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Pharmacotherapy Rounds
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Objectives:
1. Describe the effects benzodiazepines have on posttraumatic stress disorder
2. Describe the epidemiology, diagnosis, pathophysiology, and treatment of posttraumatic stress disorder
3. Understand the mechanism of action of benzodiazepines
4. Evaluate the literature on the use of benzodiazepines in posttraumatic stress disorder
5. Formulate a recommendation regarding the use of benzodiazepines in posttraumatic stress disorder based on evaluation of published literature
Introduction:

- **Is it a problem?**
  - 30% and 50% of veteran and civilian patients diagnosed with posttraumatic stress disorder (PTSD) are prescribed benzodiazepines
  - 41% of New Hampshire Medicaid PTSD patients prescribed benzodiazepines
  - > 132,000 (37%) of PTSD Veterans Health Administration patients received a benzodiazepine in fiscal year 2009
    - Despite the lack of efficacy and potential harms of therapy

PTSD:

- **Epidemiology:**
  - 60.7% of men and 51.2% of women in the United States are exposed to at least one traumatic event
  - Lifetime prevalence of 7.8%
  - Prevalence increases in soldiers returning from Iraq or Afghanistan to 13%
  - 500,000 veterans in the Veterans Affairs (VA) health care system in 2010 treated for PTSD
  - Prevalence increases in intensive care unit (ICU) patients
    - One in five ICU patients will develop PTSD symptoms within the first 12 months post-ICU admission

- **Risk Factors:**
  - In ICU patients:
    - Pre-ICU psychopathology
    - Receipt of benzodiazepines
    - Higher doses of benzodiazepines
    - Early post-ICU memories of frightening ICU experiences
      - Hallucinations
      - Paranoid delusions
      - Nightmares
    - Post-ICU psychopathology
  - Higher among veterans and those whose vocation increases the risk of traumatic exposure (e.g., police, firefighters, emergency medical personnel)
  - Refer to the DSM V for further break down and examples of PTSD risk factors

- **Diagnosis:**
  - Placed under a new chapter called “Trauma- and Stress-Related Disorders”
  - Exposure to actual or threatened death, serious injury, or sexual violence in ≥ 1 of the following ways:
    - Directly experiencing or witnessing in person
      - Event
      - Learning that the event occurred to close family member or close friend
    - Experiencing repeated or extreme exposure to aversive details of the traumatic event
      - First responders collecting human remains
      - Police officers repeatedly exposed to details of child abuse
  - Presence of ≥ 1 of the following *intrusion symptoms* associated with the traumatic event:
    - Distressing memories
    - Dreams of the traumatic event
    - Marked physiological reactions to internal or external cues
    - Dissociative reactions
Intense or prolonged psychological distress at exposure to internal or external

- **Avoidance:**
  - Distressing memories, thoughts, or feelings
  - External reminders
    - People
    - Places
    - Conversations
    - Activities
    - Objects
    - Situations

- **Alterations in arousal and reactivity** beginning or worsening after the traumatic event occurred as evidenced by > 2 of the following:
  - Irritable behavior and angry outbursts
  - Reckless or self-destructive behavior
  - Hypervigilance
  - Exaggerated startle response
  - Problems with concentration
  - Sleep disturbance

- **Negative alterations** in cognitions and mood beginning or worsening after the traumatic event occurred as evidenced by ≥ 2 of the following:
  - Inability to remember an important aspect of the traumatic event
  - Persistent and exaggerated negative beliefs or expectations
  - Distorted cognitions about the cause or consequences that lead the individual to blame himself/herself or others
  - Negative emotional state
    - Fear
    - Horror
    - Anger
    - Guilt
    - Shame
  - Markedly diminished interest or participation in significant activities
  - Feelings of detachment or estrangement from others
  - Inability to experience positive emotions

- Duration of the disturbance is **more than 1 month**

- **Comorbidities:**
  - Over 90% of PTSD patients have at least one comorbid mental disorder
  - Increased odds of mood, anxiety, and substance use disorders
    - Odds ratios (ORs) = 2.2-19.1
  - Suicidal ideation
    - OR = 9.7
  - Suicide attempts
    - OR = 11.8

- **Pathophysiology:**
  - Fewer serotonin 1B receptors in their brain stress circuits as compared to healthy controls
  - Smaller bilateral hippocampal volume and anterior cingulate cortex
    - Involved in memory formation and emotional processing
  - Enhanced processing of trauma-related stimuli and reduced processing of neutral stimuli
  - Biologic dysregulation:
    - Glutamatergic
    - Noradrenergic
- Serotonergic
- Neuroendocrine pathways
- Spindle and kinetochore-associated complex subunit 2 (SKA2) methylation
- Biomarker for risk of suicide

