Medical Marijuana for the Treatment of Posttraumatic Stress Disorder (PTSD): Real Symptom Re-Leaf or Just High Hopes?

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Learning Objectives

By the end of the presentation, the audience should be able to:
1. Describe epidemiology, clinical presentation, diagnostic criteria, and risk factors of PTSD
2. Identify pathophysiology of PTSD to help govern treatment modalities
3. Explain medical marijuana’s role in the treatment of PTSD
4. Provide appropriate treatment recommendations for medical marijuana use in PTSD according to evidence-based medicine
Background: PTSD

I. Epidemiology

A. United States (U.S.) lifetime risk at age 75 years is 8.7%
B. U.S. 12 month prevalence in adults is 3.5%
C. One-third to one-half of cases are survivors of rape, military combat/captivity, ethnic/political internment, genocide
D. Higher rates among:
   1. Veterans and high-risk employment (police, firefighters, emergency medical personnel)
   2. U.S. Latinos, African Americans, American Indians
   3. Women
E. Incidence up to 24% in the veteran population

![Figure 1: Occurrence of PTSD in Veterans (%)](image)

II. Clinical presentation

Table 1: Clinical Presentation of PTSD

<table>
<thead>
<tr>
<th>Physical</th>
<th>Mental/Cognitive</th>
<th>Behavior</th>
<th>Dissociative</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pain, shortness of breath, grinding teeth, ↑ blood pressure (BP)/heart rate (HR), migraines, vague somatic symptoms (chills, fatigue, nausea), sweating</td>
<td>Substance use, anxiety, depression, blaming, alertness, intrusive thoughts, ↓ concentration</td>
<td>Irritability, taking risks, anger, avoidance, aggression, non-adherence, depression, intoxication, sexual dysfunction</td>
<td>Flashbacks, feeling as in a dream-like state and unable to escape</td>
<td>Difficulty with employment, family, self needs</td>
</tr>
</tbody>
</table>

III. Many co-occurring psychiatric conditions: depression (80%), alcohol and substance use (50%), attempted suicide (20%)

IV. Diagnostic criteria per Diagnostic and Statistical Manual of Mental Disorders (DSM)-5\(^1\) (Appendix A)

A. Classified as a trauma and Stressor-Related Disorder
B. **Criteria A:** Exposure to actual or threatened death, serious injury, or sexual violence
C. **Criteria B:** ≥ 1 intrusive symptoms associated with traumatic event(s)
D. **Criteria C:** ≥ 1 avoidance of stimuli associated with traumatic event(s)
E. **Criteria D:** ≥ 2 negative alterations in cognitions and mood associated with traumatic event(s)
F. **Criteria E:** ≥ 2 alterations in arousal and reactivity associated with traumatic event(s)
G. Symptoms present ≥ 1 month
H. Disturbances cause clinically significant distress/impairment in areas of functioning
I. Disturbances not attributed to physiological effects of substances or other medical condition

V. Diagnostic criteria per DSM-IV grouped criteria C and D together (avoidance and numbing)

VI. Subtypes and specifiers\(^1,5\)

A. Subtypes based on onset: acute (< 3 months), chronic (> 3 months), delayed (> 6 months)
B. Subtypes: with dissociative symptoms or delayed expression
VII. Risk Factors$^{1,4,12}$

<table>
<thead>
<tr>
<th>Table 2: Risk Factors for Developing PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-traumatic</strong></td>
</tr>
<tr>
<td>- Lack of social support</td>
</tr>
<tr>
<td>- Younger age</td>
</tr>
<tr>
<td>- Psychiatric disorders (including PTSD)</td>
</tr>
<tr>
<td>- History of traumatic exposure (abuse)</td>
</tr>
<tr>
<td>- Childhood adversity (family dysfunction, parental separation/death)</td>
</tr>
<tr>
<td>- Female</td>
</tr>
<tr>
<td>- socioeconomic status/education level/intelligence</td>
</tr>
<tr>
<td>- Race</td>
</tr>
<tr>
<td>- Childhood emotional problems (externalizing)</td>
</tr>
<tr>
<td>- Family history</td>
</tr>
<tr>
<td>- Traumatic brain injury</td>
</tr>
<tr>
<td>- Personality disorder (borderline)</td>
</tr>
<tr>
<td>- History of substance use</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

VIII. Pathophysiology$^{2,5}$

A. Brain structure abnormalities$^{11}$

1. ↑ amygdala (fear center) activity: associated with ↑ fear/flashbacks
2. ↓ volume of prefrontal cortex (executive function): ↑ arousal/impulsivity/exaggerated response
3. ↓ hippocampus (memory center) volume: ↑ intrusive thinking

![Figure 2: Brain Structures Involved in PTSD][1]

B. Dysregulation of neurotransmitters: failure in stress response system to react, adapt, and recover

1. Hypothalamic-pituitary axis (HPA)
   a. Dysfunction leading to ↑ stress response
   b. ↓ cortisol (adrenal exhaustion) = ↑ negative feedback

![Figure 3: HPA System and Effects][2]
2. ↑ Norepinephrine (NE)
   a. Presynaptic α2 antagonism = exaggerated central nervous system (CNS) response, hypersensitivity to stimuli, and autonomic hyperactivity (e.g. ↑ BP/HR)
   b. Peripheral α1 agonism = ↑ startle and ↑ nightmares (NM)/intrusive thoughts
3. ↓ Serotonin (5-HT)
   a. ↓ hippocampal neurogenesis, ↑ activation in amygdala, modulates HPA axis
   b. May contribute to irritability, depression, anxiety, suicidality, variability in sleep
4. ↑ Glutamate
   a. Excitatory; acts on N-methyl-D-aspartic acid (NMDA) receptors
   b. Involved in memory
C. Other abnormalities: disruption in diurnal sleep cycle, ↑ thyroid function, dysregulation of opioid system, suppressed immune function, kindling/behavioral sensitization in limbic nuclei, altered memory function

Assessment and Treatment of PTSD

I. Many screening tools/diagnostic scales developed
   A. Screen initially then at least annually if suspicious of diagnosis, recent trauma, or history of PTSD
   B. Insufficient evidence to recommended one screening tool over another

