in the elderly; a cognitive “slowness” that can be difficult to differentiate from cognitive decline (Lader, 2011).

Recent work has noted, however, that all psychotropic medications including SSRIs and atypical antipsychotics are associated with increased risks of falling in the elderly so policies that promote movement from benzodiazepines to SSRIs are not necessarily a safer alternative (Lader, 2011). Another group of concern is composed of Veterans who are on opiates for chronic pain and also on a benzodiazepine, a combination that is particularly toxic and associated with an increased risk of adverse clinical outcomes (Seal et al., 2012). This makes it all the more important that the use of medication management be given careful consideration in these subgroups and that evidence-based cognitive-behavioral therapies be more widely disseminated including those aimed specifically at the treatment of insomnia and chronic pain.

Research Using National VA Administrative Data

Recent work has focused on characterizing benzodiazepine prescribing trends in the VA for Veterans with PTSD over the last decade. Using VA administrative data, investigators identified Veterans who were diagnosed with PTSD (primary or secondary diagnosis) and who used VA inpatient and outpatient healthcare services (Lund et al., 2012). The investigators examined outpatient prescriptions for all Veterans with PTSD including first line-recommended antidepressants, benzodiazepines, atypical antipsychotics, as well as prazosin, an inexpensive alpha-1 blocker used to treat hypertension and considered by the CPG to have some benefit for targeting PTSD-related sleep problems and nightmare symptoms (Bernardy, Lund, Alexander, and Freidman, 2012).

The research noted that the number of Veterans being treated for PTSD in the VA healthcare system increased nearly three-fold, from 171,000 in 1999 prior to the wars in Afghanistan and Iraq to 498,000 in 2009. The majority of these Veterans (80%) received one of the medications recommended in the CPG for the treatment of this disorder (Bernardy et al., 2012). The proportion of Veterans receiving either of the two CPG-recommended first-line pharmacotherapy treatments for PTSD, SSRIs and SNRIs, increased from 50% in 1999 to 59% in 2009, and there was also a reduction in benzodiazepine prescriptions from 37% in 1999 to 30% in 2009 (Lund et al., 2012). The decrease in benzodiazepine prescribing to 30% is encouraging yet the frequency of use remains high and suggests that minimizing benzodiazepine exposure is a vital policy issue for the VA. Additionally, the work confirmed that sleep concerns continue to be a major factor in PTSD treatment. Non-benzodiazepine hypnotic drug prescribing tripled when zolpidem was added to the VA national formulary in 2008. Prazosin use increased more than six-fold to 9% in 2009, suggesting it is now more widely prescribed to Veterans with PTSD across the country. The results of a large VA cooperative clinical trial of prazosin will soon be released and will help inform the field if prazosin should be more widely used in the management of PTSD.

Although higher rates of benzodiazepine use are associated with PTSD; little is known about the patient-specific factors associated with the increased benzodiazepine use among Veterans. Additional work has now identified explicit patient and facility factors influencing benzodiazepine prescribing in the VA [10]. At the patient level the following characteristics were independently associated with benzodiazepine use: female gender, age > 30 years, rural residence, service connection > 50%, Vietnam-era service, an increased duration of PTSD diagnosis and a comorbid anxiety disorder.

Additional analyses, however, for these patient factors found that they accounted for less than 1% of prescribing variation refuting prescribers' suggestions that "their patients are different." It was the medical center characteristics that were independently associated with higher use and included clinics with lower PTSD volume, higher rates of duplicate prescribing (concurrent use of more than one drug from a class), and lower rates of trazodone prescribing (Lund, Bernardy, Vaughn-Sarrazin, Alexander, and Friedman, in press). These findings suggested that interventions could be designed to target individual high-volume prescribers or influence prescribing culture at the medical center level to improve access to guideline concordant PTSD treatment across VA. When gender comparisons were made, women Veterans with PTSD were more likely than men to receive medications across all classes of drugs except prazosin. The most notable gender disparity in prescribing involved benzodiazepines: prescriptions decreased for men 7% over the 10-year study period but increased for women over 5% (Bernardy et al., in press). This finding held even after controlling for co-occurring disorders in women Veterans where benzodiazepines might be indicated and were particularly noted in women with a co-occurring substance use disorder. Thus, a number of specific factors for a targeted intervention to reduce prescribing of benzodiazepines in PTSD have been identified through this body of work.

Conclusions

There is a tremendous need for research to find new medications to manage PTSD. The two currently recommended first-line agents both work on the same serotonin neurotransmitter system and are estimated to help only about half the people who take them. Practical problems have existed with the use of benzodiazepines for over 50 years now but they continue to be widely prescribed in PTSD patients. However, since the use of these medications is now being questioned in anxiety disorders where they previously were indicated, mounting evidence suggests that the long-term harms imposed by benzodiazepine use outweigh any short-term symptomatic benefits in patients with PTSD. Similar to the culture change in psychotherapy that saw movement from supportive group treatment to evidence-based cognitive behavioral psychotherapies, alternative treatments including the increased use of safer medications and evidence-based nonpharmacologic therapies should be actively promoted and made more widely available.

FEATURED ARTICLES

Amin, M.M., Parisi, J.A., Gold, M.S., and Gold, A.R. (2010). **War-related illness symptoms among Operation Iraqi Freedom/Operation Enduring Freedom returnees.** *Military Medicine*, 175, 155-157.