**Treatment:**

**Pharmacological:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose (mg)</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors (SSRIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20-40</td>
<td>A; 1</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20-40</td>
<td>A; 1</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50-100</td>
<td>A; 1</td>
</tr>
<tr>
<td><strong>Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75-225</td>
<td>A; 1</td>
</tr>
<tr>
<td><strong>Tricyclic Antidepressants (TCAs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>75-200</td>
<td>B; 3</td>
</tr>
<tr>
<td>Imipramine</td>
<td>75-200</td>
<td>B; 3</td>
</tr>
<tr>
<td><strong>MAO Inhibitors (MAOIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenelzine</td>
<td>45-90</td>
<td>D; 5</td>
</tr>
<tr>
<td><strong>Atypical Antipsychotics (AAPs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.5-6</td>
<td>B; 3</td>
</tr>
</tbody>
</table>

Noradrenergic and specific Serotoninergic Antidepressant (NasSA)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose (mg)</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirtazapine</td>
<td>30-60</td>
<td>B; 3</td>
</tr>
</tbody>
</table>

Adapted from Table III. Recommendations for drug treatment of anxiety disorders and OCD.18

- **Non-pharmacological:**
  - Prolonged imaginal exposure6
  - Trauma-focused CBT and eye movement desensitization and reprocessing were efficacious and superior to “stress management”10

**Mechanism of Action (MOA) of benzodiazepines**19:

- Bind to benzodiazepine receptors on the postsynaptic GABA neuron
- Enhancement of the inhibitory effect of GABA
  - Increased neuronal membrane permeability to chloride ions
  - Hyperpolarization and stabilization

**Alprazolam**19:

- **Indications:** Treatment of generalized anxiety disorder (GAD), short-term relief of symptoms of anxiety, panic disorder, with or without agoraphobia, and anxiety associated with depression
- **Adverse Reactions:**
  - **Central nervous system:** Ataxia, cognitive dysfunction, depression, dizziness, drowsiness, dysarthria, fatigue, irritability, memory impairment, sedation
  - **Endocrine & metabolic:** Decreased libido, weight gain, weight loss
  - **Gastrointestinal:** Change in appetite, constipation, xerostomia
  - **Genitourinary:** Difficulty in micturition
  - **Respiratory:** Nasal congestion
- **Pharmacokinetics/Pharmacodynamics (PK/PD):**
### Chlordiazepoxide

- **Indications**: Management of anxiety disorder or short-term relief of symptoms of anxiety, withdrawal symptoms of acute alcoholism, and preoperative apprehension and anxiety
- **Adverse Reactions**:
  - **Cardiovascular**: Edema, syncope
  - **Central nervous system**: Abnormal electroencephalogram, ataxia, confusion, drowsiness, drug-induced extrapyramidal reaction
  - **Dermatologic**: Skin rash
  - **Endocrine & metabolic**: Change in libido, menstrual disease
  - **Gastrointestinal**: Constipation, nausea
  - **Hematologic & oncologic**: Agranulocytosis, bone marrow depression
  - **Hepatic**: Hepatic insufficiency, jaundice
  - **Miscellaneous**: Paradoxical reaction
- **PK/PD**:

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Over several hours (orally)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>$V_d$: 3.3 L/kg</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Extensively hepatic to desmethyldiazepam (active and long-acting), desmethylchlordiazepoxide, and demoxepam.</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine (minimally as unchanged drug)</td>
</tr>
<tr>
<td>Half-Life (hours)</td>
<td>Parent: 6.6 to 28; Demoxepam: 14 to 95</td>
</tr>
</tbody>
</table>

### Clonazepam

- **Indications**: Panic disorder and seizures, bipolar disorder, manic or mixed episodes, burning mouth syndrome, essential tremor, rapid eye movement sleep behavior disorder, restless leg syndrome, tardive dyskinesia, and tic disorders
- **Adverse Reactions**:
  - **Cardiovascular**: Edema (ankle or facial), palpitation
  - **Central nervous system**: Amnesia, ataxia (seizure disorder ~30%; panic disorder 5%), behavior problems (seizure disorder ~25%), coma, confusion, coordination impaired, depression, dizziness, drowsiness (seizure disorder ~50%), emotional lability, fatigue, fever, hallucinations, headache, hysteria, insomnia, intellectual ability reduced, memory disturbance, nervousness; paradoxical reactions (including aggressive behavior, agitation, anxiety, excitability, hostility, irritability, nervousness, nightmares, sleep disturbance, vivid dreams); psychosis, slurred speech, somnolence (panic disorder 37%), vertigo
  - **Dermatologic**: Hair loss, hirsutism, skin rash
  - **Endocrine & metabolic**: Dysmenorrhea, libido increased/decreased
  - **Gastrointestinal**: Abdominal pain, anorexia, appetite increased/decreased, coated tongue, constipation, dehydration, diarrhea, encopresis, gastritis, gum soreness, nausea, weight changes (loss/gain), xerostomia
- **Genitourinary:** Colpitis, dysuria, ejaculation delayed, enuresis, impotence, micturition frequency, nocturia, urinary retention, urinary tract infection
- **Hematologic:** Anemia, eosinophilia, leukopenia, thrombocytopenia
- **Hepatic:** Alkaline phosphatase increased (transient), hepatomegaly, transaminases increased (transient)
- **Neuromuscular & skeletal:** Choreiform movements, coordination abnormal, dysarthria, hypotonia, muscle pain, muscle weakness, myalgia, tremor
- **Ocular:** Blurred vision, eye movements abnormal, diplopia, nystagmus
- **Respiratory:** Bronchitis, chest congestion, cough, hypersecretions, pharyngitis, respiratory depression, respiratory tract infection, rhinitis, rhinorrhea, shortness of breath, sinusitis

