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[1]
   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[2]

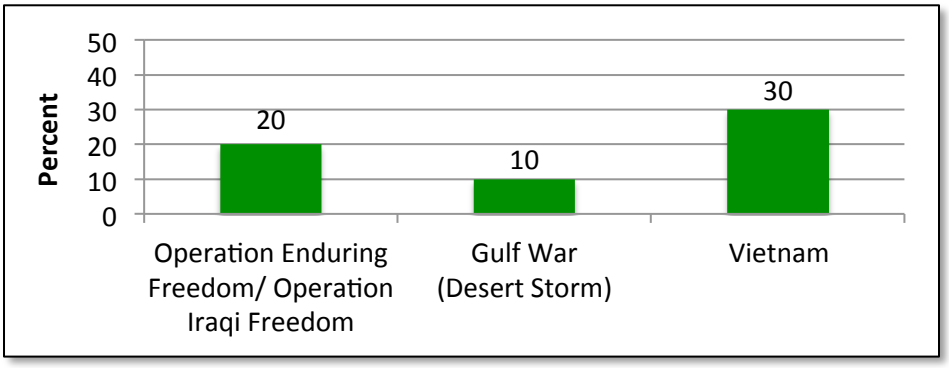


Figure 1: Occurrence of PTSD in Veterans (%)[3]

II. Clinical presentation[4]

Table 1: Clinical Presentation of PTSD

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

III. Many co-occurring psychiatric conditions: depression (80%), alcohol and substance use (50%), attempted suicide (20%)[12]
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 2: Risk Factors for Developing PTSD

Pre-traumatic	Peri- /Post-traumatic
▪ Lack of social support ▪ Younger age ▪ Psychiatric disorders (including PTSD) ▪ History of traumatic exposure (abuse) ▪ Childhood adversity (family dysfunction, parental separation/death) ▪ Female ▪ ↓ socioeconomic status/education level/intelligence ▪ Race ▪ Childhood emotional problems (externalizing) ▪ Family history ▪ Traumatic brain injury ▪ Personality disorder (borderline) ▪ History of substance use	▪ Severity/nature/duration of trauma ▪ Physical injury ▪ High perceived threat to life ▪ Dissociation ▪ Interpersonal trauma ▪ Emotional response ▪ Lack of social support ▪ Acute stress disorder ▪ Ongoing stress ▪ Bereavement/traumatic grief ▪ Major loss of resources ▪ Negative appraisal (shaming/blaming) ▪ Poor coping strategies ▪ Reminders

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

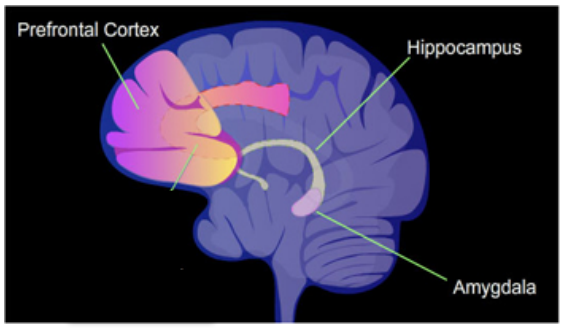


Figure 2: Brain Structures Involved in PTSD[49]

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

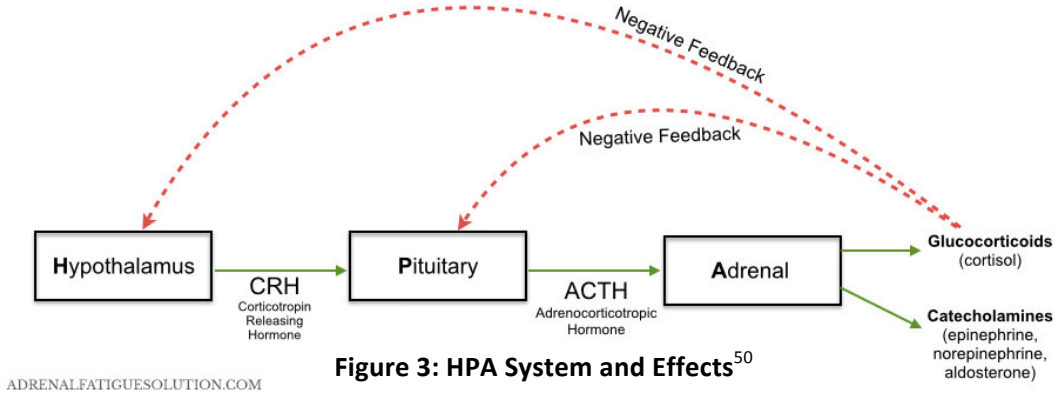


Figure 3: HPA System and Effects[50]