Objective: To determine the pattern of war-related illness (WRI) symptoms among returnees of Operation Iraqi Freedom/ Operation Enduring Freedom (OIF/OEF) living on Long Island, NY. **Method:** We conducted an anonymous mail survey of WRI symptoms of a random cohort of 786 returnees (718 male, 68 female) living on Long Island from among 5,500 who registered with the OIF/OEF Registry. **Results:** From among the 786 returnees whom we surveyed, we subsequently excluded 111 whose surveys were either returned unopened or who changed address. Two hundred seventy-four of the remaining 675 returnees responded to the survey (a 41% response rate). Disabling WRI symptoms were documented in approximately 2/3 of the responders and 75% of these responders had two or more symptoms.

Conclusions: War-related illness symptoms are very common among OIF/OEF returnees suggesting the need for management strategies targeting their symptoms. Military conflicts have produced war-related illness (WRI) among our troops and Veterans since the Civil War. Common to all these WRIs are a group of symptoms including body pain, fatigue, headache, sleep disturbance, diarrhea, forgetfulness, and impaired concentration. Also common to them is the absence of a discernable pathophysiology. Because WRI is poorly understood, we cannot prevent new occurrences with each new engagement of our armed forces.

Bernardy, N.C., Lund, B.C., Alexander, B., Jenkyn, A.B., Schnurr, P.P., & Friedman, M.J. (In Press). **Gender differences in prescribing among Veterans diagnosed with posttraumatic stress disorder** *Journal of General Internal Medicine*. **Objective:** VA and DoD issued a revised PTSD CPG in 2010 with specific pharmacotherapy recommendations for evidence-based quality care. The authors examined prescribing frequencies over an 11-year period prior to the release of the new guideline to determine gender differences in pharmacotherapy treatment in Veterans with PTSD. **Method:** National administrative VA data from 1999 through 2009 were used to identify Veterans with PTSD using ICD-9 codes extracted from inpatient discharges and outpatient clinic visits. Prescribing of antidepressants, antipsychotics and hypnotics was determined for each year using prescription drug files. **Results:** Women were more likely than men to receive medication across all classes except prazosin where men had higher prescribing frequency. The proportion of women receiving either of the first-line pharmacotherapy treatments for PTSD, selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI), increased from 56.4% in 1999 to 65.7% in 2009, higher rates than seen in men (49.2% to 58.3%). Atypical antipsychotic prescriptions increased from 14.6% to 26.3% and nonbenzodiazepine hypnotics increased from 3.8% to 16.9% for women, higher frequencies than seen in men in both medications (OR=1.31, 1.43 respectively). The most notable gender discrepancy was observed for benzodiazepines where prescriptions decreased for men (36.7% in 1999 to 29.8% in 2009) but steadily increased for women from 33.4% to 38.3%. **Conclusions:** A consistent pattern of increased prescribing of psychotropic medications among women with PTSD was seen compared to men. Prescribing frequency for benzodiazepines showed a marked gender difference with a steady increase for women despite guideline recommendations against use and a decrease for men. Common co-occurring disorders and sleep symptom management are important factors of PTSD pharmacotherapy and may contribute to gender differences seen in prescribing benzodiazepines in women but do not fully explain the apparent disparity.

Bernardy, N.C., Lund, B.C., Alexander, B., & Friedman, M.J. (2012). **Prescribing trends in Veterans with posttraumatic stress disorder.** *Journal of Clinical Psychiatry*, 73, 297-303. doi: 10.4088/JCP.11m07311. **Objective:** The revised VA and DoD CPG for Management of Post-Traumatic Stress recommends against long-term use of benzodiazepines to manage PTSD. An analysis of recent trends among Veterans receiving care for PTSD in the VA noted a decreasing proportion receiving benzodiazepines. The authors examined prescribing patterns for other medications to better understand the general context in which the changes in benzodiazepine prescribing have occurred in the VA.

Method: Administrative VA data from fiscal years 1999 through 2009 were used to identify Veterans with PTSD using ICD-9 codes extracted from inpatient discharges and outpatient encounters. Prescribing of antidepressants, antipsychotics, and hypnotics was determined for each fiscal year using prescription drug files. *Results:* The proportion of Veterans receiving either of the 2 Clinical Practice Guideline-recommended first-line pharmacotherapy treatments for PTSD, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, increased from 49.7% in 1999 to 58.9% in 2009. In addition to reduced benzodiazepine prescriptions, the overall frequency of antipsychotic use declined 6.1%, from 20.0% in 1999 to 13.9% in 2009. Nonbenzodiazepine hypnotic prescribing tripled when zolpidem was added to the VA national formulary in 2008. Buspirone prescribing decreased steadily, while prazosin prescribing expanded nearly 7-fold. *Conclusions:* This work highlights several clinically important trends in prescribing over the past decade among Veterans with PTSD that are generally consistent with the revised VA/DoD CPG recommendations. However, the findings illustrate the limitations of administrative data and point to a need to supplement this work with a qualitative examination of PTSD prescribing from interviews with providers to better understand the strategies used to make medication management decisions.

Braun, P., Greenberg, D., Dasberg, H., & Lerer, B. (1990). **Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment.** *Journal of Clinical Psychiatry, 51*, 236-238. *Objective:* To report a random-assignment, double-blind crossover trial comparing alprazolam and placebo in PTSD. *Method:* Ten patients fulfilling DSM-III criteria for PTSD completed 5 weeks of treatment on each agent. *Results:* Improvement in anxiety symptoms was significantly greater during alprazolam treatment but modest in extent. *Conclusions:* Symptoms specific to PTSD were not significantly altered. The impact of nonspecific symptomatic effects on the outcome of drug trials in PTSD is considered.