**PK/PD:**

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Rapid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>( V_d ): 1.5 to 64.4 L/kg</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatically via glucuronide and sulfate conjugation</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine (&lt;2% unchanged drug); excreted as metabolites</td>
</tr>
<tr>
<td>Half-Life (hours)</td>
<td>17 to 60</td>
</tr>
</tbody>
</table>

**Clorazepate\(^{19}\):**

- **Indications:** Treatment of generalized anxiety disorder, management of alcohol withdrawal and adjunct anticonvulsant in management of partial seizures
- **Adverse Reactions:**
  - **Cardiovascular:** Hypotension
  - **Central nervous system:** Drowsiness, fatigue, ataxia, lightheadedness, memory impairment, insomnia, anxiety, headache, depression, slurred speech, confusion, nervousness, dizziness, irritability
  - **Dermatologic:** Rash
  - **Endocrine & metabolic:** Libido decreased
  - **Gastrointestinal:** Xerostomia, constipation, diarrhea, salivation decreased, nausea, vomiting, appetite increased or decreased
  - **Hepatic:** Jaundice, transaminase increased
  - **Neuromuscular & skeletal:** Dysarthria, tremor
  - **Ocular:** Blurred vision, diplopia

**PK/PD:**

<table>
<thead>
<tr>
<th>Absorption(^{20})</th>
<th>91% bioavailability orally</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>( V_d ): 0.7 to 2.2 L/kg (as nordiazepam)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Decarboxylated to nordiazepam (active) in acidic stomach prior to absorption; nordiazepam is hepatically hydroxylated by CYP2C19 and CYP3A4 to oxazepam (active) and undergoes glucuronidation to form a glucuronide conjugate</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine (62% to 67%) and feces (15% to 19%)</td>
</tr>
<tr>
<td>Half-Life (hours)</td>
<td>Nordiazepam (20 to 160) and oxazepam (6 to 24)</td>
</tr>
</tbody>
</table>

**Diazepam\(^{19}\):**

- **Indications:** Management of anxiety disorders, alcohol withdrawal symptoms, skeletal muscle relaxant, treatment of convulsive disorders, preoperative or preprocedural sedation and amnesia, panic disorders, sedation in the ICU, and spasticity with cerebral palsy
Adverse Reactions:
- Cardiovascular: Hypotension, localized phlebitis, vasodilatation
- Central nervous system: Amnesia, ataxia, confusion, depression, drowsiness, dysarthria, fatigue, headache, slurred speech, vertigo
- Dermatologic: Skin rash
- Endocrine & metabolic: Change in libido
- Gastrointestinal: Altered salivation (dry mouth or hypersalivation), constipation, diarrhea, nausea
- Genitourinary: Urinary incontinence, urinary retention
- Hepatic: Jaundice
- Neuromuscular & skeletal: Tremor, weakness
- Ophthalmic: Blurred vision, diplopia
- Respiratory: Apnea, asthma, bradypnea
- Miscellaneous: Paradoxical reaction

PK/PD:
- Absorption: Well absorbed unless given with a moderate fat meal (delayed and decreased)
- Distribution: $V_d$: 0.8 to 1.9 L/kg
- Metabolism: Hepatic; diazepam is N-demethylated by CYP3A4 and 2C19 to the active metabolite N-desmethyldiazepam, and is hydroxylated by CYP3A4 to the active metabolite temazepam. N-desmethyldiazepam and temazepam are both further metabolized to oxazepam. Temazepam and oxazepam are largely eliminated by glucuronidation.
- Excretion: Urine
- Half-Life (hours): Parent (44 to 48) and Desmethyldiazepam (100). Accumulates with multiple dosing

Lorazepam

- Indication: Management of anxiety disorders (short-term relief of symptoms, associated with depressive symptoms, or anxiety/stress-induced insomnia), anesthesia, status epilepticus, agitation in the ICU, alcohol withdrawal syndrome and delirium, chemotherapy-associated nausea and vomiting (adjunct, anticipatory, and breakthrough), partial complex seizures, and psychogenic catatonia

