TITLE: Benzodiazepines for the Treatment of Post Traumatic Stress Disorder: A Review of the Clinical Effectiveness and Guidelines

DATE: 07 December 2009

CONTEXT AND POLICY ISSUES:

Treatment goals of post-traumatic stress disorder (PTSD) include reduction of symptom severity, prevention or treatment of comorbid disorders, a reduction in functional impairment, prevention of relapse, and improvement quality of life.¹ A number of pharmacotherapies have been used to treat PTSD however response is often suboptimal.¹ For example, with the selective serotonin reuptake inhibitor antidepressants, 60% of PTSD sufferers may show a response to treatment but only 20% to 30% achieve remission.¹ This report will review the evidence for the use of benzodiazepines for the management of PTSD.

RESEARCH QUESTIONS:

1. What is the clinical effectiveness of benzodiazepines for the treatment of post traumatic stress disorder?
2. What are the guidelines regarding the use of benzodiazepines for the treatment of post traumatic stress disorder?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 3, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and November 2009. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, and guidelines.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, systematic reviews are presented first, followed by randomized controlled trials, and evidence-based guidelines.

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SUMMARY OF FINDINGS:

The search identified five systematic reviews, one RCT, and seven guidelines.

Systematic reviews and meta-analyses

The US Department of Veterans Affairs commissioned the Institute of Medicine to review the evidence on pharmacotherapies and psychotherapies for the treatment of PTSD.\(^2\) The report, published in 2008, contained a robust review of the available literature and explored issues related to PTSD research. A systematic search was conducted using multiple electronic databases for published English language studies of treatments for veterans with PTSD. Only data from RCTs were used to inform core questions of treatment efficacy. The authors stated that the variability of treatments, outcome measures, course of the disorder, and patient and provider preferences make other study designs unreliable when making causal inferences. A total of 37 studies were included in the review of drug therapies; only one (Braun 1990) included a benzodiazepine. This study showed alprazolam was ineffective in reducing overall symptoms of PTSD. The review authors stated the overall body of evidence on the use of benzodiazepines was scant and of low quality. They concluded that the evidence is inadequate to determine the efficacy of benzodiazepines in the treatment of PTSD.\(^2\)

The systematic review by Berger et. al. 2009\(^1\) evaluated pharmacotherapies other than antidepressants for persons with PTSD. They searched multiple databases for relevant studies in any language, and included case reports (minimum five cases), non-randomized, and randomized controlled studies. A total of 63 articles were included, three of which evaluated a benzodiazepine. The RCT by Braun et. al. (1990), enrolled 16 chronic PTSD sufferers in a 12-week cross-over study. Participants received alprazolam 1.5 mg to 6 mg per day or placebo for five weeks and then crossed over to the other treatment after a two week washout period. Alprazolam significantly alleviated anxiety symptoms (p value not reported) but overall, no statistically significant differences were detected in PTSD symptoms based on the revised Impact Event Scale. An open label study by Gelphin et. al. (1996) included 13 victims of recent trauma who received either clonazepam (mean 2.7 mg/day) or alprazolam (mean 2.5 mg/day) for PTSD prevention. Treated victims were compared to 13 matched controls who did not receive benzodiazepines (i.e. usual care). No differences were detected between groups after six months based on the Impact Event Scale or the Mississippi Rating Scale for Combat-related PTSD-civilian trauma version score. Nine people in the benzodiazepine group and three in the control group met the diagnostic criteria for PTSD after six months using the Clinician Administered PTSD Scale (CAPS). The third included study was an open trial by Mellman et. al. (2002) which evaluated temazepam for PTSD prevention in 22 patients following civilian trauma. The study found subjective sleep improved in the temazepam group during the seven day treatment period, but not over the six week follow-up period. Short term temazepam (15 to 30 mg per day for 7 days) did not prevent the development of PTSD at six weeks; 55% in the temazepam group and 27% in the control group met the diagnostic criteria for PTSD according to the CAPS. The systematic review authors graded the evidence for benzodiazepine as grade D (few case reports with positive results, however without any expert panel endorsement). The authors concluded that there is no consistent empirical evidence to support the use of benzodiazepines in the treatment or prevention of PTSD. Benzodiazepines may however, alleviate some non-specific symptoms such as insomnia or anxiety.\(^1\)
The report by van Liempt et. al. 2006 searched multiple electronic databases for English language studies evaluating pharmacotherapy for disordered sleep in PTSD sufferers. Forty-eight reports were included in the review; study design varied from case reports to randomized controlled trials. Two placebo controlled trials and four case reports evaluated the use of a benzodiazepine, including the cross-over trial by Cates et. al. which is described in detail in the RCT section of this HTIS inquiry. The Cates study found no benefit with clonazepam compared to placebo. The other placebo controlled trial (Mellman 2002) found that temazepam had no effect on sleep at six weeks. Four case reports showed temazepam improved symptoms of acute stress including sleep. The review authors concluded that pharmacotherapies for PTSD-related sleep disorders have been poorly investigated and large randomized controlled trials need to be conducted.