2. ↑ Norepinephrine (NE)
    a. Presynaptic α_2 antagonism = exaggerated central nervous system (CNS) response, hypersensitivity to stimuli, and autonomic hyperactivity (e.g. ↑ BP/HR)
    b. Peripheral α_1 agonism = ↑ startle and ↑ nightmares (NM)/intrusive thoughts[10]
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[12]

Assessment and Treatment of PTSD

I. Many screening tools/diagnostic scales developed[4]
   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)

Scale	Description	Interpretation
Clinician Administered PTSD Scale-5 (CAPS-5)[5] ***Gold Standard***	• 30-item; assesses 20 PTSD symptoms • Clinician-rated • Used to diagnose, assess symptoms, and assess treatment response • Can assess impact on functioning and clinical improvement • Three versions: assessing symptoms om the past week, month, or worst month (lifetime) • Can take 45-60 minutes	• Score ranges from 0-150 • Each question rated from Likert 0-4 (absent, mild, moderate, severe, extreme) • Score calculated by summing frequency/intensity of reported symptoms • **Remission**: ↓ ≥ 70% in symptoms and maintained for 3 months • **Adequate response**: ↓ ≥ 50% in symptoms • **Partial response**: ↓ 25-50% in symptoms • **Non response**: ↓ < 25% in symptoms
PTSD Checklist-5 (PCL-5)[6]	• 20-item • Self-rated • Used for provisional diagnosis, screening, and monitoring symptoms • Can take 5-10 minutes	• Score ranges from 0-80 • Each question rated from Likert 0-4 (not at all, a little bit, moderately, quite a bit, extremely) • Score calculated by summing all responses • Score ≥ 38: requires further evaluation for diagnosis • **Reliable change**: ↓ 5-10 points • **Clinically significant change**: ↓ ≥ 10 points

II. Treatment Guidelines

Figure 4: VA/DoD Practice Guidelines for PTSD[4]

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[12]

Psychotherapy	Description
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[4]

Class (FDA approved)	Place in therapy	Mechanism of action	Side effects
SSRIs (paroxetine and sertraline)	1st/2nd line; improves all symptom criteria of PTSD (global improvement)	Inhibit 5-HT reuptake	**Anxiety/agitation, gastrointestinal (GI) upset, sexual dysfunction, headaches**, serotonin syndrome, **sweating**, hyponatremia/syndrome of inappropriate anti-diuretic hormone (SIADH)
SNRIs: venlafaxine	1st/2nd line	Inhibition of 5-HT and NE reuptake	**Same as SSRIs** + ↑ **BP, tremor, insomnia**
Noradrenergic and specific serotonergic antidepressant-NaSSA: mirtazapine[7-8]	3rd line	α_2 antagonist (increase NE and 5-HT), 5-$HT_{2A/C}$ antagonist, 5-HT_3 antagonist, histamine (H_1) antagonist	**Anxiety**, sedation, increased appetite/weight gain
Antihypertensive: prazosin	3rd line; adjunct for nightmares	α_1 antagonist → ↓ NE	**Dizziness**, **drowsiness,** ↑ **HR**, hypotension/orthostasis
Serotonin antagonist/reuptake inhibitor-SARI: nefazodone[7]	4th line	Weak SSRI/SNRI/α_1 antagonist, 5-HT antagonist, H_1 antagonist	**Anxiety, GI upset, headaches, insomnia/somnolence**, orthostasis/**dizziness**, hepatotoxicity, **sexual dysfunction**
TCAs: amitriptyline and imipramine[7]	4th line	SSRI/SNRI, muscarinic (M_1)/ α_1/H_1 antagonist, Block voltage-sensitive Na channels	**Same as SSRIs/SNRI + anticholinergic**, orthostasis, **dizziness**, sedation, weight gain, coma, seizures, cardiac arrhythmias, cardiac arrest
Monoamine oxidase inhibitor (MAO-I): phenelzine[7,9]	4th line	Nonselective irreversible MAOI inhibitor = ↑ 5-HT, NE, H, dopamine, epinephrine	**Same as SSRIs/SNRI +** hypertensive crisis