Table 3: Most Common PTSD Rating Scales (Appendix B)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician Administered</td>
<td>• 30-item; assesses 20 PTSD symptoms</td>
<td>• Score ranges from 0-150</td>
</tr>
<tr>
<td>PTSD Scale-5 (CAPS-5)</td>
<td>• Clinician-rated</td>
<td>• Each question rated from Likert 0-4 (absent, mild, moderate, severe, extreme)</td>
</tr>
<tr>
<td><em>Gold Standard</em></td>
<td>• Used to diagnose, assess symptoms, and assess treatment response</td>
<td>• Score calculated by summing frequency/intensity of reported symptoms</td>
</tr>
<tr>
<td></td>
<td>• Can assess impact on functioning and clinical improvement</td>
<td>• <strong>Remission:</strong> ↓ ≥ 70% in symptoms and maintained for 3 months</td>
</tr>
<tr>
<td></td>
<td>• Three versions: assessing symptoms om the past week, month, or worst month</td>
<td>• <strong>Adequate response:</strong> ↓ ≥ 50% in symptoms</td>
</tr>
<tr>
<td></td>
<td>(lifetime)</td>
<td>• <strong>Partial response:</strong> ↓ 25-50% in symptoms</td>
</tr>
<tr>
<td></td>
<td>• Can take 45-60 minutes</td>
<td>• <strong>Non response:</strong> ↓ &lt; 25% in symptoms</td>
</tr>
</tbody>
</table>

Table 4: Most Common PTSD Rating Scales (Appendix B)

II. Treatment Guidelines

Step 1: Psychotherapy or SSR/SSRI
Step 2: Switch to another SSRI/SNRI +/- psychotherapy
Step 3: Add psychotherapy +/- switch to mirtazapine +/- prazosin
Step 4: Switch to mirtazapine, TCA, nefazadone, phenelzine + psychotherapy

Figure 4: VA/DoD Practice Guidelines for PTSD

Key: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs)
III. Non-pharmacologic Treatment

Table 4: Psychotherapy for the Treatment of PTSD

<table>
<thead>
<tr>
<th>Psychotherapy</th>
<th>Description</th>
</tr>
</thead>
</table>
| Cognitive Behavioral Therapy (CBT) | • Typically 8-12 sessions  
• Cognitive Processing Therapy (CPT): taught to identify/alter maladaptive or dysfunctional cognitions  
• Prolonged Exposure Therapy (PE): confrontation with trauma cues to address and lessen importance |
| Eye Movement Desensitization and Reprocessing (EMDR) | • 8 stages: history gathering, treatment planning, preparation, assessment of trauma relevant target, desensitization and reprocessing, instillation of alternative positive cognition, body scan for continuing discomfort or trouble spots, address constructive coping needs for future use |
| Anxiety Management Techniques | • 8-15 sessions  
• Stress management skills to anxiety (e.g. breathing exercises, muscle relaxation) |

IV. Pharmacotherapy

Table 5: Pharmacotherapy for the treatment of PTSD

<table>
<thead>
<tr>
<th>Class (FDA approved)</th>
<th>Place in therapy</th>
<th>Mechanism of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs (paroxetine and sertraline)</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;/2&lt;sup&gt;nd&lt;/sup&gt; line; improves all symptom criteria of PTSD (global improvement)</td>
<td>Inhibit 5-HT reuptake</td>
<td>Anxiety/agitation, gastrointestinal (GI) upset, sexual dysfunction, headaches, serotonin syndrome, sweating, hyponatremia/syndrome of inappropriate anti-diuretic hormone (SIADH)</td>
</tr>
<tr>
<td>SNRIs: venlafaxine</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;/2&lt;sup&gt;nd&lt;/sup&gt; line Inhibition of 5-HT and NE reuptake</td>
<td>Same as SSRIs + ↑ BP, tremor, insomnia</td>
<td></td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressant-NaSSA: mirtazapine&lt;sup&gt;7,8&lt;/sup&gt;</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line</td>
<td>α&lt;sub&gt;2&lt;/sub&gt; antagonist (increase NE and 5-HT), 5-HT&lt;sub&gt;2A/C&lt;/sub&gt; antagonist, 5-HT&lt;sub&gt;3&lt;/sub&gt; antagonist, histamine (H&lt;sub&gt;1&lt;/sub&gt;) antagonist</td>
<td>Anxiety, sedation, increased appetite/weight gain</td>
</tr>
<tr>
<td>Antihypertensive: prazosin</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line; adjunct for nightmares</td>
<td>α&lt;sub&gt;1&lt;/sub&gt; antagonist → ↓ NE</td>
<td>Dizziness, drowsiness, ↑ HR, hypotension/orthostasis</td>
</tr>
<tr>
<td>Serotonin antagonist/reuptake inhibitor-SARI: nefazodone&lt;sup&gt;7&lt;/sup&gt;</td>
<td>4&lt;sup&gt;th&lt;/sup&gt; line</td>
<td>Weak SSRI/SNRI/α&lt;sub&gt;1&lt;/sub&gt; antagonist, 5-HT antagonist, H&lt;sub&gt;1&lt;/sub&gt; antagonist</td>
<td>Anxiety, GI upset, headaches, insomnia/somnolence, orthostasis/dizziness, hepatotoxicity, sexual dysfunction</td>
</tr>
<tr>
<td>TCAs: amitriptyline and imipramine&lt;sup&gt;7&lt;/sup&gt;</td>
<td>4&lt;sup&gt;th&lt;/sup&gt; line</td>
<td>SSRI/SNRI, muscarinic (M&lt;sub&gt;1&lt;/sub&gt;)/α&lt;sub&gt;1&lt;/sub&gt;/H&lt;sub&gt;1&lt;/sub&gt; antagonist, Block voltage-sensitive Na channels</td>
<td>Same as SSRIs/SNRI + anticholinergic, orthostasis, dizziness, sedation, weight gain, coma, seizures, cardiac arrhythmias, cardiac arrest</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitor (MAO-I): phenelzine&lt;sup&gt;7,9&lt;/sup&gt;</td>
<td>4&lt;sup&gt;th&lt;/sup&gt; line</td>
<td>Nonselective irreversible MAOI inhibitor = ↑ 5-HT, NE, H, dopamine, epinephrine</td>
<td>Same as SSRIs/SNRI + hypertensive crisis</td>
</tr>
</tbody>
</table>

* Bolded side effects are similar to PTSD presentation

V. Average duration of symptoms<sup>12</sup>

A. Undergoing treatment: ~ 36 months
B. Not treated: 5 years
C. One-third develop do not remit
VI. Benefit of current treatment options
   A. Number Needed to Treat (NNT) for response
      1. Psychotherapy: 2-4
      2. Pharmacotherapy: 8-9
   B. Psychotherapy
      1. Meta-analysis by Bradley and Colleagues
         a. Completed treatment: 67% no longer met criteria
      2. High dropout rates: 13-39%
   C. Pharmacotherapy
      1. 2005 National Institute for Health and Clinical Excellence (NICE) guidelines do not recommend pharmacotherapy as first line treatment
      2. Remission rates: 20-30%
      3. Cochrane review by Stein and Colleagues
         a. Pharmacotherapy: 59% response rate in PTSD and 39% in placebo
         b. Included patients with comorbid psychiatric disorder (e.g. depression)
         c. Intervention: included concomitant psychotherapy
         d. Combat veterans more resistant to pharmacotherapy
      4. 2009 American Psychiatric Association (APA) Guidelines: pharmacotherapy not as effective for combat related trauma vs. civilian PTSD
      5. Estimated ~ 20% of veterans are effectively treated possibly due to medications being most effective for woman and acute PTSD