Cates, M.E., Bishop, M.H., Davis, L.L., Lowe, J.S., & Woolley, T.W. (2004). **Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder.** *Annals of Pharmacotherapy, 38*, 1395-1399. doi: 10.1345/aph.1E043. *Background:* Clonazepam is widely used for the treatment of PTSD-related sleep disturbances despite very limited published data supporting its use for this indication. *Objective:* We conducted a pilot-controlled trial to provide more data on this clinical practice and lay the foundation for more definitive studies. *Method:* The study was designed as a randomized, single-blind (i.e., patient only), placebo-controlled, crossover clinical trial involving administration of clonazepam 1 mg at bedtime for one week followed by 2 mg at bedtime for one week. The following week served as a washout period before the alternate treatment was begun. Patients completed sleep diaries each morning upon awakening throughout the study. Parameters included quantity of sleep, quality of sleep, frequency and intensity of difficulty falling or staying asleep, and frequency and intensity of recurrent distressing dreams. *Results:* Six patients with combat-related PTSD participated in the study. There were no statistically significant differences between clonazepam and placebo for any measure, although clonazepam therapy resulted in mild to moderate numeric improvements in difficulty falling or staying asleep.

Adverse effects of clonazepam were generally mild and essentially indiscernible from those attributed to placebo. Only one patient elected to receive further treatment with clonazepam at the conclusion of the trial. *Conclusions:* Clonazepam therapy was largely ineffective in improving sleep disturbances, particularly nightmares, associated with combat-related PTSD. The small sample size was a significant limitation of this study, but the prospective design and single-blind, placebo-control parameters were strengths. Further studies are needed to further define the role of this widespread clinical practice.

Cloos, J.M. (2010). **Benzodiazepines and addiction: Myths and realities (Part 1).** *Psychiatric Times (July) 26-29.* www.ama.lu/docs/Psytimes_part1.pdf. *Background:* The advent of benzodiazepines in the 1960s and their use in a variety of neuropsychiatric conditions allowed the discontinuation of potentially lethal and addicting barbiturates. The myorelaxing and anticonvulsive effects of benzodiazepines benefit patients with epilepsy or spasmodic disorders. Their anxiolytic and hypnotic properties make benzodiazepines the treatment of choice for insomnia and anxiety problems. These agents are also used in alcohol withdrawal and in anesthesia. Benzodiazepines have low toxicity if they are not combined with other respiratory depressors, and they have a favorable adverse-effect profile. However, soon after the first benzodiazepine, chlordiazepoxide (Librium), came into use in 1960, reports appeared about withdrawal symptoms and a potential risk of dependence. Diazepam (Valium), introduced in 1963, was much more potent than its predecessor and became the most prescribed drug in the United States in the 1970s. Yet, its potential for abuse and increased tolerance (necessitating dosage escalations) were also frequently discussed in the scientific literature and in popular media (e.g., the 1966 Rolling Stones' song, "Mother's Little Helper"). In the early 1980s, the dangers of benzodiazepines were described in Barbara Gordon's autobiography, *I'm Dancing as Fast as I Can*, which became a bestseller and was made into a movie. The positive attitude toward benzodiazepines started to decline, which gave rise to the prescription controversy. This article will appear in two parts. Here the focus is on the use of benzodiazepines for anxiety disorders and sleep problems. It also discusses their use in substance abusers and in elderly patients. In part 2, considerations related to long-term use of and withdrawal from benzodiazepine therapy will be emphasized.

Department of Veterans Affairs (2010). **VA/DoD clinical practice guideline for posttraumatic stress disorder.** [October 4, 2012]; www.healthquality.va.gov/Post_Traumatic_Stress_Disorder_PTSD.asp. *Background:* This 2010 VA/DoD Post-Traumatic Stress Guideline update builds on the 2004 VA/DoD CPG for the Management of Post-Traumatic Stress. The 2004 Post-Traumatic Stress Guideline was the first effort to bring evidence-based practice to clinicians providing care to trauma survivors and patients with stress disorders in the VA and DoD. The development of the Guideline originated with recognition of the need to diagnose and treat posttraumatic stress among the military and veteran population. The Guideline presented evidence-based recommendations that were thoroughly evaluated by practicing clinicians and reviewed by clinical experts from the Veterans Health Administration (VHA) and DoD.

Lader, M.H. (2011). **Benzodiazepines revisited—will we ever learn?** *Addiction*, 106, 2086-2109. doi: 10.1111/j.1360-0443.2011.03563.x.

Aim: To re-examine various aspects of the benzodiazepines, widely prescribed for 50 years, mainly to treat anxiety and insomnia. It is a descriptive review based on the Okey Lecture delivered at the Institute of Psychiatry, King's College London, in November 2010. **Methods:** A search of the literature was carried out in the Medline, Embase and Cochrane Collaboration databases, using the code word 'benzodiazepine(s),' alone and in conjunction with various terms such as 'dependence,' 'abuse,' etc. Further hand-searches were made based on the reference lists of key papers. As 60,000 references were found, this review is not exhaustive. It concentrates on the adverse effects, dependence and abuse. **Results:** Almost from their introduction the benzodiazepines have been controversial, with polarized opinions, advocates pointing out their efficacy, tolerability and patient acceptability, opponents deprecating their adverse effects, dependence and abuse liability. More recently, the advent of alternative and usually safer medications has opened up the debate. The review noted a series of adverse effects that continued to cause concern, such as cognitive and psychomotor impairment. In addition, dependence and abuse remain as serious problems. Despite warnings and guidelines, usage of these drugs remains at a high level. The limitations in their use both as choice of therapy and with respect to conservative dosage and duration of use are highlighted. The distinction between low-dose 'iatrogenic' dependence and high-dose abuse/misuse is emphasized.