Two other systematic reviews were identified. The Cochrane report included only one relevant study (Braun 1990) and provided no conclusions on the use of benzodiazepines in PTSD. In the review by Bisson published in 2007, no studies evaluating benzodiazepines for the treatment of PTSD met the inclusion criteria (RCT, at least single blinded, including 20 or more patients with minimum 80% follow-up). One study (Mellman 2002) on the prevention of PTSD was reviewed. The systematic review authors concluded the effectiveness of benzodiazepines for PTSD was unknown.

Randomized controlled trials

The randomized, single-blind cross-over trial by Cates et. al. enrolled six persons with combat related PTSD. Patients who were currently receiving benzodiazepines or those with active substance abuse were excluded. Participants received either clonazepam 1 to 2 mg or placebo at bedtime for two weeks. After a one week washout period, they were given the alternate study treatment. Participants completed a sleep diary, recording the quantity and quality of sleep, difficulty obtaining or remaining asleep, and intensity and frequency of nightmares. All participants were male aged 31 to 74 years and none were receiving psychotropic medications. No statistically significant differences were detected between clonazepam and placebo for any outcome measure. On average, participants reported four fewer nights with sleep onset problems or early-morning awakening over the two week treatment period with clonazepam than placebo however these differences were not statistically significant. The study's authors concluded that clonazepam was ineffective in improving sleep disturbances including nightmares in persons with combat related PTSD. They also stated that the small sample size was a serious limitation of the study.

Guidelines and recommendations

Recommendations or comments on the use of benzodiazepines in PTSD are summarized in the appendix. One guideline was not summarized because we could not find a description of the methods used in their development.

Three of the guidelines were focused on PTSD and three on the management of multiple anxiety disorders. One guideline published in 2004 was specific to military personnel. The guidelines generally used robust methods to search and evaluate the literature. All the guidelines agreed that the quality and quantity of studies on benzodiazepines for PTSD is low. The guidelines commissioned by the National Institute for Clinical Excellence (NICE) did not
specifically review the literature on benzodiazepines but instead, focused on antidepressants and antipsychotics. This guideline suggested that hypnotics may be beneficial to manage short-term sleep problems in adult PTSD sufferers.\(^8\) Four other guidelines suggested benzodiazepines may be helpful for short term use, based on expert opinion or non-controlled observational data.\(^9,10,12,13\) None of the guidelines recommended that benzodiazepines be used for the long-term management of PTSD symptoms.

Limitations

Few studies have been conducted to evaluate the efficacy of benzodiazepines in PTSD sufferers. The studies available enrolled small numbers of patients (ranging from six to 26, treatment periods were limited (seven days to five weeks), and had methodological issues (open label design). Only one randomized cross-over study was published within the last six years.\(^4\)

The studies enrolled mixed PTSD populations consisting of those exposed to civilian and to combat-related trauma. There is heterogeneity among PTSD sufferers and it is unclear if findings from studies of civilian trauma are generalizable to those exposed to military trauma.\(^2,14\) In addition, veterans of more recent conflicts in Iraq or Afghanistan may be different from those of previous wars.\(^2\)

The guidelines generally followed rigorous methods in their development, however some may be considered out of date and require an update. Recommendations regarding the use of benzodiazepines were limited by the paucity of primary studies.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

There is a paucity of primary studies evaluating the efficacy and safety of benzodiazepines for the treatment of PTSD. In the available literature, benzodiazepines showed no clear benefit in the management of PTSD. The clinical practice guidelines generally agree that the data to support the use of benzodiazepines is limited in quality and quantity. Some of the guidelines suggested that benzodiazepines may be used for short term management of anxiety or sleep disturbances. Long term use of benzodiazepines to manage core symptoms of PTSD was not recommended by any of the guidelines. The limited available data on the use of benzodiazepines for PTSD may be a consideration for decision-making.