Marijuana and PTSD

I. Marijuana (MJ)
   A. History
      1. 3rd century BC: Used in China for the treatment of gout, rheumatism, pain, childbirth, memory, anxiety, stress, and more
      2. 1850–1941: Listed in U.S. Pharmacopoeia for treatment of pain, insomnia, anorexia, gout, tetanus, and “insanity”
      3. 1937: U.S. passes “Marihuana Tax Act” which made it illegal to use MJ recreationally
      4. 1951: Classified as a narcotic
      5. 1970: Controlled Substance Act was passed to outlaw MJ and classify it as a Schedule I substance
      6. 1995: California was the first state to legalize MJ for medical purposes

Figure 5: MJ History

B. Medical use
   1. Canada and many European countries (Netherlands, the Czech Republic, Spain, Portugal)
   2. Legal in 23 states and the District of Columbia with 14 other states pending legislation
   3. Depending on the state, can be recommended by a doctor of medicine, doctor of osteopathy, or naturopathic physician
   4. As of March 1, 2016: 1,246,170 users in the U.S. (8.06/1,000 residents)
   5. As of March 14, 2016, approved for PTSD in 9 states: Arizona, Connecticut, Delaware, Hawaii, Maine, Michigan, Nevada, New Mexico (first state to approve), Oregon
C. Current legal status
   1. States: approved for various medical and/or recreational purposes
   2. Federal
      a. Scheduled I controlled substance\textsuperscript{25, 29}
      b. Bill passed prohibiting VA (Veteran Affairs) from interfering with/denying services to Veterans who participate in state-approved medical MJ programs\textsuperscript{46}
      c. Addendum to bill: allowing VA providers to recommend/provide information on medical MJ in state-approved medical MJ programs\textsuperscript{48}

D. Biochemistry and Pharmacology\textsuperscript{21, 24-25}
   1. Belongs to the Cannabaceae (hemp) plant family
      a. Derived from a plant Cannabis Sativa and Cannabis Indica (> 99% 2 cannabis species)
      b. Sativa: > 421 different chemical compounds; > 60 cannabinoids
         i. $\Delta 9$-Tetrahydrocannabinol (THC)
         ii. Lifts mood and relieves stress
      c. Indica
         i. THC, $\uparrow$ cannabidiol (CBD)
         ii. Relaxes muscles and acts as an analgesic
   2. Comprised of cannabinoids and 18 different classes of chemical compounds (nitrogenous compounds, amino acids, hydrocarbons, carbohydrates, terpenes, simple and fatty acids)
      a. THC:
         i. Highly lipophilic alkaloid
         ii. Primary psychoactive ingredient\textsuperscript{32}
         iii. Content can vary from 0.2-30%\textsuperscript{31}
      b. Cannabinol (CBN) is a THC metabolite that produces less psychoactive effects
      c. CBD:
         i. Produces NO psychoactive effects
         ii. Has antipsychotic properties
         iii. Works synergistically to minimize “high” and side effects
         iv. Neuroprotective, analgesic, sedating, antiemetic, antispasmodic, anti-inflammatory, anxiolytic
   3. Act on cannabinoid (CB) receptors\textsuperscript{21}
      a. Endogenous chemicals that act on the cannabinoid system: endocannabinoids
      b. Play a role in regulating pleasure, appetite, pain, memory, thinking, concentration, movement, coordination, sensory, time perception, immune function, chronic inflammation, metabolism
      c. Stimulation $\uparrow$ stress coping behaviors and $\uparrow$ 5-HT and NE firing in the midbrain\textsuperscript{30}
      d. Functions in conjunction with adrenergic, cholinergic, and dopaminergic system\textsuperscript{31}
      e. Protein coupled receptors regulate excitatory and inhibitory neurotransmission; therefore, assists in the role of homeostasis (e.g. prevents extreme cortisol excitation)\textsuperscript{31, 38}
      f. Absent in brainstem; therefore, no activity seen in the autonomic nervous system = none to minimal risk of lethal overdose\textsuperscript{31}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Receptor & Function & Location \\
\hline
CB-1 & Modulates neurotransmitter networks involved in movement, learning and memory, reinforce pleasure, mood, pain, regulation of food intake, and vomiting & Central nervous system (frontal cortex, basal ganglia, amygdala, hippocampus, thalamus, cerebellum), gut \\
\hline
CB-2 & Suppress immune response, pain, digestion & Gut, immune system, spleen, lymph nodes \\
\hline
\end{tabular}
\caption{Cannabinoid Receptors\textsuperscript{21, 25, 31-32}}
\end{table}
Table 7: Cannabis Pharmacokinetics

<table>
<thead>
<tr>
<th>Administration</th>
<th>Bioavailability (%)</th>
<th>Onset</th>
<th>Time to Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation</td>
<td>2-56</td>
<td>3-9 minutes</td>
<td>14-30 minutes</td>
<td>2 hours</td>
</tr>
<tr>
<td>Oral</td>
<td>4-20</td>
<td>Hours</td>
<td>1-8 hours</td>
<td>Hours</td>
</tr>
</tbody>
</table>

4. Adverse Drug Reactions (ADRs)

Table 8: MJ Adverse Reactions Classified by System

<table>
<thead>
<tr>
<th>System</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>- 20-100% ↑ HR, ↑ cardiac output up to 30%, ↓ BP, ↓ peripheral vascular resistance, ↓ skin temperature by 4-6°C</td>
</tr>
<tr>
<td>Respiratory</td>
<td>- Conflicting reports, but possible large airway obstruction, cellular inflammatory abnormalities in bronchial epithelium, ↑ respiratory symptoms (dyspnea, pharyngitis, bronchial spasms)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>- ↓ sperm count and motility in men, ↑ prolactin/follicle-stimulating hormone/growth hormones in females</td>
</tr>
<tr>
<td>Immune</td>
<td>- Impair cell-mediated and humoral immune response, ↑ risk of infection</td>
</tr>
<tr>
<td>Cognitive</td>
<td>- ↓ psychomotor activity and response, ↓ short term memory, ↓ motivation</td>
</tr>
<tr>
<td></td>
<td>- ↓ ability to learn new concepts, may affect attention/learning days-weeks after use</td>
</tr>
<tr>
<td></td>
<td>- ↑ risk of psychotic disorders with high risk genotypes and ↑ psychotic symptoms in those with schizophrenia and like disorders, ↓ remission of schizophrenia</td>
</tr>
<tr>
<td></td>
<td>- In those with bipolar disorder: ↑ time in affective episode, ↑ risk of rapid cycling, ↑ manic symptoms, ↓ global functioning, ↓ remission</td>
</tr>
<tr>
<td>Addiction</td>
<td>- 2010 National Survey on Drug Use and Health: 4.5 million Americans were dependent</td>
</tr>
<tr>
<td></td>
<td>- 9% of adults and 17% adolescents become addicted (risk = younger age and daily use)</td>
</tr>
<tr>
<td></td>
<td>- ↑ risk with other MH disorders (e.g. depression, anxiety, PTSD)</td>
</tr>
<tr>
<td>Other</td>
<td>- Dizziness, anxiety, paranoia, dry mouth, fatigue, sedation, weakness</td>
</tr>
</tbody>
</table>