Conclusions: The practical problems with the benzodiazepines have persisted for 50 years, but have been ignored by many practitioners and almost all official bodies. The risk-to-benefit ratio of the benzodiazepines remains positive in most patients in the short term (2 to 4 weeks) but is unestablished beyond that time, due mainly to the difficulty in preventing short-term use from extending indefinitely with the risk of dependence. Other research issues include the possibility of long-term brain changes and evaluating the role of the benzodiazepine antagonist, flumazenil, in aiding withdrawal.

Lund, B.C., Bernardy, N.C., Alexander, B., & Friedman, M.J. (2012). **Declining benzodiazepine use in Veterans with posttraumatic stress disorder.** *Journal of Clinical Psychiatry*, 73, 292-296. doi: 10.4088/JCP.10m06775.

Objective: Clinical practice guidelines issued by the VA and the DoD caution against benzodiazepine use among Veterans with 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.

Lund, B.C., Bernardy, N.C., Vaughan-Sarrazin, M., Alexander, B., & Friedman, M.J. (In Press). **Patient and facility characteristics associated with benzodiazepine prescribing for Veterans with PTSD.** *Psychiatric Services*. doi: 10.1176/appi.ps.201200267.

Objective: Practice guidelines used in the Veterans Health Administration (VHA) caution against benzodiazepine use by Veterans with PTSD because of inefficacy and safety concerns. Although use has declined, the VHA prescription rate is ≥30% nationally. To inform intervention design, this study examined patient- and facility-level correlates of benzodiazepine prescribing. **Methods:** This cross-sectional study used 2009 national administrative VHA data to identify Veterans with PTSD, benzodiazepine prescriptions, and various patient and facility characteristics. Correlates of benzodiazepine prescribing were determined with multivariable hierarchical logit models. **Results:** Among 137 VHA facilities, 495,309 Veterans with PTSD were identified, and 150,571 (30.4%) received a benzodiazepine prescription. Patient characteristics independently associated with benzodiazepine use included female gender, age ≥30 years, rural residence, service-connected disability ≥50%, Vietnam-era service, duration of PTSD diagnosis, and a comorbid anxiety disorder. However, case-mix adjustment for these variables accounted for <1% of prescribing variation. Facility characteristics independently associated with higher use included lower PTSD visit volume, higher rates of duplicate prescribing (concurrent use of more than one drug from a class), and lower rates of trazodone prescribing. These findings were corroborated in replication analyses.

Conclusions: The ultimate goal is to ensure consistent access to guideline-concordant PTSD treatment across the VHA. This study furthered this objective by identifying characteristics associated with benzodiazepine prescribing. Findings suggest that interventions could be designed to target individual high-volume prescribers or influence prescribing culture at the facility level.

Seal, K. H., Shi, Y., Cohen, G., Cohen, B. E., Maguen, S., Krebs, E. E., et al. (2012). **Association of mental health disorders with prescription opioids and high-risk opioid use in US Veterans of Iraq and Afghanistan.** *Journal of the American Medical Association*, 307, 940-947. doi: 10.1001/jama.2012.234.

Background: Record numbers of Iraq and Afghanistan Veterans survive their war injuries and yet continue to experience pain and mental health problems, particularly PTSD. Little is known about the association of mental health disorders and prescription opioid use. **Objective:** To investigate the effect of mental health disorders, particularly PTSD, on risks and adverse clinical outcomes associated with prescription opioid use. **Design:** Retrospective cohort study involving 141,029 Iraq and Afghanistan Veterans who received at least 1 non-cancer-related pain diagnosis within 1 year of entering the VA health care system from October 1, 2005, through December 31, 2010. **Main Outcome Measures:** Independent association of mental health disorders and the prescription of opioids, higher risk opioid use, and adverse clinical outcomes (eg, accidents and overdose) within 1 year of receiving a pain-related diagnosis. **Results:** A total of 15,676 Veterans were prescribed opioids within 1 year of their initial pain diagnosis.

FEATURED ARTICLES *continued*

Compared with 6.5% of Veterans without mental health disorders, 17.8% (adjusted relative risk [RR], 2.58; 95% CI, 2.49-2.67) of Veterans with PTSD and 11.7% (adjusted RR, 1.74; 95% CI, 1.67-1.82) with other mental health diagnoses but without PTSD were significantly more likely to receive opioids for pain diagnoses. Of those who were prescribed pain medication, Veterans with PTSD were more likely than those without mental health disorders to receive higher-dose opioids (22.7% vs. 15.9%, adjusted RR, 1.42; 95% CI, 1.31-1.54), receive 2 or more opioids concurrently (19.8% vs. 10.7%, adjusted RR, 1.87; 95% CI, 1.70-2.06), receive sedative hypnotics concurrently (40.7% vs. 7.6%, adjusted RR, 5.46; 95% CI, 4.91-6.07), or obtain early opioid refills (33.8% vs. 20.4%; adjusted RR, 1.64; 95% CI, 1.53-1.75). Receiving prescription opioids was associated with an increased risk of adverse clinical outcomes for all Veterans (9.5% vs. 4.1%; RR, 2.33; 95% CI, 2.20-2.46), which was most pronounced in Veterans with PTSD. *Conclusions:* Among U.S. Veterans of Iraq and Afghanistan, mental health diagnoses, especially PTSD, were associated with an increased risk of receiving opioids for pain, high-risk opioid use, and adverse clinical outcomes.