Adverse Reactions:
- Cardiovascular: Hypotension (≤2%)
- Central nervous system: Sedation (≤16%), dizziness (≤7%), drowsiness (2% to 4%), unsteadiness (3%), headache (1%), coma (≤1%), stupor (≤1%), aggressive behavior, agitation, akathisia, amnesia, anxiety, central nervous system stimulation, disinhibition, disorientation, dysarthria, euphoria, excitement, extrapyramidal reaction, fatigue, hostility, hypothermia, irritability, mania, memory impairment, outbursts of anger, psychosis, seizures, sleep apnea (exacerbation), sleep disturbances, slurred speech, suicidal behavior, suicidal ideation, vertigo
- Dermatologic: Alopecia, skin rash
- Gastrointestinal: Changes in appetite, constipation
- Endocrine & metabolic: Change in libido, hyponatremia, SIADH
- Genitourinary: Impotence, orgasm disturbance
- Hematologic & oncologic: Agranulocytosis, pancytopenia, thrombocytopenia
- Hepatic: Increased serum alkaline phosphatase, increased serum bilirubin, increased serum transaminases, jaundice
- Hypersensitivity: Anaphylaxis, anaphylactoid reaction, hypersensitivity reaction
- Neuromuscular & skeletal: Weakness (≤4%)
- Ophthalmic: Visual disturbances (including diplopia and blurred vision)
- **Respiratory:** Respiratory failure (1% to 2%), apnea (1%), hypoventilation (≤1%), exacerbation of obstructive pulmonary disease, nasal congestion, respiratory depression, worsening of sleep apnea

- **PK/PD:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Readily absorbed</td>
</tr>
<tr>
<td>Distribution</td>
<td>( V_d: 1.3 ) L/kg</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic to lorazepam glucuronide (inactive)</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine (88%) and feces (7%)</td>
</tr>
<tr>
<td>Half-Life (hours)</td>
<td>12</td>
</tr>
</tbody>
</table>

**Oxazepam**^{19}:  

- **Indications:** Management of anxiety disorders (including with depression) and alcohol withdrawal  
- **Adverse Reactions:**  
  - **Cardiovascular:** Edema, hypotension, syncope  
  - **Central nervous system:** Amnesia, ataxia, dizziness, drowsiness, drug dependence, dysarthria, euphoria, headache, lethargy, memory impairment, slurred speech, vertigo  
  - **Dermatologic:** Maculopapular rash, morbilliform rash, urticarial  
  - **Endocrine & metabolic:** Decreased libido, menstrual disease  
  - **Gastrointestinal:** Nausea  
  - **Genitourinary:** Urinary incontinence  
  - **Hematologic & oncologic:** Hematologic disease, leukopenia  
  - **Hepatic:** Jaundice  
  - **Hypersensitivity:** Fixed drug eruption  
  - **Neuromuscular & skeletal:** Hyporeflexia, tremor  
  - **Ophthalmic:** Blurred vision, diplopia  
  - **Miscellaneous:** Paradoxical central nervous system stimulation, paradoxical excitation

- **PK/PD:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Slowly absorbed from the gastrointestinal tract</td>
</tr>
<tr>
<td>Distribution</td>
<td>( V_d: 0.6 ) to 2 Kg</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatically via glucuronidation to inactive metabolite</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine</td>
</tr>
<tr>
<td>Half-Life (hours)</td>
<td>6 to 11</td>
</tr>
</tbody>
</table>

**Negative effects of benzodiazepines in PTSD:**  

- Not effective for treating re-experiencing, avoidance, or most arousal symptoms of PTSD^{3}  
- Enhancing gamma-aminobutyric acid (GABA) activity with benzodiazepines may interfere with fear extinction in these patients^{6}  
- Benzodiazepine use during prolonged imaginal exposure sessions showed more symptoms at follow-up^{4}  
- The Veterans Affairs/Department of Defense clinical guidelines discourage the routine use of benzodiazepines:  
  - **Safety concerns**  
  - Lack of evidence in improving the core symptoms of PTSD  
    - Re-experiencing  
    - Avoidance
- Hyperarousal
- Common risks associated with benzodiazepines:
  - Respiratory depression and oversedation
  - Increased with opioids, alcohol, and illicit substances
  - Increased risk of falls
  - Motor vehicle accidents
  - Cognitive disturbances

**Evaluation of the literature:**

**Identifying Clinical and Acute Psychological Risk Factors for PTSD After Critical Care: A Systematic Review**

| Objective | To compare 2008-2012 studies with 1997-2007 studies, with regard to PTSD prevalence, risk factors, and quality.
| Design | Systematic review

### Studies

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective cohort</td>
<td>Sample size &lt; 30</td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>Published only as conference papers or abstracts</td>
</tr>
<tr>
<td>Cross-sectional surveys</td>
<td>Full text not available in English</td>
</tr>
<tr>
<td></td>
<td>Published before 1997</td>
</tr>
<tr>
<td></td>
<td>Set in neonatal or pediatric ICUs</td>
</tr>
</tbody>
</table>