*** Bolded side effects are similar to PTSD presentation**

V. Average duration of symptoms[12]
   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[13]
    1. Psychotherapy: 2-4
    2. Pharmacotherapy: 8-9
  B. Psychotherapy
    1. Meta-analysis by Bradley and Colleagues[14]
      a. Completed treatment: 67% no longer met criteria
    2. High dropout rates: 13-39%[15]
  C. Pharmacotherapy
    1. 2005 National Institute for Health and Clinical Excellence (NICE) guidelines do not recommended pharmacotherapy as first line treatment[16]
    2. Remission rates: 20-30%[17]
    3. Cochrane review by Stein and Colleagues[18]
      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[19]
    5. Estimated ~ 20% of veterans are effectively treated possibly due to medications being most effective for woman and acute PTSD[16]

Marijuana and PTSD

I. Marijuana (MJ)
  A. History[21-22, 25, 28, 31]

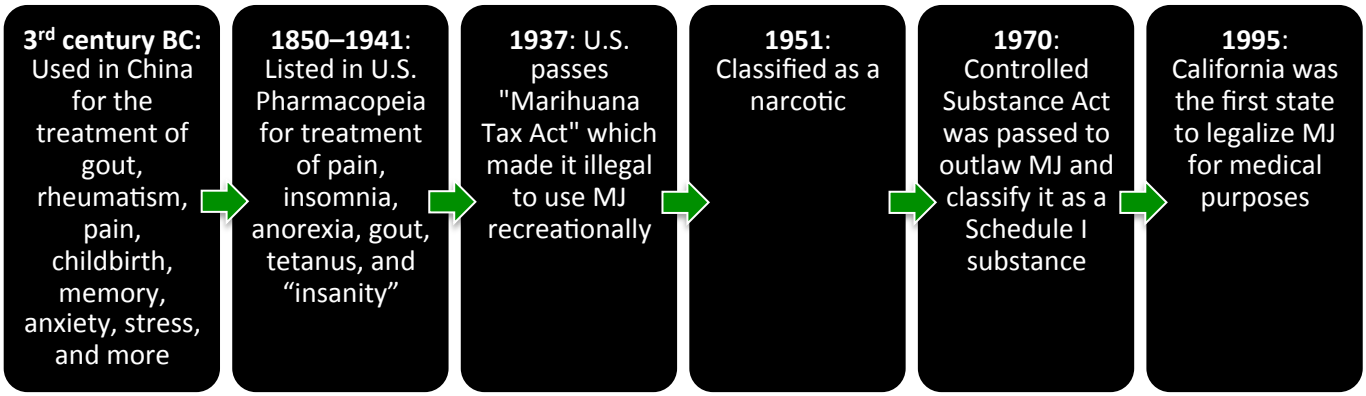


Figure 5: MJ History

  B. Medical use[22]
    1. Canada and many European countries (Netherlands, the Czech Republic, Spain, Portugal)[21]
    2. Legal in 23 states and the District of Columbia[26, 28, 29] 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[25, 29]
        b. Bill passed prohibiting VA (Veteran Affairs) from interfering with/denying services to Veterans who participate in state-approved medical MJ programs[46]
        c. Addendum to bill: allowing VA providers to recommend/provide information on medical MJ in state-approved medical MJ programs[48]

D. Biochemistry and Pharmacology[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. ↑ Δ 9-Tetrahydrocannabinol (THC)
            ii. Lifts mood and relieves stress
        c. Indica
            i. ↓ THC, ↑ 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[32]
            iii. Content can vary from 0.2-30%[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[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 ↑ stress coping behaviors and ↑ 5-HT and NE firing in the midbrain[30]
        d. Functions in conjunction with adrenergic, cholinergic, and dopaminergic system[31]
        e. Protein coupled receptors regulate excitatory and inhibitory neurotransmission; therefore, assists in the role of homeostasis (e.g. prevents extreme cortisol excitation)[31, 38]
        f. Absent in brainstem; therefore, no activity seen in the autonomic nervous system = none to minimal risk of lethal overdose[31]