ADDITIONAL CITATIONS

Abrams, T. E., Lund, B. C., Bernardy, N. C., & Friedman, M. J. (In Press). **Aligning clinical practice to PTSD treatment guidelines: Medication prescribing by provider type.** *Psychiatric Services*. doi: 10.1176/appi.ps.201200217. *Objective:* Veterans with PTSD are frequently prescribed psychiatric medications that are currently not supported by a guideline developed by the VA and DoD. To better understand this practice, this study examined prescribing frequencies for three classes of psychiatric medications and the proportion of prescribing attributable to various provider types. *Method:* This cross-sectional study analyzed fiscal year 2009 electronic pharmacy data from the VHA for 356,958 Veterans with PTSD who were receiving medications from VHA prescribers. Veterans had at least one VHA encounter with a diagnostic code of PTSD and evidence of continuous medication use. Medications of interest were SSRIs/SNRIs, second-generation antipsychotic medications, and benzodiazepines. Analyses described the proportion of prescribing attributable to mental health care providers and primary care providers for each medication class. *Results:* In 2009, among all Veterans with PTSD who had continuous VA medication use, 65.7% were prescribed SSRI/SNRIs, and 70.2% of this prescribing was attributable to mental health care providers. Second-generation antipsychotics were prescribed for 25.6% of these Veterans, and 80.2% of the prescribing was attributable to mental health care providers. Benzodiazepines were prescribed for 37.0% of the sample, and 68.8% of the prescribing was attributable to mental health care providers. *Conclusions:* The findings indicate that Veterans with PTSD were frequently prescribed medications not supported by existing guidelines. Most of these prescriptions were written by mental health care providers. Interventions to align prescribing with PTSD treatment guidelines should emphasize provider type.

ADDITIONAL CITATIONS *continued*

Cascade, E & Kalali, A.H. (2008). **Use of benzodiazepines in the treatment of anxiety.** *Psychiatry*, 2008, 5, 21-22. www.ncbi.nlm.nih.gov/pmc/articles/PMC2687085/. *Background:* We examined the role of benzodiazepines in the treatment of anxiety by both psychiatrists and primary care physicians. Over the past year, 112.8 million prescriptions were filled for a benzodiazepine: 55% were prescribed by a primary care physician, 16% by a psychiatrist, and the remaining 29% of prescriptions by another type of specialty physician. Benzodiazepine monotherapy is much more common in the treatment of anxiety by primary care physicians (42%) than psychiatrists (22%). Even when both benzodiazepine monotherapy and combination regimens are considered, total benzodiazepine use remains slightly greater in primary care than psychiatry (51% vs. 42%).

Cloos, J.M. & Ferreira, V. (2008). **Current use of benzodiazepines in anxiety disorders.** *Current Opinion in Psychiatry*, 22, 90-95. doi: 10.1097/YCO.0b013e32831a473d. *Purpose of Review:* The aim of this study is to provide a review of articles published between July 2007 and August 2008 on the current use and rationale of benzodiazepines in anxiety disorders. *Recent Findings:* Recent review articles confirm selective serotonin reuptake inhibitors as first-choice drugs for treating anxiety disorders, alongside newer agents such as pregabalin or serotonin-norepinephrine reuptake inhibitors, and combined with cognitive-behavioral therapy. Benzodiazepines are still widely used by clinicians for these disorders, as shown by recent surveys, even though their anxiolytic effectiveness is questioned. Newer agents are in development and may in the future resolve the therapeutic dilemma. *Summary:* Despite current guidelines, benzodiazepines are still considered by many clinicians to remain good treatment options, in both the acute and the chronic phase of the treatment of anxiety disorders, partially because of their rapid onset of action and their efficacy with a favorable side effect profile, and also because of the sometimes only incomplete therapeutic response and the emergence of side effects of alternative medications. Having experienced good initial symptom relief with benzodiazepine treatment, patients may also be reluctant to taper it down. Clinicians should, however, bear in mind the frequent physiological dependence associated with these substances, and suggest both pharmacological and psychological treatment alternatives before opting for a long-term benzodiazepine treatment, which may remain necessary in certain clinical conditions.

Cook, J.M., Biyanova, T., Thompson, R., & Coyne, J.C. (2007). **Older primary care patients' willingness to consider discontinuation of chronic benzodiazepines.** *General Hospital Psychiatry*, 29, 396-401. doi: 10.1016/j.genhosppsych.2007.07.001. *Objective:* To examine factors related to older primary care patients' willingness to consider tapering/discontinuation of long-term benzodiazepine use. *Method:* Forty-six long-term anxiolytic benzodiazepine users, aged 61 to 95 years, were assessed over the telephone using a semi-structured qualitative interview and standardized self-report questionnaires for anxiety (Beck Anxiety Inventory), sleep quality (Pittsburgh Sleep Quality Index), depression (Center for Epidemiological Studies Depression Scale), psychological dependence on benzodiazepines (Severity of Dependence Scale), and anxiety sensitivity (Anxiety Sensitivity Index). *Results:* Frequency of daily benzodiazepine intake and anxiety sensitivity significantly contributed to willingness to attempt taper/discontinuation of benzodiazepines. *Conclusions:* Many older long-term benzodiazepine

users and their physicians perceive tapering of use an arduous, low priority, time-intensive task. These findings highlight factors that can help identify a subpopulation of older patients who may be easier to engage in the discontinuation process.