### Subjects

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>Patients with pancreatitis</td>
</tr>
<tr>
<td>Mixed diagnosis ICU patients who received care &gt; 24 hours</td>
<td>Patients with acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Patients receiving mechanical ventilation</td>
<td></td>
</tr>
</tbody>
</table>

### Methods

- Conducted according to PRISMA recommendations
- Based on pre-specified protocol
- Used systematic and explicit methods to identify, select, and critically appraise studies
- Risk of bias assessed and higher quality studies were given greater weight

### Results

N = 26 studies (13 from 1997-2007 and 13 from 2008-2012)

Risk factors for PTSD (pooled data)

- Age: 7 No and 5 Yes
- Gender: 7 No and 3 Yes
- Psychiatric history: 5 Yes and 3 No
- Lorazepam dose: 3 Yes
- Administration of midazolam: 3 Yes 1 No
- Use of benzodiazepines: 1 Yes
- Duration of sedation: 4 Yes 1 No
- Acute psychological risk factors: 28 associations total

### Authors’ Conclusion

Evidence from this review suggests that at least one in five patients may develop PTSD after intensive care. The most consistent risk factors identified were benzodiazepine use, duration of sedation, and acute psychological issues (stress, delirium, and memory problems). The use of benzodiazepines and duration of sedation should be limited, and psychological support should be provided during and following ICU admissions.

### Reviewer’s

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large population</td>
<td>Evidence reported as yes/no</td>
</tr>
</tbody>
</table>
### Posttraumatic Stress Disorder in Critical Illness Survivors: A Metaanalysis

**Objective**
To conduct a systematic review and meta-analysis of the prevalence, risk factors, and prevention/treatment strategies for PTSD symptoms in critical illness survivors.

**Design**
Meta-analysis

#### Studies

<table>
<thead>
<tr>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population of adult critical illness survivors</td>
</tr>
<tr>
<td>PTSD assessment conducted using a validated measure</td>
</tr>
<tr>
<td>PTSD assessment conducted ≥ 1 month post-ICU discharge while patients were in their home environment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50% pediatric patients (&lt; 16 years)</td>
</tr>
<tr>
<td>&lt; 50% ICU patients</td>
</tr>
<tr>
<td>Primary focus on patients with a specific illness/disease or from a specialty ICU</td>
</tr>
<tr>
<td>Case series with &lt; 10 patients</td>
</tr>
</tbody>
</table>

#### Methods

- Two reviewers independently abstracted data from each eligible article
- Risk of bias assessment conducted using the Cochrane Risk of Bias for randomized controlled trials (RCTs) and Newcastle Ottawa Scale for observational studies

#### Statistical Analysis:

- Impact of Event Scale (IES) measure scores were pooled using binomial and linear random-effects models
- $I^2$ statistic was used to evaluate between-study statistical heterogeneity, when the value was > 50% a sensitivity analysis was performed

#### Results

- N = 40 studies and 4,260 patients
- Conducted primarily in the United Kingdom and the United States
- Point prevalence of PTSD ranged from 4-62%
- The IES (score range 0-75), most commonly used scale, at 1-6 months post-ICU was 20 and the pooled prevalence was 25% (p<0.05) for scores ≥ 35
- The mean IES score at 7-12 months post-ICU was 17 and the pooled prevalence was 17% (p<0.05) for scores ≥ 35

#### Risk Factors (number of studies):

- **Associated with PTSD (p<0.05)**
  - Pre-ICU psychopathology (5/9)
  - Receipt of benzodiazepines (2/4)
  - Higher total benzodiazepine dose (1/2)
  - Early post-ICU memories of frightening experiences [hallucinations, paranoid delusions, and nightmares] (10/12)
  - Post-ICU psychopathology [anxiety, depression, and substance abuse] (4/4)

- **Not associated with PTSD (p>0.05)**
  - Age (9/16)
  - Sex (13/18)
  - Benzodiazepine duration (1/1)
  - Differences in sedation (4/4)
  - Duration of or any ICU delirium (2/2)
  - Corticosteroids administered in the ICU (2/2)
  - Severity of illness (11/12)
  - ICU length of stay (12/14)
  - ICU admission diagnosis (7/7)
  - Mechanical ventilation or duration (5/8)
### Authors’ Conclusion

PTSD symptoms occurred in one fifth of critical illness survivors over 1-year follow-up, with higher prevalence in those who had comorbid psychopathology, received benzodiazepines, and had early post-ICU memories of frightening ICU experiences. Identification of risk factors is important to target patients for prevention/treatment of PTSD.