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REFERENCES:


**APPENDIX: Summary of Guidelines**

<table>
<thead>
<tr>
<th>Organization, Title</th>
<th>Year</th>
<th>Recommendations or statements on the use of benzodiazepines for PTSD</th>
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<tr>
<td>World Federation of Societies of Biological Psychiatry</td>
<td>2008</td>
<td>“In the only placebo-controlled trial of benzodiazepines in PTSD, improvement in anxiety symptoms was significantly greater with alprazolam than with placebo but modest in extent. Symptoms specific to PTSD were not significantly altered. However, the sample size of this study (10 patients, cross-over) was too small to draw definite conclusions (Braun 1990).” (page 284) Grade F: lack of evidence to prove efficacy or non-efficacy</td>
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<td>Canadian Psychiatric Association Management of Anxiety Disorders</td>
<td>2006</td>
<td>Benzodiazepines: not recommended “In small controlled trials, alprazolam and clonazepam failed to show significant benefits over placebo as monotherapy for the treatment of PTSD. Clinically, these drugs might be beneficial in combination with other agents for treating acute exacerbations of anxiety in patients with PTSD.” Grade D evidence: controlled trials show lack of efficacy</td>
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<tr>
<td>Royal College of Psychiatrists &amp; The British Psychological Society (NICE)</td>
<td>2005</td>
<td>“Where sleep is a major problem for an adult PTSD sufferer, hypnotic medication may be appropriate for short-term use but, if longer-term drug treatment is required, consideration should also be given to the use of suitable antidepressants at an early stage in order to reduce the later risk of dependence.” Grade C evidence: expert opinion</td>
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| Quality assessment                                                                 |
|-------------------------------------------------------------------------------------|------|
| Methods stated                                                                     | UC   |
| Based on systematic review                                                          | UC   |
| External peer review conducted                                                       | UC   |
| Level of evidence stated for recommendations                                        | Y    |

Note: Y denotes Yes, UC denotes Uncertain.
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<tr>
<th>Organization, Title</th>
<th>Year</th>
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<th>Quality assessment</th>
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<tr>
<td>British Association for Psychopharmacology</td>
<td>2005</td>
<td>No recommendations were made regarding benzodiazepine use in the acute or long-term management of PTSD. General recommendations: &quot;Benzodiazepines are effective in many anxiety disorders but their use should be short term and only considered beyond this in treatment-resistant cases because of problems with side effects and dependence.&quot; (page 573) grade C evidence: based on observational studies, case reports or surveys, or extrapolated from higher levels of evidence.</td>
<td>Y UC UC UC Y</td>
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<td>Evidence-based guidelines for the pharmacological treatment of anxiety disorders</td>
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<td>American Psychiatric Association</td>
<td>2004</td>
<td>&quot;Benzodiazepines may be useful in reducing anxiety and improving sleep. Although their efficacy in treating the core symptoms of PTSD has not been established, benzodiazepines are often used in trauma-exposed individuals and patients with PTSD. However, clinical observations include the possibility of dependence, increased incidence of PTSD after early treatment with these medications, or worsening of PTSD symptoms after withdrawal of these medications. Thus, benzodiazepines cannot be recommended as monotherapy for PTSD.&quot; (page 5) grade III evidence: may be recommended on the basis of individual circumstances. Partial update and review of PTSD literature revealed no new data on the use of benzodiazepines.</td>
<td>Y Y Y Y Y</td>
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<td>Practice guideline for the treatment of patients with acute stress disorder and post-traumatic stress disorder</td>
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<td>Guideline Watch (March 2009)</td>
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<td>Veterans Health Administration, Department of Defense</td>
<td>2004</td>
<td><strong>Acute Stress Disorder</strong>&lt;br&gt;Benzodiazepines: inconclusive due to insufficient evidence&lt;br&gt;“Recommend the use of medication only for individuals that do not respond to non-pharmacological treatment”&lt;sup&gt;10&lt;/sup&gt; Grade III: expert opinion, case reports&lt;br&gt;“Consider a short course of medication targeted for specific symptoms.&lt;br&gt; - sleep disturbance/insomnia: benzodiazepines up to 5 days.&lt;br&gt; - Hyperarousal/excessive arousal/panic attacks: benzodiazepines up to 5 days; avoid short acting agents (e.g., alprazolam)”&lt;sup&gt;10&lt;/sup&gt; Grade II-2: cohort or case-control study</td>
<td>Y</td>
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<td>VA/DoD clinical practice guideline for the management of post-traumatic stress&lt;sup&gt;10&lt;/sup&gt;</td>
<td></td>
<td><strong>PTSD</strong>&lt;br&gt;Benzodiazepine: considered not effective or may be harmful&lt;br&gt;“Recommend against the long-term use of benzodiazepines to manage core symptoms in PTSD.”&lt;sup&gt;10&lt;/sup&gt; Grade II-2: cohort or case-control study</td>
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NICE=National Institute of Clinical Evidence; PTSD=post-traumatic stress disorder; UC=unclear; VA/DoD=Veterans Affairs/Department of Defense; Y=yes;