Table 6: Cannabinoid Receptors[21, 25, 31-32]

Receptor	Function	Location
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
CB-2	Suppress immune response, pain, digestion	Gut, immune system, spleen, lymph nodes

Table 7: Cannabis Pharmacokinetics[24-25]

Administration	Bioavailability (%)	Onset	Time to Peak	Duration
Inhalation	2-56	3-9 minutes	14-30 minutes	2 hours
Oral	4-20	Hours	1-8 hours	Hours

4. Adverse Drug Reactions (ADRs)

Table 8: MJ Adverse Reactions Classified by System

System	Effects
Cardiovascular[25, 31]	• 20-100% ↑ HR, ↑ cardiac output up to 30%, ↓ BP, ↓ peripheral vascular resistance, ↓ skin temperature by 4-6° C
Respiratory[25, 31]	• Conflicting reports, but possible large airway obstruction, cellular inflammatory abnormalities in bronchial epithelium, ↑ respiratory symptoms (dyspnea, pharyngitis, bronchial spasms)
Endocrine[25]	• ↓ sperm count and motility in men, ↑ prolactin/follicle-stimulating hormone/growth hormones in females
Immune[25]	• Impair cell-mediated and humoral immune response, ↑ risk of infection
Cognitive[25, 31, 28]	• ↓ psychomotor activity and response, ↓ short term memory, ↓ motivation • ↓ ability to learn new concepts, may affect attention/learning days-weeks after use • ↑ risk of psychotic disorders with high risk genotypes and ↑ psychotic symptoms in those with schizophrenia and like disorders, ↓ remission of schizophrenia • In those with bipolar disorder: ↑ time in affective episode, ↑ risk of rapid cycling, ↑ manic symptoms, ↓ global functioning, ↓ remission
Addiction[25-26, 31, 38]	• 2010 National Survey on Drug Use and Health: 4.5 million Americans were dependent • 9% of adults and 17% adolescents become addicted (risk = younger age and daily use) • ↑ risk with other MH disorders (e.g. depression, anxiety, **PTSD**)
Other[30]	• Dizziness, anxiety, paranoia, dry mouth, fatigue, sedation, weakness

II. Current MJ use: medically, recreationally, spiritually[31]
   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[33]
      b. Cougle et al.: in 5,672 U.S. adults, 65% with PTSD vs. 41% without PTSD used MJ[34]
   F. In 2009, 30% of Veterans within the VA with a PTSD diagnosis also had Cannabis Use Disorder (CUD)[44]

III. Pharmacology of the cannabinoid system in PTSD
   A. Endocannabinoid system may play a role in PTSD[30]
      1. ↑ availability of CB1 receptors and ↓ CB1 agonism in those with PTSD[29, 40]
      2. Alleviate anxiety through actions in the prefrontal cortex, amygdala, and hippocampus [30]
      3. Alterations in CB1 receptors seen in depression[30]
      4. Sensitization of CB1 receptor-mediated G-protein signaling in prefrontal cortex may play a role in suicide and suicidal behavior[30]
   B. Benefit: sleep, NM, potency of flashbacks, modulate emotional response, decrease/eradicate intrusive thoughts (memories), hyperarousal, negative affect, anxiety, aggression, anger[25, 29-30, 38]
      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[38]
6. ↓ REM sleep, enhance non-REM phase 4 sleep = ↓ NM, ↑ sleep quality[38, 40]

C. Many studies demonstrate PTSD severity associated with MJ use coping mechanism[35, 36, 41]

D. Reported anecdotal benefit in PTSD and suicidality[25, 29, 30, 38, 41]

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

Study (year)	Population	Design	Results
Reznik et al. (2012)[37]	167 Israeli adults with PTSD +/- comorbid conditions applying for medical MJ license	3 year, prospective cohort; 2-3g of daily Sativa	• Significant improvement in quality of life per QOLS, CGI-I, and pain scores • Positive changes in CAPS scores • MJ use resulted in discontinuation/dose reduction of pain medications/sedatives • Most beneficial in comorbid pain/depression • No serious ADRs seen
Mashiah et al. (2012)[39]	29 Israeli male combat veterans	1 year, open label pilot study; max 100g of Indica (23% THC, 1% CBD)/month; encouraged daily use	• 10 participants completed study • CAPS score ↓ from 97.7 ± 13.3 to 53.7 ± 18.3 • All still met criteria for moderate-severe PTSD at the conclusion of the study
Roitman et al. (2014)[40]	10 Israelis with chronic PTSD on stable meds (5 combat related PTSD)	3 week, open label, adjusted dose study; 5mg of THC BID	• Significant improvement in global symptom severity (CGI-S/I), sleep quality (PSQI, NES), frequency of NM (NFQ), hyperarousal (CAPS) • Complete remission of NM in 2 patients • Mild ADR (n=3): dry mouth, headache, dizziness

Literature Review

I. Effect of MJ use on immediate emotional response

Tull MT, McDermott MJ, Gratz KL. Marijuana dependence moderates the effect of posttraumatic stress disorder on trauma cue reactivity in substance dependent patients. Drug and Alcohol Dependence. 2016; 159, 219-226.[42]	
Objectives	To evaluate subjective and biological reactivity in those with MJ dependence and PTSD
Design	Placebo controlled prospective trial
Population	202 patients with/without PTSD admitted to a Substance Use Disorder (SUD) treatment facility
	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

	PTSD; n (%)	No PTSD; n (%)	Total; n (%)
MJ dependence	21	38	59 (29.2)
No MJ dependence	33	110	143 (70.8)
Total	54 (29.2)	148 (73.3)	202

% 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:

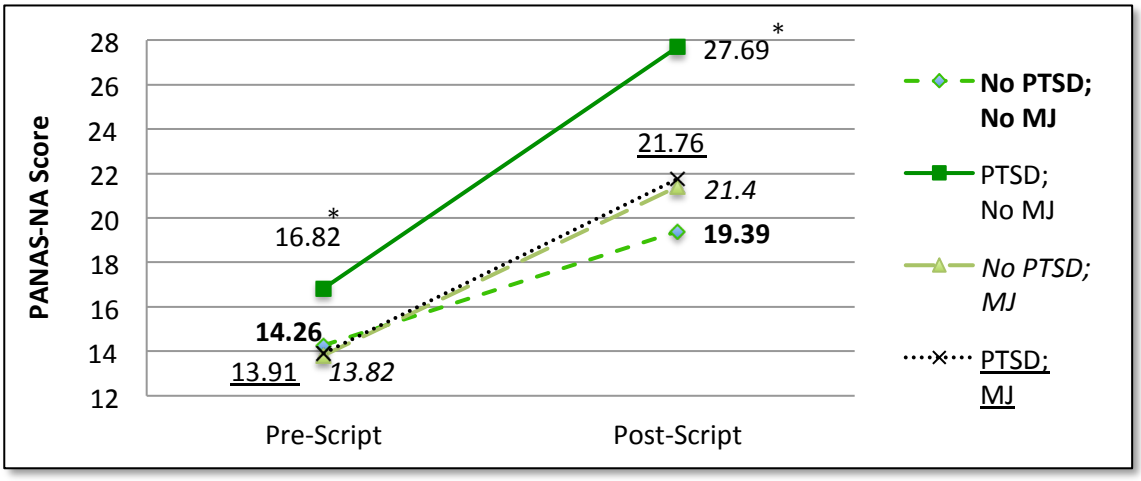
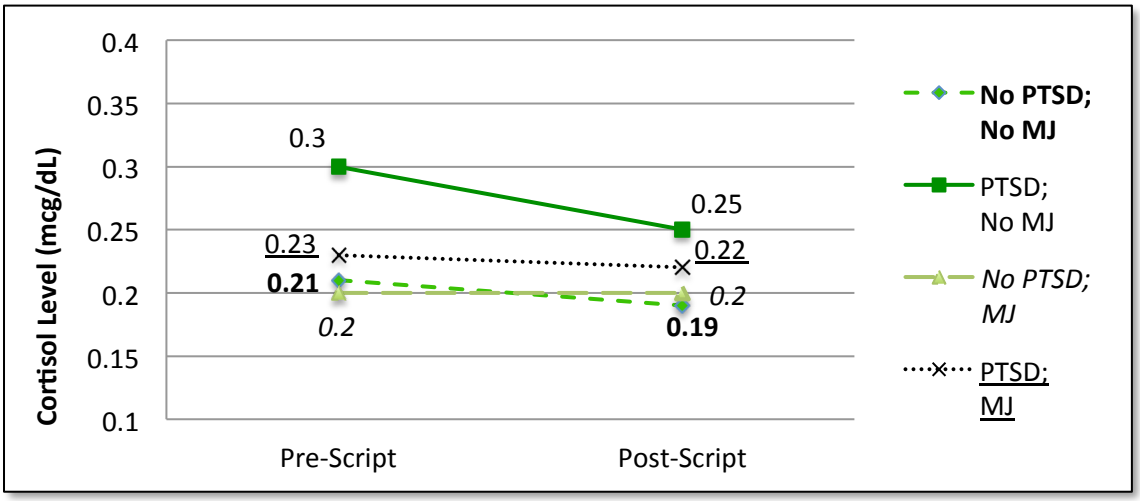
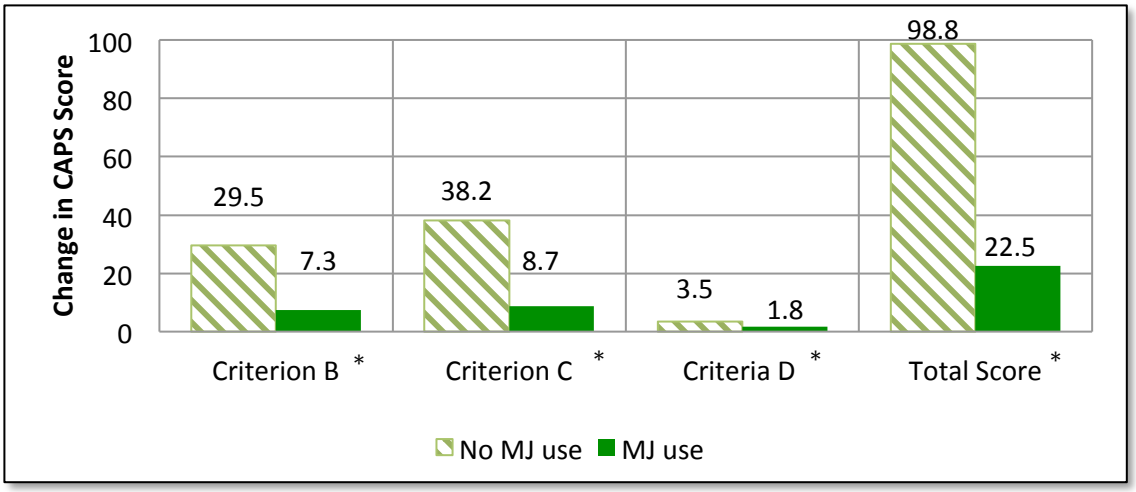


Figure 6: Change in PANAS-NA Score (*significant)

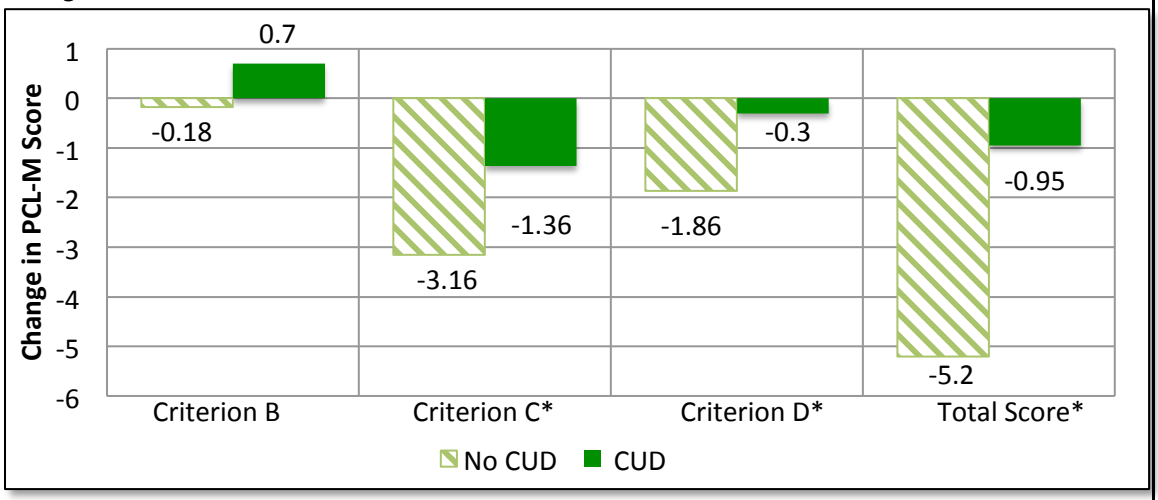
- Significantly associated with emotional activity: age (p=0.04), anxiety disorders (p=0.006), number of potentially traumatic events experienced (p<0.001), BPD (p=0.03)

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:***  **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.[43]	
Objectives	To evaluate the effects of MJ use on global PTSD symptoms
Design	Retrospective chart review
Population Continued	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***  **Figure 8: Change in CAPS Score (*significant)** ▪ 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

Bonn-Miller MO, Boden MT, Vujanovic AA, et al. Prospective investigation of the impact of cannabis use disorders on posttraumatic stress disorder symptoms among veterans in residential treatment. Psychological Trauma: Theory, Research, Practice, and Policy. 2013; 5(2), 193.[44]	
Objectives	To evaluate the effects of CUD on changes in PTSD symptoms after MJ discontinuation
Design	Prospective, longitudinal study
Population	260 male combat veterans admitted to residential rehabilitation program for PTSD at the VA Palo Alto Health Care System from 2000-2008
	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***  **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.[45]	
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 ▪ α=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,

Results Continued

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)

	Never uses (n=850)	Stoppers (n=299)	Continuing users (n=296)	Starters (n=831)
Age, mean (SD), y	**53.2 (8.1)**	49.3 (9.6)	49.8 (10.0)	**51.8 (8.0)**
Married, n (%)	**395 (46.5)**	119 (39.8)	110 (37.2)	302 (36.3)
Separated/divorced, n (%)	308 (36.2)	117 (39.1)	129 (43.6)	**373 (44.9)**
White race, n (%)	597 (70.2)	215 (72.4)	**243 (82.1)**	597 (71.9)
African American race, n (%)	**212 (24.9)**	61 (20.5)	36 (12.2)	**173 (20.8)**
War zone service, n (%)	**795 (93.6)**	275 (92.3)	259 (87.5)	**783 (94.2)**
Drug abuse on admission (ASI), mean (SD)**	0.026 (0.039)	**0.103 (0.100)**	**0.114 (0.097)**	0. 039 (0.061)
Alcohol abuse on admission (ASI), mean (SD)**	0.063 (0.098)	**0.099 (0.12)**	**0.086 (0.086)**	**0.080 (0.119)**
Chronic medical problems, n (%)	**631 (74.4)**	192 (64.2)	203 (68.6)	578 (69.6)
Employment status on admission (ASI), mean (SD)**	**0.589 (0.258)**	0.536 (0.273)	**0.592 (0.242)**	0.560 (0.259)
Violence on admission, mean (SD) rating**	1.37 (1.36)	**1.63 (1.32)**	1.48 (1.28)	**1.68 (1.42)**
History of incarceration, n (%)	366 (43.2)	153 (51.2)	**165 (55.7)**	**485 (58.4)**
Willingness to attend reunions, n (%)	**599 (70.9)**	168 (56.8)	151 (51.7)	**534 (65.4)**
Length of stay in treatment program, mean (SD), d	**44.8 (22.4)**	39.3 (23.9)	38.2 (25.2)	**42.8 (22.0)**
Expelled from treatment program, n (%)	16 (1.9)	**24 (8.1)**	9 (3.1)	24 (2.9)
Was on waiting list for treatment program, n (%)	**578 (68.2)**	166 (56.3)	158 (53.9)	**535 (64.9)**

Outcomes after adjustment for covariates

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

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

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[21, 31]
    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[47]
II. Legal status: many bills introduced to change current federal law and reclassify MJ[51]

Recommendations

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

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Appendices

Appendix A. PTSD DSM-5 Diagnostic Criteria Examples[1]

Criteria	Brief Description	Examples
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)

Appendix B. Rating Scales used in Studies		
Rating Scale	**Description**	**Interpretation**
Quality Of Life Scale (QOLS)[52-53]	▪ Measures QOL across diverse patients ▪ 16-items, self-rated ▪ 5 minutes ▪ Assesses: material and physical well-being, relationships, independence, social/community/civic activities, personal development/fulfillment, recreation ▪ Reliability and validity established	▪ Scores calculated via sum ▪ 7-item Likert scale (1: terrible, 2: unhappy, 3: most dissatisfied, 4: mixed, 5: mostly satisfied, 6: pleases, 7: delighted) ▪ Score ranges from 16-112 ▪ Higher score = higher QOL ▪ Average total score for healthy population = 90
Clinical Global Impression Scale (CGI)[54]	▪ Assesses global level of functioning for the past 7 days ▪ 2 components: Improvement (CGI-I), Severity (CGI-S) ▪ Clinician-rated ▪ Used in clinical trials ▪ Well established	▪ 7-item Likert scale ▪ S: 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 most extremely ill ▪ 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
Pittsburgh Sleep Quality Index (PSQI)[55]	▪ Assess sleep quality ▪ 19-items, 5 rated by bed partner/roommate ▪ Self-rated	▪ Only self-rated question included in scoring ▪ 4-item Likert scale (0: no difficulty-3: severe difficulty) ▪ 19 questions combined into 7 "component" scores → sum = global score ▪ Total score: 0 (no difficulty)-21 (severe difficulties)
Nightmare Effects Survey (NES)[56]	▪ Assesses emotional disturbance and interference caused by nightmares (adverse effects on sleep, work, relationships, energy, school, etc.) ▪ 11-items, self-rated	▪ 5-item Likert scale (0: not at all-4: a great deal) ▪ Total score (sum of 11 items): 0-44 ▪ Any score indicates impairment ▪ Higher score = higher impairment
Nightmare Frequency Questionnaire (NFQ)[56]	▪ Measure of frequency of nightmares and time in the past 3 months ▪ 2-items ▪ Reliable	▪ Select one time and frequency (e.g. 3 NM x weekly)
Drug Use Questionnaire (DUQ)[57]	▪ Assesses drug use within the past 12 months ▪ 10-items, self-rated or clinician-rated ▪ Sensitive and specific	▪ Yes/no responses ▪ Yes = 1 ▪ 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)
Mini-Mental State Exam (MMSE)[58-59]	▪ Assess memory and other mental abilities (attention, language) ▪ Helps diagnose dementia and asses prognosis/severity ▪ 11-items, clinician-rated ▪ Validated	▪ Total 30 points: sum of all items ▪ < 24 abnormal for college education ▪ 18-23: mild cognitive impairment ▪ 0-17: severe cognitive impairment

Rating Scale	Description	Interpretation
The Positive and Negative Affect Schedule (PANAS-NA)[60]	▪ Measures positive and negative affect-NA (negative affect) ▪ Consists of words that describe different feelings/emotions ▪ 20-items, self-rated ▪ Validated for anxiety disorders	▪ 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
Beck Depression Inventory (BDI)[61]	▪ Assess depression symptom severity over the past 2 week ▪ 21-items, self-rated ▪ Used in clinic trials/practice	▪ 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
Combat Exposure Scale (CES)[62]	▪ Assesses wartime stressors experienced in combat ▪ 7-items, self-rated	▪ 6-item Likert scale (1:no/never-5: greatest frequency) ▪ Total score calculated by sum ▪ Total score: 0-41
Short-Form Mississippi Scale for Combat-Related PTSD (SF-MISS)[63-64, 67]	▪ Assess combat related PTSD in Veteran population ▪ Symptoms per DSM-III ▪ 10-items, self-rated ▪ Validated	▪ 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
Addiction Severity Index (ASI)[45, 65, 68]	▪ 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	▪ 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)
Self-reported questionnaire from the National Vietnam Veterans' Readjustment Study[66]	▪ Assess violent behavior ▪ 4-items ▪ Cronbach [alpha] = 0.71 (acceptable reliability)	▪ 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