### Reviewer’s Evaluation

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large population</td>
<td>United Kingdom data may not be comparable</td>
</tr>
<tr>
<td>Validated PTSD assessments used</td>
<td>Patient demographics limits to ICU</td>
</tr>
<tr>
<td>Evaluated patients at home</td>
<td>Conflicting data</td>
</tr>
<tr>
<td>Sensitivity analysis performed</td>
<td>Different PTSD questionnaires used across the studies</td>
</tr>
<tr>
<td>Independent reviewers</td>
<td>Hard to differentiate if patients needing benzodiazepines are more at risk or if benzodiazepines cause the increased risk</td>
</tr>
<tr>
<td>Risk of bias assessment</td>
<td>Long-term follow-up</td>
</tr>
<tr>
<td>Long-term follow-up</td>
<td>Evaluation of prevention techniques</td>
</tr>
<tr>
<td>Evaluation of prevention techniques</td>
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### A Randomized, Double-Blind Evaluation of D-cycloserine or Alprazolam Combined with Virtual Reality Exposure Therapy for Posttraumatic Stress Disorder in Iraq and Afghanistan War Veterans

#### Objective

To determine the effectiveness of Virtual Reality Exposure (VRE) augmented with D-cycloserine (50 mg) or alprazolam (0.25 mg), compared to placebo, in reducing PTSD due to military trauma in Iraq and Afghanistan.

#### Design

Double-blind, placebo-controlled randomized clinical trial

#### Subjects

**Inclusion**

- 156 medically stable Iraq/Afghanistan veterans between 22 and 55 years who met DSM-IV criteria for PTSD due to military trauma

**Exclusion**

- Lifetime history of psychosis
- Bipolar disorder
- Current suicidal risk
- Current alcohol or drug dependence
- Pregnancy
- Current use of glucocorticoids, benzodiazepines, or chronic opioids

#### Endpoints

- Clinician Administered PTSD Scale (CAPS)
- PTSD Symptom Scale (PSS)
- Cortisol data
- Startle data

#### Methods

**Interventions:**

- Randomized 1:1:1 to either: virtual reality exposure (VRE) + D-cycloserine 50 mg, VRE + 0.25 mg alprazolam, or VRE + placebo
- CAPS and PSS scores were obtained at baseline, six treatment visits, and follow-up assessments at 3, 6, and 12 months post-treatment
- One 90-minute introductory session followed by 5 once weekly 90-minute VRE sessions
- Participants arrived 30 minutes early and took a pill provided by study staff

**Statistical Analyses:**

- Piecewise mixed-effect model used to test hypothesis
- PTSD diagnostic rates were compared using \( \chi^2 \) tests
- Outcomes analyzed using intent-to-treat sample
Repeated-measures analysis of variance was used to analyze the effects of VR scenes on cortisol levels, and on startle response

**Results**

- Significant decrease in both CAPS and PSS over the course of the trial for all interventions (p<0.001), CAPS reduction maintained over 12 month follow-up (p<0.001) but not for PSS (p=.191)
- D-cycloserine conditions reported better post-treatment outcomes (CAPS) than alprazolam or placebo (Table 3)
- Alprazolam group showed greater rates of PTSD versus placebo at 3-month post-treatment (79.2% versus 47.85)
- Startle response and cortisol levels, when exposed to virtual reality, decreased significantly (p<0.05) in D-cycloserine conditions, but not alprazolam or placebo

<table>
<thead>
<tr>
<th></th>
<th>D-cycloserine (N = 53)</th>
<th>Alprazolam (N = 50)</th>
<th>Placebo (N = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Did not meet criteria</td>
<td>Met criteria</td>
<td>Did not meet criteria</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>6 (21.4)</td>
<td>22 (78.6)</td>
<td>9 (25.7)</td>
</tr>
<tr>
<td>3-month</td>
<td>7 (35.0)</td>
<td>13 (65.0)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>6-month</td>
<td>7 (41.2)</td>
<td>10 (58.8)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>12-month</td>
<td>9 (52.9)</td>
<td>8 (47.1)</td>
<td>8 (36.4)</td>
</tr>
</tbody>
</table>

Table 3. Percentages in parentheses. Superscript denotes alpha of 0.05

**Authors’ Conclusion**

Six sessions (5 VRE) were associated with significant improvement in PTSD symptoms post-treatment and was maintained at follow-up (no control group). Alprazolam use during treatment may diminish the efficacy of exposure therapy, with more severe post-treatment symptoms and higher rates of PTSD diagnosis at 3-month follow-up. Providers should use benzodiazepines with caution in PTSD patients, as they seemed to have attenuated the long term response to therapy.

**Reviewer’s Evaluation**

- Randomized and blinded
- Widely used scales of symptom measurement
- Assessment interviews videotaped and watched by another clinician

**Strengths**

- P-value not given for 3 month alprazolam claim
- Lower than average dose of alprazolam
- No placebo for VRE
- Subjects were paid to participate
- 12 month difference not significant for alprazolam

**Limitations**

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**Comparative Safety of Benzodiazepines and Opioids Among Veterans Affairs Patients With Posttraumatic Stress Disorder**

**Objective**

To compare the 2 year incidence of adverse events among VA patients with PTSD exposed to combinations of selective serotonin reuptake inhibitors (SSRIs) or serotonin/norepinephrine reuptake inhibitors (SNRIs), benzodiazepines and opioids.