Cook, J.M., Marshall, R., Masci, C., & Coyne, J.C. (2007).

Physicians' perspectives on prescribing benzodiazepines for older adults: A qualitative study. *Journal of General Internal Medicine*, 22, 303-307. doi: 10.1007/s11606-006-0021-3.

Background: There is a continued high prevalence of benzodiazepine use by older community-residing adults and of their continued prescription by practitioners, despite well known adverse effects and the availability of safer, effective alternatives. **Objective:** To understand factors influencing chronic use of benzodiazepines in older adults. **Design:** Qualitative study, semi-structured interviews with physicians. **Participants:** Thirty-three practicing primary care physicians around Philadelphia. **Approach:** Qualitative interviews were audiotaped, transcribed, and entered into a qualitative software program. A multidisciplinary team coded transcripts and developed themes. **Results:** Physicians generally endorsed benzodiazepines as effective treatment for anxiety, citing quick action and strong patient satisfaction. The use of benzodiazepines in older adults was not seen to be problematic because they did not show drug-seeking or escalating dose behavior suggesting addiction. Physicians minimized other risks of benzodiazepines and did not view monitoring or restricting renewal of prescriptions as an important clinical focus relative to higher-priority medical issues. Many physicians expressed skepticism about risks of continued use and considerable pessimism in the successful taper/discontinuation in older patients with long-term use and prior failed attempts. Physicians also anticipated patient resistance to any such efforts, including switching physicians. **Conclusions:** Primary care physicians are averse to addressing the public health problem of benzodiazepine overuse in the elderly. Their attitudes generally conflict with practice guidelines and they complain of a lack of training in constructive strategies to address this problem. A two-pronged effort should focus on increasing skill level and preventing new cases of benzodiazepine dependency through improved patient education and vigilant monitoring of prescription renewal.

Ennaceur, A., Michalikova, S., Van Rensburg, R. & Chazot, P.L.

(2008). **Are benzodiazepines really anxiolytic? Evidence from a 3D maze spatial navigation task.** *Behavioural Brain Research*, 188, 136-153. doi: 10.1016/j.bbr.2007.10.026. **Background:** The effects of diazepam and chlordiazepoxide were assessed in a 3D maze which is a modification of an 8-arm radial maze. Each arm of the maze is attached to a bridge radiating from a central platform. Animals exposed for the first time to the maze do not venture beyond the line that separate a bridge from an arm. The prime criteria set for an anxiolytic effect is whether mice would increase the frequency of entries onto arms and increase arm/bridge entries ratio. C57 mice readily cross the line on first exposure and make more than 8 arm visits onto arms on second exposure, while other strains (CD-1 and Balb/c) hold back and rarely cross the line on first exposure and require more sessions to make more than 8 arm entries. An anxiolytic drug is expected to encourage intermediate (CD-1) and high (Balb/c) anxiety mice to adventure onto the arms of the maze and make more visits to the arms to comparable levels seen with low anxiety c57 mice. In the present report, administration of different doses of

diazepam (0.625, 1.25, 2.5, and 5 mg kg(-1) i.p.) and chlordiazepoxide (5, 10, and 15 mg kg(-1) i.p.) did not reduce anxiety in animals, with the lowest dose of diazepam increasing motor activity in Balb/c and increasing anxiety in c57 mice while the highest doses of both diazepam (2.5 and 5 mg kg(-1) i.p.) and chlordiazepoxide (15 mg kg(-1) i.p.) induced mild sedation. Our results raise some concerns about the methodological foundations in the current assessment of anxiety and anxiolytic compounds both in animal and human studies.

Hawkins, E.J., Malte, C.A., Imel, Z.E., Saxon, A.J., & Kivlahan, D.R. (2012). **Prevalence and trends of benzodiazepine use among Veterans Affairs patients with posttraumatic stress disorder, 2003-2010.** *Drug and Alcohol Dependence*, 124, 154-161. doi: 10.1016/j.drugalcdep.2012.01.003.

Background: Although the VA and DoD clinical guidelines for management of PTSD recommend against routine benzodiazepine use, little is known about the trends and clinical and prescription profiles of benzodiazepine use since these guidelines were released in 2004. **Method:** This retrospective study included 64,872 patients with a PTSD diagnosis received from care at facilities in VA Northwest Veterans Integrated Service Network (VISN 20) during 2003–2010. Annual prevalence of any use was defined as any prescription for benzodiazepines, and long-term use was defined as > 90 days supply, in a year. Gender-specific logistic regressions were fit to estimate any and long-term benzodiazepine use, test for linear trends over 8 years and explore factors associated with trends. **Results:** The trend of age-adjusted benzodiazepine use over 8 years rose significantly from 25.0 to 26.8% among men and 31.2 to 38.8% among women. Long-term use in men and women increased from 15.4 to 16.4% and 18.0 to 22.7%, respectively. Comorbid psychiatric and alcohol use disorders (AUD) were associated with a greater increase in long-term use of benzodiazepines. In 2010, 61% of benzodiazepine users received > 90 days supply. Among those prescribed benzodiazepines long-term, 11% had AUD and 47% were also prescribed opioids long-term. **Conclusions:** Despite VA/DoD clinical guidelines recommending against routine use of benzodiazepines for PTSD, the adjusted prevalence of long-term use increased among men and women with PTSD in VISN 20. Widespread concomitant use of benzodiazepines and opioids suggests risk management systems and research on the efficacy and safety of these medications are needed.

Hearon, B.A. & Otto, M.W. (2012). **Benzodiazepines.** In Stefan G. Hofman (Ed.) *Psychobiological approaches for anxiety disorders: Treatment combination strategies.* (pp. 25-39). Chichester, England: Wiley-Blackwell. **Background:** Benzodiazepines represent one of the most widely prescribed classes of medications for the treatment of anxiety disorders over the past 50 years (Macaluso et al., 2010). Their rapid onset of action and efficacy coupled with a reasonable side-effect profile has contributed to their use in both the acute and chronic phases of anxiety disorder treatment (Worthington et al., 1998; Davidson, 2004; Cloos and Ferreira, 2009). Yet some of the many benefits of benzodiazepine medication have been tempered by difficulties with discontinuing chronic treatment (Otto et al., 2002), as well as specific concerns about their use in combination with cognitive-behavior therapy (Otto et al., 2010a). These concerns include issues of impairment in learning, impairment in the retention of treatment effects, attribution of treatment gains, as well as medication discontinuation difficulties. [pp. 25, Text]

Hermos, J.A., Young, M.M., Lawler, E.V., Rosenbloom, D., & Fiore, L.D. (2007). **Long-term, high-dose benzodiazepine prescriptions in veteran patients with PTSD: Influence of preexisting alcoholism and drug-abuse diagnoses.** *Journal of Traumatic Stress, 20*, 909-914. doi: 10.1002/jts.20254. *Background:* Databases from the New England Veterans Integrated Service Network were analyzed to determine factors associated with long-term, high-dose anxiolytic benzodiazepine prescriptions dispensed to patients with PTSD and existing alcoholism and/or drug abuse diagnoses. Among 2,183 PTSD patients, 234 received the highest 10% average daily doses for alprazolam, clonazepam, diazepam, or lorazepam, doses above those typically recommended. Highest doses were more commonly prescribed to patients with existing drug abuse diagnoses. Among patients with PTSD and alcoholism, younger age, drug abuse, and concurrent prescriptions for another benzodiazepine and oxycodone/acetaminophen independently predicted high doses. Results indicate that for veteran patients with PTSD, alcoholism alone is not associated with high-dose benzodiazepines, but existing drug abuse diagnoses do increase that risk.

Kosten, T.R., Fontana, A., Sernyak, M.J., & Rosenheck, R. (2000). **Benzodiazepine use in posttraumatic stress disorder among Veterans with substance abuse.** *Journal of Nervous and Mental Disease, 188*, 454-459. *Background:* Veterans with PTSD and substance abuse may abuse benzodiazepines and develop violent dyscontrol when using them. A total of 370 Veterans were compared by substance abuse diagnosis (50%), benzodiazepine use (36%), and their interaction on 1-year outcomes after inpatient discharge. Substance abusers were less likely to be prescribed benzodiazepines (26% vs. 45%). No outcome showed a differential worsening by substance abuse or benzodiazepines, although some baseline differences were noted. Outpatient health care utilization was lower in benzodiazepine users (47 vs. 33 visits). Among PTSD patients with comorbid substance abuse, benzodiazepine treatment was not associated with adverse effects on outcome, but it may reduce health care utilization.

Marienfild, C.B., Tek, E., Diaz, E., Shottenfeld, R. & Chuwarski, M. (2012). **Psychiatrist decision-making towards prescribing benzodiazepines: The dilemma with substance abusers.** *Psychiatric Quarterly 83*, 521-529. doi: 10.1007_s11126-012-9220-8. *Background:* Psychiatrists' decision making about prescribing benzodiazepines was evaluated in a community mental health center. An anonymous survey of outpatient psychiatrists in an academic-affiliated public mental health center was conducted using a 45-item questionnaire developed based on the results of a previous study. Sixty-six percent of responses indicate that, at times, psychiatrists experienced requests for behaviors suspicious for abuse, including 'lost/missing prescriptions' and 'use of benzodiazepines by others.' Patient characteristics such as 'history of abuse,' 'unknown patient,' and 'patient use of illicit substances' were occasional or common reasons for NOT prescribing benzodiazepines (75 %). The most common contexts in which the majority of our sample was uncomfortable prescribing benzodiazepines involved a patient history of substance abuse, fear of initiation of dependence, diversion, and feeling manipulated by the patient. Time limitations were a dilemma for 20%. Psychiatrist self-reported dilemma and behavior in prescribing benzodiazepines largely reflected concerns with substance abuse and less frequently workload or time issues.

Martin, J.L.R., Sainz-Pardo, M., Furukawa, T.A., Martín-Sánchez, E., Seoane, T., & Galán, C. (2007). **Benzodiazepines in generalized anxiety disorder: Heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trials.** *Journal of Psychopharmacology 21*, 774-782. doi: 10.1177/0269881107077355. *Background:* No systematic review or meta-analysis using a hard outcome has been conducted on the role of benzodiazepines for generalized anxiety disorder. The objective of this study was to assess the effectiveness and efficacy of benzodiazepines in the treatment of generalized anxiety disorder based on trial drop-out rates. We used a systematic review of randomized controlled trials that compared any of the three best established benzodiazepines (diazepam, Lorazepam, and alprazolam) against placebo. Our primary outcome for effectiveness was withdrawal for any reason. Our secondary outcome tapping efficacy was withdrawal due to lack of efficacy, and that tapping side effects was withdrawals due to adverse events. We included 23 trials. Pooled analysis indicated less risk of treatment discontinuation due to lack of efficacy for benzodiazepines, compared to placebo, relative risk 0.29 (95% CI 0.18—0.45; $p < 0.00001$). Nevertheless, pooled analysis showed no conclusive results for risk of all-cause patient discontinuation, relative risk 0.78 (95% CI 0.62—1.00; $p = 0.05$). Meta-regression model showed that 74% of the variation in log relative risk across the studies was explained by year of publication ($p < 0.001$). This systematic review did not find convincing evidence of the short-term effectiveness of the benzodiazepines in the treatment of generalized anxiety disorder. On the other hand, for the outcome of efficacy, this review found robust evidence in favor of benzodiazepines. Due to the heterogeneity induced by year of publication, three hypotheses are plausible when it comes to being able to account for the differences between efficacy and effectiveness observed in the outcomes (publication bias, quality of the trial literature, and a nondifferential response to the placebo effect).

Mohamed, S. & Rosenheck, R.A. (2008). **Pharmacotherapy of PTSD in the U.S. Department of Veterans Affairs: Diagnostic- and symptom-guided drug selection.** *Journal of Clinical Psychiatry, 69*, 959-65. *Background:* Although increasing numbers of war Veterans are seeking treatment for PTSD at the VA, information on the role of psychotropic pharmacotherapy in their treatment has not been available. *Method:* Records of psychotropic prescriptions for all VA patients diagnosed with ICD-9 PTSD ($N = 274,297$) in fiscal year 2004 (October 1, 2003, to September 30, 2004) were examined. Descriptive statistics and multivariable logistic regression were used to identify veteran characteristics and measures of service use that were associated with receipt of any psychotropic medication and, among users of such medications, with use of each of three medication classes: antidepressants, anxiolytics/sedative-hypnotics, and antipsychotics. *Results:* Most Veterans diagnosed with PTSD received psychotropic medication (80%), and among these, 89% were prescribed antidepressants, 61% anxiolytics/sedative-hypnotics, and 34% antipsychotics. Greater likelihood of medication use was associated with greater mental health service use and comorbid psychiatric disorders. Among comorbidities, medication-appropriate comorbid diagnoses were the most robust predictors of use of each of the three medication subclasses, i.e., depressive disorders were associated with antidepressant use, anxiety disorders with anxiolytic/sedative-hypnotic use, and psychotic disorders with antipsychotic use. Use of anxiolytics/sedative-hypnotics and antipsychotics in the

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absence of a clearly indicated diagnosis was substantial. *Conclusions:* Diverse psychotropic medication classes are extensively used in the treatment of PTSD in the VA. While disease-specific use for both PTSD and comorbid disorders is common, substantial use seems to be unrelated to diagnosis and thus is likely to be targeted at specific symptoms (e.g., insomnia, anxiety, nightmares, and flashbacks) rather than diagnosed illnesses. A new type of efficacy research may be needed to determine symptom responses to psychotropic medications as well as disorder responses, perhaps across diagnoses.

Otto, M.W. & Pollack, M.H. (2009). *Stopping anxiety medication: Therapist guide. 2nd ed.* New York: Oxford University Press.

Background: This guide is written for mental health professionals with experience in the treatment of panic disorder. It provides session-by-session instructions for exposure-based cognitive-behavior therapy that can be presented in either an individual or group format. This program represents the minimal level of intervention we recommend for benzodiazepine discontinuation. [Abstract Adapted]

Viola, J., Ditzler, T., Batzer, W., Harazin, J., Adams, D., Lettich, L., et.al. (1997). **Pharmacological management of posttraumatic stress disorder: Clinical summary of a five-year retrospective study, 1990-1995.** *Military Medicine, 162*, 616-619. *Background:* Beginning in 1990, the Department of Psychiatry, Tripler Army Medical Center developed a formal treatment program for PTSD. Between 1990 and 1996, 632 patients, the vast majority of whom suffered from combat-related PTSD, were treated. Historically, many PTSD patients were treated with benzodiazepines, often in high dosages. The risks attendant to benzodiazepine management of PTSD, coupled with poor clinical outcome, prompted the staff to explore treatment alternatives. This paper describes the role of pharmacotherapy in the management of PTSD. The medications described in this paper have other primary uses in clinical practice (e.g., hypertension, insomnia, seizure control, depression, and anxiety). Medications were selected for use based on the putative modes of action and the degree of symptom relief. The therapeutic rationale was to decrease hyperarousal and sleep disturbance to permit the patients to engage in other psychotherapeutic efforts.

Zohar, J., Juven-Wetzler, A., Myers, V., & Fostick, L. (2008).

Posttraumatic stress disorder: Facts and fiction. *Current Opinion in Psychiatry, 21*, 74-77. *Purpose of Review:* This review provides an update on contemporary perspectives on PTSD and challenges myths about the disorder and its treatment. PTSD has recently attracted public attention because of the impact of international terrorism, although the vast majority of PTSD cases actually relate to civilian events such as car accidents, rape, and violent robbery. This disorder requires deeper understanding and consensus among professionals. *Recent Findings:* Advances have been made in elucidating the neurobiology of this disorder, partly by using an animal model of PTSD. Recent studies have focused on memory processes and the therapeutic role played by plasticity of the hypothalamic-pituitary-adrenal axis, and how this fits (or does not fit) in with the current therapeutic interventions. Guidelines have been established by various bodies in an attempt to streamline treatment options. *Summary:* Understanding of PTSD is incomplete. Future research should attempt to determine what treatments given during the 'window of opportunity' — the time from exposure until PTSD develops — are effective. Care should be taken not to interfere with spontaneous recovery.