II. Current MJ use: medically, recreationally, spiritually

A. Studies have demonstrated significant overlap between medical and recreational users
B. Most widely used illicit drug in the world; peak late teens-early 20's
C. Those under the influence describe experiencing euphoria, relaxation, perceptual alterations (time distortion), and intensification of ordinary experiences (e.g. eating)
D. Some report dysphoria, anxiety, paranoia, and psychosis (and other side effects listed above)
E. High prevalence of MJ use in those with PTSD
   a. Bremner et al.: in 61 Vietnam Veterans, 6% abused and 55% dependent on MJ
   b. Cougle et al.: in 5,672 U.S. adults, 65% with PTSD vs. 41% without PTSD used MJ
F. In 2009, 30% of Veterans within the VA with a PTSD diagnosis also had Cannabis Use Disorder (CUD)

III. Pharmacology of the cannabinoid system in PTSD

A. Endocannabinoid system may play a role in PTSD
   1. ↑ availability of CB1 receptors and ↓ CB1 agonism in those with PTSD
   2. Alleviate anxiety through actions in the prefrontal cortex, amygdala, and hippocampus
   3. Alterations in CB1 receptors seen in depression
   4. Sensitization of CB1 receptor-mediated G-protein signaling in prefrontal cortex may play a role in suicide and suicidal behavior
B. Benefit: sleep, NM, potency of flashbacks, modulate emotional response, decrease/eradicate intrusive thoughts (memories), hyperarousal, negative affect, anxiety, aggression, anger
   1. ↑ activation CB1 receptors in amygdala = ↓ aversive memories, fear, and anxiety
   2. ↑ activation receptors in prefrontal cortex = ↑ 5-HT and antidepressant effect
3. ↑ activation induce hippocampal neurogenesis demonstrating effect on anxiety, depression, memory, and cortisol = ↓ hypervigilance/hyperarousal/intrusive memories
4. ↑ activation in limbic and paralimbic areas = ↓ amygdala and hypothalamus activity = ↓ HPA axis and cortisol = ↓ hypervigilance/hyperarousal
5. Sedative properties may help with sleep
6. ↓ REM sleep, enhance non-REM phase 4 sleep = ↓ NM, ↑ sleep quality
C. Many studies demonstrate PTSD severity associated with MJ use coping mechanism
D. Reported anecdotal benefit in PTSD and suicidality

Table 9: Reported MJ Use in Those with PTSD (Appendix B)

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Population</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reznik et al. (2012)</td>
<td>167 Israeli adults with PTSD +/- comorbid conditions applying for medical MJ license</td>
<td>3 year, prospective cohort; 2-3g of daily Sativa</td>
<td>• Significant improvement in quality of life per QOLS, CGI-I, and pain scores</td>
</tr>
<tr>
<td>Mashiah et al. (2012)</td>
<td>29 Israeli male combat veterans</td>
<td>1 year, open label pilot study; max 100g of Indica (23% THC, 1% CBD)/month; encouraged daily use</td>
<td>• 10 participants completed study</td>
</tr>
<tr>
<td>Roitman et al. (2014)</td>
<td>10 Israelis with chronic PTSD on stable meds (5 combat related PTSD)</td>
<td>3 week, open label, adjusted dose study; 5mg of THC BID</td>
<td>• Significant improvement in global symptom severity (CGI-S/I), sleep quality (PSQI, NES), frequency of NM (NFQ), hyperarousal (CAPS)</td>
</tr>
</tbody>
</table>

Literature Review

I. Effect of MJ use on immediate emotional response


<table>
<thead>
<tr>
<th>Objectives</th>
<th>To evaluate subjective and biological reactivity in those with MJ dependence and PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Placebo controlled prospective trial</td>
</tr>
<tr>
<td>Population</td>
<td>202 patients with/without PTSD admitted to a Substance Use Disorder (SUD) treatment facility</td>
</tr>
</tbody>
</table>

Inclusion
- 18-60 years old (mean = 34.32)
- Exposure to at least 1 potentially traumatic event
- Dependent on cocaine and/or alcohol
- Mini-Mental State Exam score ≥ 24 (appendix B)
- ≥ 72 hours post entry into facility

Exclusion
- Psychotic disorder

Interventions (Appendix B)
- Session one (baseline interview): reimbursed $25
  - Evaluated: CAPS per DSM-IV, structural clinical interview for DSM-IV Axis I Disorders (SCID-I), MJ withdrawal, frequency of MJ use in the past year, mini international
Interventions Continued
(Appendix B)
- Neuropsychiatric interview (MINI), borderline personality disorder module of the diagnostic interview for DSM-IV personality disorders (DIPD-IV), trauma
- Session two (occurred on average 6.23 days post session one): reimbursed $15
  - Subjects listened to 1 minute scripts of traumatic experience and instructed to close eyes and imagine event vividly taking place in real time
  - Emotional reactivity: Negative affect (NA) subscale of positive and negative affect scale (PANAS-NA) prior and post trauma script
  - Biological cortisol: saliva samples obtained prior and 20 minutes post trauma script

Endpoints
- Change in PANAS-NA and biological cortisol levels between groups

Statistics
- Zero order associations between potential covariates and salivary cortisol
- Standardized residual scores: subjective and biological emotional reactivity
- Analyses of variance (ANOVAS): 2 (pre- vs. post-trauma script) x 2 (PTSD vs. no PTSD) x 2 (MJ vs. no MJ) analysis repeated with covariance to account for confounders
- Tukey honest significant difference test: significant interactions

Results

Enrollment
Table 10: Subject Enrollment

<table>
<thead>
<tr>
<th></th>
<th>PTSD; n (%)</th>
<th>No PTSD; n (%)</th>
<th>Total; n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MJ dependence</td>
<td>21</td>
<td>38</td>
<td>59 (29.2)</td>
</tr>
<tr>
<td>No MJ dependence</td>
<td>33</td>
<td>110</td>
<td>143 (70.8)</td>
</tr>
<tr>
<td>Total</td>
<td>54 (29.2)</td>
<td>148 (73.3)</td>
<td>202</td>
</tr>
</tbody>
</table>

% out of total study enrollment

Cortisol analysis
- 34 subjects excluded: collection error, inadequate saliva volume, refusal to provide sample
- Samples did not differ between groups

Baseline characteristics:
- No difference in MJ use in the past year between subjects with/without PTSD (p=0.083)
- MJ dependent group used more often in the past year (p <0.001)
- MJ dependent group reported negligible withdrawal symptoms
- No difference in PTSD severity between the MJ use groups
- Other characteristics not reported between groups

Change in PANAS-NA:

Figure 6: Change in PANAS-NA Score (*significant)
- Significantly associated with emotional activity: age (p=0.04), anxiety disorders (p=0.006), number of potentially traumatic events experienced (p<0.001), BPD (p=0.03)
Results Continued

- Significance: PTSD shows greater ↑ in NA pre- to post-trauma script in those without MJ dependence (p<0.001); still significant when controlling for confounders (p=0.048)
- MJ dependence: no significant difference in NA reactivity compared to PTSD status (p=0.99)
- MJ groups combined: significantly less NA reactivity than PTSD without MJ (p=0.049)

Change in cortisol levels:

<table>
<thead>
<tr>
<th>Cortisol Level (mcg/dL)</th>
<th>Pre-Script</th>
<th>Post-Script</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PTSD; No MJ</td>
<td>0.3</td>
<td>0.25</td>
</tr>
<tr>
<td>PTSD; No MJ</td>
<td>0.23</td>
<td>0.22</td>
</tr>
<tr>
<td>No PTSD; MJ</td>
<td>0.21</td>
<td>0.19</td>
</tr>
<tr>
<td>PTSD; MJ</td>
<td>0.3</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Figure 7: Change in Cortisol Levels

- Significantly associated with cortisol reactivity: white race (p=0.04), time since last caffeine consumption (p=0.05)
- No significance seen in diagnosis of PTSD or in MJ use

Author’s Conclusions

- PTSD without MJ dependence associated with ↑ emotional reactivity to trauma script
- MJ dependence: no change seen in subjective emotional reactivity regardless of PTSD status
- No significant difference seen in cortisol reactivity between groups
- Co-occurring PTSD and MJ dependence may exhibit dampened subjective emotional response to trauma due to reduced amygdala activation

Critique

Advantages

- Included other psychiatric conditions: externally valid
- Placebo vs. control
- No difference in PTSD symptoms between groups at baseline
- Adjusted for confounders

Disadvantages

- Controlled environment = no active use may be the reason why cortisol levels not affected?
- Not adequately powered (even less in cortisol arm)
- Baseline characteristics not divided between groups: affects internal validity
- Absence in data: baseline characteristics of risk factors for PTSD and last MJ use
- Potential discrepancy in MJ potency/content/components/use patterns between users
- Did not fully account for factors affecting cortisol (medication, physical health, collection time)
- Excluded elderly; affects external validity
- Only included patients with substance use disorders
- Unsure if investigators were blinded

Take Home

MJ use in those with PTSD subjectively may dampen emotional response to trauma cues

II. Effect of MJ on global PTSD symptoms
Greer GR, Grob CS, Halberstadt AL. PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. Journal of psychoactive drugs. 2014;46(1), 73-77.

Objectives
To evaluate the effects of MJ use on global PTSD symptoms

Design
Retrospective chart review

Population
80 patients applying to New Mexico Medical MJ program from mid-2009 to late-2011

Inclusion
- Adults ≥ 18 years old
- Experience of and emotional response to trauma per DSM-IV criteria A
- Presence of several symptoms in criterion B, C, D per DSM-IV
- Significant relief of several major PTSD symptoms with MJ use
- Lack of harm or problems in functioning from MJ use

Interventions
- Telephone screen conducted asking patients to answer questions based on the CAPS-IV retrospectively for a time when they were not using MJ and a time when they were using MJ

Endpoints
Change in CAPS-IV score

Statistics
- Analysis of variance (ANOVA): CAPS symptoms criteria (A, B, C) vs. time (no-MJ vs. MJ)
- When significance detected: post-hoc pairwise comparison performed by one-way ANOVA
- α=0.01

Results
Change in CAPS Score

<table>
<thead>
<tr>
<th>Change in CAPS Score</th>
<th>No MJ use</th>
<th>MJ use</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>29.5</td>
<td>7.3</td>
</tr>
<tr>
<td>20</td>
<td>38.2</td>
<td>8.7</td>
</tr>
<tr>
<td>40</td>
<td>35</td>
<td>1.8</td>
</tr>
<tr>
<td>60</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Significant reduction in total CAPS score, criteria B, C, D pre and post MJ use (p<0.0001)

Author’s Conclusions
MJ use resulted in 75% reduction in all areas of PTSD criteria as well as total score

Critique
Advantages
- Powered to show significance
- Patients were their own control

Disadvantages
- Patients volunteered and were prescreened prior to entry
- Inclusion criteria: significant relief of several major PTSD symptoms and lack of harm with MJ use = selection bias; therefore, expected benefit and not externally applicable
- Retrospectively assessed CAPS to generate scores = recall bias
- Baseline characteristics not provided: unsure if externally or internally valid
- Observational study; unable to determine causality
- Did not meet full PTSD inclusion

Take Home
Maybe an association between the MJ use and reduction in global PTSD symptoms
### III. Effect of MJ on long term PTSD symptoms


<table>
<thead>
<tr>
<th>Objectives</th>
<th>To evaluate the effects of CUD on changes in PTSD symptoms after MJ discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective, longitudinal study</td>
</tr>
<tr>
<td>Population</td>
<td>260 male combat veterans admitted to residential rehabilitation program for PTSD at the VA Palo Alto Health Care System from 2000-2008</td>
</tr>
</tbody>
</table>

#### Inclusion
- Primary diagnosis of PTSD
- Abstinent from alcohol and illicit substances ≥ 15 days before treatment
- Severe PTSD not successfully treated outpatient

#### Exclusion
- Psychotic symptoms
- Medical conditions with high probability of interfering or preventing psychological treatment

#### Interventions (Appendix B)
- Baseline (treatment intake): SCID-I, PCL-M, general psychological distress measured by Beck Depression Inventory (BDI), trauma severity via seven-item Combat Exposure Scale (CES)
- Treatment discharge: PCL-M
- CBT provided in group setting, relapse prevention embedded into the program, and those with SUD were encouraged to attend 12-step self-help meetings

#### Endpoints
- Change in PCL scores

#### Statistics
- Four hierarchical linear regression analyses: CUD vs. PTSD symptoms
- Separate analyses for total PTSD symptoms and specific criteria change (adjust for covariates)

#### Results

**Baseline characteristics:**
- Race: 51% Caucasian, 20.8% AA, 11.9% Hispanic/Latino, 2.3% Asian/Pacific Islander
- Co-morbid psychiatric conditions: 80% mood d/o, 18.1% anxiety d/o, 31.2% CUD, 79.6% alcohol, 33.1% cocaine, 19.2% amphetamine, 12.7% opioid, 6.5% sedative use d/o
- No difference in PCL-M scores between CUD and no-CUD patients; CUD: 66.25 (± 10.3)

**Change in PCL-M Scores**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>No CUD</th>
<th>CUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>0.7</td>
<td>-0.18</td>
</tr>
<tr>
<td>C*</td>
<td>-1.36</td>
<td>-0.3</td>
</tr>
<tr>
<td>D*</td>
<td>-3.16</td>
<td>-0.95</td>
</tr>
<tr>
<td>Total</td>
<td>-5.2</td>
<td>-5.2</td>
</tr>
</tbody>
</table>

**Figure 9: Change in PCL-M Score (*significant)**

- PCL-M at discharge: 62.37 (± 13.8)
- Significantly lower level of change in total score, criteria C, criteria D (p<0.05 for all)
## Author's Conclusions
- CUD results in lower levels of change in PTSD symptoms over time (criteria C/D, total)
- CUD associated with worse PTSD treatment outcomes

## Critique
### Advantages
- Adjusted for variables (age, trauma severity, psychological distress, co-occurring SUD)
- Placebo controlled
- No difference in PTSD severity at baseline

### Disadvantages
- No active MJ use
- Power not reported
- May not be externally valid: only included male veterans in California with severe PTSD
- Some baseline characteristics not reported between groups
- Observational study: unable to determine causality
- Last cannabis use not reported
- Withdrawal symptoms not accounted for

## Take Home
CUD may be associated with worse PTSD outcomes, but, clinical significance is questionable

---

**Wilkinson ST, Stefanovics E, Rosenheck RA. Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder. The Journal of clinical psychiatry. 2015; 76(9), 1174-1180.**

### Objectives
To evaluate the effects of long term MJ use on PTSD symptoms

### Design
Retrospective, longitudinal, observational study

### Population
47,310 veterans admitted to intensive PTSD VA treatment programs from 1992-2011

#### Inclusion
- Severe PTSD (Per DSM III criteria until 1994, then DSM-IV criteria thereafter)

#### Exclusion
- Issues with alcohol or other SUD 30 days prior to admission
- Problematic alcohol use (> 2 drinks on 1 occasion)
- Those who transferred from inpatient or residential programs

### Interventions (Appendix B)
- Patients classified into 4 groups: no MJ use on admission or after discharge (never users), MJ use on admission but not after discharge (stoppers), MJ use on admission and after discharge (continuing users), no MJ use on admission but use after discharge (starters)
- Baseline: PTSD per DSM
- 4 months post discharge: MJ use, PTSD symptoms severity per the Mississippi Scale for Combat-Related PTSD (SF-MISS), violent behavior based on 4-item self-reported questionnaire from the National Vietnam Veterans’ Readjustment Study, employment status per Addiction Severity Index (ASI), alcohol/drug use per ASI

### Endpoints
- PTSD symptoms severity, employment status, violent behavior, alcohol/drug use

### Statistics
- Analysis of variance compared baseline characteristics and identified covariates
- Analysis of covariance (ANCOVA): controlled potential baseline confounders, t-test
- Covariates compared to PTSD symptoms, drug/alcohol use, violent behavior, employment
- $\alpha=0.01$
- Linear multiple regression model analysis used to examine association between MJ use and change in determined endpoints controlling for confounders
- Standardized regression coefficients used to evaluate strength of associations

### Results
#### Enrollment
- 12,770 met inclusion criteria, 2,276 participants included in the study

#### Baseline characteristics:
- Mean age: 51.7 y/o, 96.7% male, 72.7% white, 40.7% married, 40.7% separated/divorced,
mean education level: 12.9 years, 51.4% history incarceration, 28.4% affective d/o, 86.2% has been prescribed psychotropic meds within the past 30 days, 63.6% entered treatment program from waiting status, mean length of stay in treatment program: 42.5 days

- Difference found in the following baseline characteristics (Bivariate analysis):

Table 11: Significant Baseline Characteristics (bolded=significant, **=outcomes)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Never uses (n=850)</th>
<th>Stoppers (n=299)</th>
<th>Continuing users (n=296)</th>
<th>Starters (n=831)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>53.2 (8.1)</td>
<td>49.3 (9.6)</td>
<td>49.8 (10.0)</td>
<td>51.8 (8.0)</td>
</tr>
<tr>
<td>Married, n (%)</td>
<td>395 (46.5)</td>
<td>119 (39.8)</td>
<td>110 (37.2)</td>
<td>302 (36.3)</td>
</tr>
<tr>
<td>Separated/divorced, n (%)</td>
<td>308 (36.2)</td>
<td>117 (39.1)</td>
<td>129 (43.6)</td>
<td>373 (44.9)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>597 (70.2)</td>
<td>215 (72.4)</td>
<td>243 (82.1)</td>
<td>597 (71.9)</td>
</tr>
<tr>
<td>African American race, n (%)</td>
<td>212 (24.9)</td>
<td>61 (20.5)</td>
<td>36 (12.2)</td>
<td>173 (20.8)</td>
</tr>
<tr>
<td>War zone service, n (%)</td>
<td>795 (93.6)</td>
<td>275 (92.3)</td>
<td>259 (87.5)</td>
<td>783 (94.2)</td>
</tr>
<tr>
<td>Drug abuse on admission (ASI), mean (SD)**</td>
<td>0.026 (0.039)</td>
<td>0.103 (0.100)</td>
<td>0.114 (0.097)</td>
<td>0.039 (0.061)</td>
</tr>
<tr>
<td>Alcohol abuse on admission (ASI), mean (SD)**</td>
<td>0.063 (0.098)</td>
<td>0.099 (0.12)</td>
<td>0.086 (0.086)</td>
<td>0.080 (0.119)</td>
</tr>
<tr>
<td>Chronic medical problems, n (%)</td>
<td>631 (74.4)</td>
<td>192 (64.2)</td>
<td>203 (68.6)</td>
<td>578 (69.6)</td>
</tr>
<tr>
<td>Employment status on admission (ASI), mean (SD)**</td>
<td>0.589 (0.258)</td>
<td>0.536 (0.273)</td>
<td>0.592 (0.242)</td>
<td>0.560 (0.259)</td>
</tr>
<tr>
<td>Violence on admission, mean (SD) rating**</td>
<td>1.37 (1.36)</td>
<td>1.63 (1.32)</td>
<td>1.48 (1.28)</td>
<td>1.68 (1.42)</td>
</tr>
<tr>
<td>History of incarceration, n (%)</td>
<td>366 (43.2)</td>
<td>153 (51.2)</td>
<td>165 (55.7)</td>
<td>485 (58.4)</td>
</tr>
<tr>
<td>Willingness to attend reunions, n (%)</td>
<td>599 (70.9)</td>
<td>168 (56.8)</td>
<td>151 (51.7)</td>
<td>534 (65.4)</td>
</tr>
<tr>
<td>Length of stay in treatment program, mean (SD), d</td>
<td>44.8 (22.4)</td>
<td>39.3 (23.9)</td>
<td>38.2 (25.2)</td>
<td>42.8 (22.0)</td>
</tr>
<tr>
<td>Expelled from treatment program, n (%)</td>
<td>16 (1.9)</td>
<td>24 (8.1)</td>
<td>9 (3.1)</td>
<td>24 (2.9)</td>
</tr>
<tr>
<td>Was on waiting list for treatment program, n (%)</td>
<td>578 (68.2)</td>
<td>166 (56.3)</td>
<td>158 (53.9)</td>
<td>535 (64.9)</td>
</tr>
</tbody>
</table>

Outcomes after adjustment for covariates

Table 12: Endpoints Prior to Adjusting for Covariates (*significant)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Never users (n=850)</th>
<th>Stoppers (n=299)</th>
<th>Continuing users (n=296)</th>
<th>Starters (n=831)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD symptoms (SF-MISS)</td>
<td>37.71</td>
<td>36.64</td>
<td>38.92</td>
<td>39.67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Violence</td>
<td>0.87</td>
<td>0.76</td>
<td>0.93</td>
<td>1.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol abuse (ASI)</td>
<td>0.096</td>
<td>0.079</td>
<td>0.129</td>
<td>0.229</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Drug Abuse (ASI)</td>
<td>0.037</td>
<td>0.034</td>
<td>0.128</td>
<td>0.130</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Employment status (ASI)</td>
<td>0.578</td>
<td>0.575</td>
<td>0.594</td>
<td>0.577</td>
<td>0.5752</td>
</tr>
</tbody>
</table>

Effect size after adjusting for covariates and using never-users as a comparison:
- Starting MJ on PTSD symptoms: + 0.34
- Stopping MJ on PTSD symptoms: - 0.18
- Significant association between change in days MJ used and change in PTSD symptoms, severity of violent behavior, ASI alcohol index, and ASI drug abuse index
### Author’s Conclusions
- MJ significantly associated with worse outcomes in PTSD symptoms severity, violent behavior, and alcohol/drug use
- At follow-up, stoppers/never users had lower levels of PTSD symptoms and starters had highest levels of violent behaviors

### Critique

#### Advantages
- National longitudinal study
- Large sample size
- Adjusted for covariates

#### Disadvantages
- Observational study
- Drug use was self-reported measure; not verified by UDS
- Based on chart reviews: documentation error
- Evaluated primarily older white male veterans with severe PTSD and excluded other substance use disorders: external validity?
- Did not account for frequency/quantity of MJ use
- Did not account for MJ withdraw during treatment program period
- ASI questionnaire included MJ as a substance

### Take Home
MJ use may be associated with worse PTSD symptoms severity, violent behavior, and alcohol/drug use; however, based on the study, clinical significance is questionable. The study did not suggest improvement in PTSD symptom as hypothesized in literature.

### Summary

I. High percentage of patients do not tolerate/respond to conventional treatment options for PTSD
II. The cannabinoid system plays a role in PTSD and may be a novel mechanism for treatment
III. MJ use in patients with PTSD is common and may be associated with self-medicating
IV. It has been theorized that medical MJ may help with global improvement of PTSD
V. Per Consolidation Appropriations Act, providers are unable to interfere with patients seeking medical MJ and may actually recommend treatment
VI. Although some positive data exists for the use of MJ in PTSD, current evidence is limited to anecdotal experiences, case reports, and observational studies
VII. Concerns/barriers with the use of medical MJ
   A. Drug abuse/addiction
   B. Mental health issues
   C. Dose/potency/strength/dispensing reputability
   D. Long term effects
   E. Research limited due to legal status
   F. Eligibility
   G. State variability in authorized prescribers: no definition of patient physician relationship
   H. Financial: not covered by insurance

### Future Direction

I. Bonn-Miller and colleagues: placebo-controlled, triple-blind, randomized crossover pilot study of the safety and efficacy of five potencies of smoked or vaporized MJ in 76 Veterans with chronic, PTSD
II. Legal status: many bills introduced to change current federal law and reclassify MJ
I. MJ may be considered as an alternative option in the states it is approved in if all conventional options fail or are contraindicated. However, at this time, due to lack of evidence and unknown factors such as strength/dose, potency, strain, and frequency, unable to widely recommend its use.

II. Psychotherapy (e.g. CBT, EMDR, and anxiety management) and current available pharmacotherapy (SSRI/SNRI) are still the preferred treatments due to the level of evidence.

III. Risk vs. benefit should be assessed on an individual basis. MJ should be avoided in the younger population, history of substance use/dependence, comorbid schizophrenia and related disorders as well as bipolar disorder.

IV. If medical MJ is used must monitor for dependence, abuse, side effects, and worsening of symptoms.

References

Appendix A. PTSD DSM-5 Diagnostic Criteria Examples

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Brief Description</th>
<th>Examples</th>
</tr>
</thead>
</table>
| A        | Trauma exposure (actual/threatened death, serious injury, sexual violence) | - Directly experience  
- Witnessing  
- Learning about to close family member/friend  
- Repeated/extreme exposure to aversive details |
| B        | Intrusive symptoms | - Recurrent, involuntary, distressing memories, dreams/nightmares  
- Dissociative reactions (flashbacks)  
- Intense or prolonged psychological distress to triggers |
| C        | Avoidance | - Memories, thoughts, feelings  
- External reminders (people, places, conversations, situations) |
| D        | Negative alterations in cognitions and mood | - Inability to remember  
- Negative beliefs/expectations about oneself, others, or the world  
- Blame oneself/others  
- Negative emotional state (fear, horror, anger, guilt, shame)  
- Diminished interest/participation in activities  
- Detached or estranged from others  
- Inability to experience positive emotions (happiness, satisfaction, love) |
| E        | Arousal | - Irritability/anger outburst  
- Reckless/self-destructive behavior  
- Hypervigilance/exaggerated startle response  
- Difficulty concentrating  
- Sleep disturbances (difficulty falling/staying asleep) |


<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>Description</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Of Life Scale (QOLS)(^{52-53})</td>
<td>Measures QOL across diverse patients</td>
<td>Scores calculated via sum</td>
</tr>
<tr>
<td></td>
<td>16-items, self-rated</td>
<td>7-item Likert scale (1: terrible, 2: unhappy, 3: most dissatisfied, 4: mixed, 5: mostly satisfied, 6: pleases, 7: delighted)</td>
</tr>
<tr>
<td></td>
<td>5 minutes</td>
<td>Score ranges from 16-112</td>
</tr>
<tr>
<td></td>
<td>Assesses: material and physical well-being, relationships, independence,</td>
<td>Higher score = higher QOL</td>
</tr>
<tr>
<td></td>
<td>social/community/civic activities, personal development/fulfillment,</td>
<td>Average total score for healthy population = 90</td>
</tr>
<tr>
<td></td>
<td>recreation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reliability and validity established</td>
<td></td>
</tr>
<tr>
<td>Clinical Global Impression Scale (CGI)(^{54})</td>
<td>Assesses global level of functioning for the past 7 days</td>
<td>7-item Likert scale</td>
</tr>
<tr>
<td></td>
<td>2 components: Improvement (CGI-I), Severity (CGI-S)</td>
<td>5: 1: normal, not ill at all, 2: borderline mentally ill, 3: mildly ill, 4: moderately ill, 5: markedly ill, 6: severely ill, 7: among the</td>
</tr>
<tr>
<td></td>
<td>Clinician-rated</td>
<td>most extremely ill</td>
</tr>
<tr>
<td></td>
<td>Used in clinical trials</td>
<td>I: 1: very much improved, 2: much improved, 3: minimally improved, 4: no change from baseline, 5: minimally worse, 6: much worse, 7: very much worse</td>
</tr>
<tr>
<td></td>
<td>Well established</td>
<td></td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index (PSQI)(^{55})</td>
<td>Assess sleep quality</td>
<td>Only self-rated question included in scoring</td>
</tr>
<tr>
<td></td>
<td>19-items, 5 rated by bed partner/roommate</td>
<td>4-item Likert scale (0: no difficulty-3: severe difficulty)</td>
</tr>
<tr>
<td></td>
<td>Self-rated</td>
<td>19 questions combined into 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“component” scores (\rightarrow) sum = global score</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total score: 0 (no difficulty)-21 (severe difficulties)</td>
</tr>
<tr>
<td>Nightmare Effects Survey (NES)(^{56})</td>
<td>Assesses emotional disturbance and interference caused by nightmares</td>
<td>5-item Likert scale (0: not at all-4: a great deal)</td>
</tr>
<tr>
<td></td>
<td>(adverse effects on sleep, work, relationships, energy, school, etc.)</td>
<td>Total score (sum of 11 items): 0-44</td>
</tr>
<tr>
<td></td>
<td>11-items, self-rated</td>
<td>Any score indicates impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher score = higher impairment</td>
</tr>
<tr>
<td>Nightmare Frequency Questionnaire (NFQ)(^{56})</td>
<td>Measure of frequency of nightmares and time in the past 3 months</td>
<td>Select one time and frequency (e.g. 3 NM x weekly)</td>
</tr>
<tr>
<td></td>
<td>2-items</td>
<td></td>
</tr>
<tr>
<td>Drug Use Questionnaire (DUQ)(^{57})</td>
<td>Assesses drug use within the past 12 months</td>
<td>Yes/no responses</td>
</tr>
<tr>
<td></td>
<td>10-items, self-rated or clinician-rated</td>
<td>Yes = 1</td>
</tr>
<tr>
<td></td>
<td>Sensitive and specific</td>
<td>Score interpretation 0: no problems, 1-2: low level (monitor), 3-5: moderate level (further investigation), 6-8: substantial level (assessment required), 9-10: severe (assessment required)</td>
</tr>
<tr>
<td>Mini-Mental State Exam (MMSE)(^{58-59})</td>
<td>Assess memory and other mental abilities (attention, language)</td>
<td>Total 30 points: sum of all items</td>
</tr>
<tr>
<td></td>
<td>Helps diagnose dementia and assess prognosis/severity</td>
<td>&lt; 24 abnormal for college education</td>
</tr>
<tr>
<td></td>
<td>11-items, clinician-rated</td>
<td>18-23: mild cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>Validated</td>
<td>0-17: severe cognitive impairment</td>
</tr>
<tr>
<td>Rating Scale</td>
<td>Description</td>
<td>Interpretation</td>
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<tr>
<td>The Positive and Negative Affect Schedule (PANAS-NA)&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Measures positive and negative affect-NA (negative affect) Consists of words that describe different feelings/emotions 20-items, self-rated Validated for anxiety disorders</td>
<td>6-item Likert scale based on your feelings (1: very slight/not at all, 1: a little, 3: moderately, 4: quite a bit, 5: extremely) Add score for 10 negative words Total score 10-50 Low score = low negative affect</td>
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<tr>
<td>Beck Depression Inventory (BDI)&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Assess depression symptom severity over the past 2 weeks 21-items, self-rated Used in clinic trials/practice</td>
<td>6-item Likert scale (0: absent-3: severe) 30-63: severe depression 17-29: moderate depression 10-16: mild depression 0-9: no depression Response: ≥ 50% reduction in score Remission: score ≤ 10</td>
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<tr>
<td>Combat Exposure Scale (CES)&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Assesses wartime stressors experienced in combat 7-items, self-rated</td>
<td>6-item Likert scale (1: no/never-5: greatest frequency) Total score calculated by sum Total score: 0-41</td>
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<td>Short-Form Mississippi Scale for Combat-Related PTSD (SF-MISS)&lt;sup&gt;63-64, 67&lt;/sup&gt;</td>
<td>Assess combat related PTSD in Veteran population Symptoms per DSM-III 10-items, self-rated Validated</td>
<td>5-item Likert scale (1: not at all-5: extremely true) Total score: sum off all items Score ranges from 11-55 Higher scores indicate symptom severity</td>
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<td>Addiction Severity Index (ASI)&lt;sup&gt;45, 65, 68&lt;/sup&gt;</td>
<td>Addresses 7 potential problems in substance abuse (e.g. medical status, employment and support, etc.) within the past 30 days Used for treatment planning outcomes evaluation 200-items; 7 subscales Clinician-rated 1 hour semi structured interview Validated</td>
<td>5-item Likert scale (0: not at all-4: extremely) Provides 2 scores: severity rating developed by the interviewer and composite scores measure problem severity past 30 days Wilkinson and colleagues evaluated composite scores (ranging 0-1) for: Employment strength (higher score = less severity) Alcohol/drug use (higher score = greater problem severity)</td>
</tr>
<tr>
<td>Self-reported questionnaire from the National Vietnam Veterans' Readjustment Study&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Assess violent behavior 4-items Cronbach [alpha] = 0.71 (acceptable reliability)</td>
<td>Score ranges from 1-4 1: destruction of property 2: threatening someone with physical violence without a weapon 3: threatening someone with a weapon 4: physically fighting with someone</td>
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</tbody>
</table>