**Design**

Retrospective cohort study

**Subjects**

N = 5236

- Veterans who received a diagnosis of PTSD at 1 or more outpatient visits
- Started a new episode of SSRIs/SNRIs only, concurrent SSRIs/SNRIs and benzodiazepines, or concurrent SSRIs/SNRIs, benzodiazepines, and opioids during the year after PTSD diagnosis

**Endpoints**

2-year incidence of adverse events among VA patients with PTSD, who were newly
prescribed SSRIs/SNRIs, with those prescribed SSRIs/SNRIs and benzodiazepines, and those prescribed SSRIs/SNRIs with benzodiazepines and opioids

**Methods**
- Administrative data from fiscal year 2003 to 2010
- Identified patients were followed for 24 months
- Emergency department, mental health and medicine/surgery hospitalization services received during the 2-year period were obtained
- Harmful events included: falls, accidents, suicide events, poisonings, drug adverse events, injuries and death

**Statistical Analysis:**
- Descriptive statistics compared baseline demographic and diagnostic characteristics and adverse events
- Weibull proportional hazard regression models were used to calculate hazards ratio of each adverse event
- Number needed to harm was calculated over a 90-day period

**Results**

**Main Analysis:**
- Adverse events were observed in 23% of patients prescribed SSRIs/SNRIs, 22% in the SSRi/SNRI and benzodiazepines group, and 47% in the SSRI/SNRI, benzodiazepine, and opioid group (P<0.001)
- Risk of mental health and any hospitalization was significantly higher in the SSRI/SNRI and benzodiazepine group versus SSRI/SNRI alone (not significant when adjusted for baseline severity of mental health condition)
- The risk of any hospitalization, emergency department visit, any harmful event, and any adverse event was higher in the SSRI/SNRI, benzodiazepine, and opioid group
- NNH = 7.2 to observe any adverse event in the SSRI/SNRI, benzodiazepine, and opioid group (P<0.05)

**Authors’ Conclusion**
More than 1 in 5 veterans with PTSD who received SSRIs/SNRIs alone or in combination with benzodiazepines had an adverse event and more than 2 in 5 had an adverse event when prescribed SSRI/SNRI, benzodiazepine, and opioids. Future efforts are warranted to monitor patients prescribed these combinations of medications with the goal of preventing adverse events and to explore alternative treatments for anxiety, sleep disorders, and pain.

**Reviewer’s Evaluation**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Large population</td>
<td>Outpatient prescription history used</td>
</tr>
<tr>
<td>Only included adverse events that occurred during active prescription</td>
<td>ICD-9 codes used for adverse events</td>
</tr>
<tr>
<td>Sensitivity analyses performed</td>
<td>Illicit drug use data not available</td>
</tr>
</tbody>
</table>

**Take-Home Points:**
- **Study 1:**
  - Increased risk of development of PTSD
  - Recommendation: limit the use of benzodiazepines in these patients
- **Study 2:**
  - Statistically significant increased risk of developing PTSD
  - Validated measurement tool Impact of Event Scale
- **Study 3:**
  - Use in combination with VRE for PTSD
    - Statistically significant decrease in efficacy at 3 month follow-up
    - No longer statistically significant after 12 months
  - Recommendation was to use benzodiazepines with caution in PTSD
- **Study 4:**
- NNH = 7.2 with SSRIs/SNRIs, benzodiazepines, and opioids combination
- Benzodiazepine plus SSRIs/SNRIs versus SSRI/SNRI monotherapy was equal in number of adverse events
- Recommendation to use alternative therapy to treat comorbidities

**Conclusions and Recommendations:**

**Conclusions:**
- Benzodiazepine use in PTSD patients is still a problem despite multiple studies and guidelines warning against their use in this population
- Benzodiazepines are not first line therapy for PTSD patients and are not indicated (on or off-label) for use in these patients
- PTSD patients typically have multiple psychologic co-morbidities, including substance use disorders, which puts them at increased risk for abuse and adverse events, including overdose
- PTSD patients are almost 12 times more likely to attempt suicide than patients without PTSD
- Benzodiazepine use appears to be a risk factor in the development of PTSD in ICU patients
- Benzodiazepine use appears to be detrimental to a known efficacious treatment of PTSD (VRE)
- Benzodiazepine use is associated with a large number of adverse events, especially when used in combination with opioid medications, in PTSD patients
- One upcoming trial on clinicaltrials.gov
  - NCT00270959

**Recommendations:**
- Benzodiazepines should be avoided in PTSD patients and patients currently receiving them should be tapered off
- It is important to explain the risks of benzodiazepine use and help the patient become invested in discontinuing the use of these agents
References:


### Appendix A. Abbreviation Key

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CAPS</td>
<td>clinician administered PTSD Scale</td>
</tr>
<tr>
<td>CBT</td>
<td>cognitive behavioral therapy</td>
</tr>
<tr>
<td>ER</td>
<td>extended release</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
</tr>
<tr>
<td>GAD</td>
<td>generalized anxiety disorder</td>
</tr>
<tr>
<td>ICU</td>
<td>intensive care unit</td>
</tr>
<tr>
<td>IES</td>
<td>impact of event scale</td>
</tr>
<tr>
<td>IR</td>
<td>immediate release</td>
</tr>
<tr>
<td>MOA</td>
<td>mechanism of action</td>
</tr>
<tr>
<td>ODT</td>
<td>orally-disintegrating tablet</td>
</tr>
<tr>
<td>OEF/OIF</td>
<td>Operation Enduring Freedom/Operation Iraqi Freedom</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PK/PD</td>
<td>Pharmacokinetics/Pharmacodynamics</td>
</tr>
<tr>
<td>PSS</td>
<td>PTSD symptom scale</td>
</tr>
<tr>
<td>PTSD</td>
<td>posttraumatic stress disorder</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>SKA2</td>
<td>spindle and kinetochore-associated complex subunit 2</td>
</tr>
<tr>
<td>SNRIs</td>
<td>serotonin/norepinephrine reuptake inhibitors</td>
</tr>
<tr>
<td>SSRIs</td>
<td>selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VA</td>
<td>Veterans Affairs</td>
</tr>
<tr>
<td>$V_d$</td>
<td>volume of distribution</td>
</tr>
<tr>
<td>VRE</td>
<td>virtual reality exposure</td>
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</table>
Appendix B. Helpful Hyperlinks

DSM V
The PRISMA Statement
The Impact of Event Scale (IES)
Supplemental Table 5
Clinician Administered PTSD Scale (CAPS)
PTSD Symptom Scale (PSS)

Appendix C. Charts, Tables, and Graphs

<table>
<thead>
<tr>
<th>Category of evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Full evidence from controlled studies</td>
</tr>
<tr>
<td>B</td>
<td>Limited positive evidence from controlled studies</td>
</tr>
<tr>
<td>C</td>
<td>Evidence from uncontrolled studies or case reports/expert opinion</td>
</tr>
<tr>
<td>D</td>
<td>Inconsistent results</td>
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</table>

<table>
<thead>
<tr>
<th>Recommendation grade</th>
<th>Based on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Category A evidence and good risk-benefit ratio</td>
</tr>
<tr>
<td>2</td>
<td>Category A evidence and moderate risk-benefit ratio</td>
</tr>
<tr>
<td>3</td>
<td>Category B evidence</td>
</tr>
<tr>
<td>4</td>
<td>Category C evidence</td>
</tr>
<tr>
<td>5</td>
<td>Category D evidence</td>
</tr>
</tbody>
</table>

Adapted from Table I. Recommendations for drug treatment of anxiety disorders and OCD.14
Appendix D. Treatment Recommendations for PTSD

**Recommendations: managing patients with post-traumatic stress disorder**

Detection and diagnosis

- Ask about a history of traumatic events when patients present with psychological symptoms [S]
- Become familiar with the symptoms and signs of post-traumatic stress disorder [S]
- Ask about the presence of coexisting depressive symptoms [A]

Prevention of post-traumatic symptoms

- After major trauma, discuss the potential for preventing the emergence of post-traumatic symptoms, and providing there are no contra-indications, consider preventive treatment with propranolol or sertraline [A] or trauma-focused CBT [A]
- Do not recommend routine single-session or multiple-session ‘debriefing’ [A]

Acute treatment of chronic post-traumatic stress disorder

- Choose an evidence-based acute treatment [A]
  - pharmacological: paroxetine, sertraline, venlafaxine [A]
  - psychological: trauma-focused individual CBT or EMDR [A]
- Consider an SSRI for first-line pharmacological treatment [A]
- Take account of patient clinical features, needs and preference and local service availability when choosing treatment, as the comparative efficacy of drug and psychological approaches is not established [S]
- Advise the patient that treatment periods of up to 12 weeks may be needed to assess efficacy [A]

Longer-term treatment

- Use an approach that is known to be efficacious in preventing relapse [S]
- Continue drug treatment for at least 12 months in patients who have responded to treatment [A]
- Monitor effectiveness and acceptability regularly over the course of treatment [S]

Combination of drugs with psychological treatment

- Routinely combining drug and psychological approaches is not recommended for initial treatment in the absence of consistent evidence for enhanced efficacy over each treatment when given alone [A]: but paroxetine may enhance the effectiveness of exposure therapy [A]

When initial treatments fail

- Consider raising the dosage if the current dosage is well tolerated [D]
- Consider switching to another evidence-based treatment [D]
- Consider combining evidence-based treatments only when there are no contraindications [S]
- Consider combining evidence-based pharmacological and psychological treatments [A]
- Consider augmentation of antidepressants with olanzapine [A] risperidone [A] or prazosin [A]
- Consider referral to regional or national specialist services in treatment refractory patients [S]

Adapted from The evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology