SUBSTANCES OF MISUSE, USEFUL IN PTSD?

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Objectives
■ Summarize the prevalence and pathophysiology theories for Post-Traumatic Stress Disorder (PTSD)
■ Compare emerging therapies in the treatment of PTSD
■ Evaluate clinical literature regarding stimulants and cannabinoids use in PTSD
■ Discuss potential place in therapy of stimulants and cannabinoids for PTSD therapy

Post-Traumatic Stress Disorder (PTSD)
■ Incapacitating chronic syndrome that reflects changes from an initial traumatic experience in
  - Cognitive
  - Emotional
  - Physiological
■ Refers to PTSD with persistent recurrence of traumatic memories
  - Nightmares
  - Intrusive thoughts
  - Increased avoidance of trauma-related stimuli
  - Negative alteration in cognition and mood
  - Hyperarousal
  - Hypervigilance

Prevalence
■ PTSD affects approximately 78% of the adult American population
  - Isolated trauma affects 50% of women and 60% of men
■ Majority of patients affected by PTSD experience at least one traumatic event:
  - Witnessed severe injury or death
  - Involved in natural disaster
  - Life threatening accident
  - Sexual assault
  - Combat exposure

Prevalence cont.
■ PTSD and the Military
  - Operations Iraqi Freedom (OIF) and Enduring Freedom (OEF)
    - 13.3% out of 100 Veterans
  - Gulf War Desert Storm
    - 12 out of every 100 Veterans
  - Vietnam War
    - 13 out of every 100 Veterans
  - Military sexual trauma (MST) sexual harassment or sexual assault
    - 28% of women = sexual assault
    - 52% of women and 38% of men experience sexual harassment

Risk Factors
■ Pre-traumatic factors
  - Gender – female > male
  - Age
  - Lower socioeconomic status
  - Poor social support
  - Personal psychiatric history
■ Risk factors
  - Witnessing or living through dangerous events or trauma
  - Feeling horror, helplessness, or extreme fear
  - No social support after experience of event
  - History of mental illness or substance abuse
PTSD Pathophysiology

- PTSD a common chronic anxiety disorder that results from exposure to a traumatic event provoking a neural biological response in many systems
  - Noradrenergic
  - Serotonergic
  - Endogenous cannabinoid

Brain Areas affected in PTSD

Noradrenergic Theory

Noradrenergic Theory

Serotonergic Theory

Endogenous Cannabinoids Theory

Diagnosis and Clinical Symptoms

Summary of criteria per Diagnostic and Statistical Manual of Mental Disorders (DSM-5):

- **Criterion A** (one required)
  - Significant Stressor or trauma experienced

- **Criterion B** (one required)
  - Intrusive symptoms

- **Criterion C** (one required)
  - Avoidance of trauma-related stimuli

- **Criterion D** (one required)
  - Alteration in arousal & reactivity

- **Criterion E** (two required)
  - Negative alterations in cognition and mood

- Motor restless, difficulty initiating or maintaining

- Sensory
  - Hypersensitivity to sounds, sights, tastes, smells

- Sensory
  - Auditory
    - Sensitivity to sounds
    - Hearing loss, tinnitus
  - Visual
    - Sensitivity to light
    - Photophobia
  - Olfactory
    - Sensitivity to odors
    - Halitosis
  - Gustatory
    - Sensitivity to taste
    - Dysgeusia
  - Somatosensory
    - Sensitivity to touch
    - Pruritus

- Cognitive
  - Memory
    - Difficulty remembering, forgetfulness
    - Concentration, memory, learning, attention
  - Thinking
    - Irritability, impulsivity, difficulty making decisions
  - Perception
    - Hallucinations, illusions

- Mood
  - Mood swings
  - Depression, anxiety, irritability
  - Frustration, anger, aggression

- Sleep
  - Difficulty initiating or maintaining sleep
  - Restless legs, sleepwalking

- Autonomic
  - Changes in heart rate, blood pressure
  - Hypervigilance

- Exaggerated startle response

- Hypervigilance

- Exaggerated startle response
Guidelines

■ American Psychological Association 2015 (APA)
  - Strong recommendation for adult patients with PTSD to participate in psychotherapy
  - Conditional recommendation for adult patients with PTSD for the use of
    - Sertraline - preferred SSRI
    - Venlafaxine ER - preferred SNRI
    - Paroxetine
    - Fluoxetine

  - Strong recommendation - psychotherapy (i.e., Prolonged Exposure, Cognitive Processing Therapy, Brief Elective Psychotherapy, and writing narratives)
  - Strong recommendation - pharmacotherapy same as APA 2015 recommendations

Pharmacological therapeutic goals

- Psychotherapy for processing PTSD-related trauma
- Other agents: • Antidepressants • Stimulants • Cannabinoids

Decrease severity of PTSD symptoms

Pharmacological therapeutic goals

- Psychotherapy for processing PTSD-related trauma
- Other agents: • Antidepressants • Stimulants • Cannabinoids

Hoskins et al. 2015

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis</td>
<td>Evaluate the efficacy of pharmacological treatment of PTSD</td>
<td>Intention-to-treat (ITT) groups to avoid bias in data</td>
</tr>
<tr>
<td>51 RCT studies; Only 3 did not employ placebo comparator arms</td>
<td>Average n=130 (13-538)</td>
<td>Using SMD to measure efficacy and standardized mean difference</td>
</tr>
<tr>
<td>Included reviews of all existing literature</td>
<td>Average age 41 (18-82)</td>
<td></td>
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</tbody>
</table>

Hoskins et al. 2015 - Results

<table>
<thead>
<tr>
<th>Agent vs placebo</th>
<th>PTSD symptoms per CAPS (SMD)</th>
<th>No. of studies (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5600 ± 0.46 (95% CI: 0.35 to 0.56)</td>
<td>Four studies, n=1526</td>
</tr>
<tr>
<td>Sertraline</td>
<td>5600 ± 0.13 (95% CI: 0.07 to 0.21)</td>
<td>Nine studies, n=3459</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>5600 ± 0.24 (95% CI: 0.14 to 0.35)</td>
<td>Three studies, n=711</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>5600 ± 0.28 (95% CI: 0.19 to 0.39)</td>
<td>Two studies, n=587</td>
</tr>
</tbody>
</table>

Clinical Consideration

■ Do stimulants and cannabinoids provide viable treatment for patients with PTSD?
■ What are associated risks for utilizing these agents in patients with PTSD?
Pharmacologic Action: Stimulants

- Methylphenidate (MPH)
  - Blocks NE and DA transporters and vesicular monoamine transporter (VMAT) (i.e., NET/DAAT)
  - Increased NE and DA in synaptic space
- MDMA
  - Enter neuron through DAT, causing release of DAT, DA, NE, and HT
  - Increased NE and DA in synaptic space
  - Commonly referred to as the street drug Ecstasy

Oehen et al. 2013 (cont.)

| GP| Change in Mean Score (p>|Oehen et al. 2013 (cont.)

- CT1 -3.4 -3.3
- CT2 -22.2 6.5
- T2 -6.6 -3.3
- T3 20.4 20.6
- T2 (end of treatment) 6.5 7.2
- T0 -10 10

Oehen et al. 2013

- Study Design
  - Randomized, double-blind, active vs "placebo"
- Study Population
  - PTSD and Traumatic Brain Injury (TBI) patients
- Primary Outcomes
  - Mental health, Multifaceted, administered by examining depression symptoms, PTSD symptoms by PCL

McAllister et al. 2015

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Discussions

- "Add to placebo" group findings, associated with
  - Significant limitations of study and methodology
  - Withdrawal of participants associated with increased positive and negative emotions
  - Conclusions
  - While this trial demonstrated safe administration and no significant treatment-related adverse events, it is important to consider the limitations of the study design and the potential for variability in patient response.
Crum et. al (2015) - Stimulants

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort study conducted from 2001 to 2008</td>
<td>Stimulant use</td>
<td>Examine association between prescription stimulant use and PTSD symptoms</td>
</tr>
<tr>
<td>Data obtained from Pharmacy Data Transaction Service (PDTS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=25,971</td>
<td></td>
<td>Evaluated use of MPH, dextroamphetamine, and various other stimulants in patients with PTSD</td>
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</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>Stimulant Prescription</th>
<th>Days Supply</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td>- 89 days vs none</td>
<td>5.70 (95% CI 3.66 to 8.87)</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td>- 89 days vs none</td>
<td>5.09 (95% CI 3.05 to 8.50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 90+ days vs none</td>
<td>2.84 (95% CI 1.18 to 6.87)</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td>- 90+ days vs none</td>
<td>3.32 (95% CI 1.39 to 7.93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 90+ days vs none</td>
<td>8.57 (95% CI 5.15 to 14.25)</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td>- 90+ days vs none</td>
<td>6.70 (95% CI 3.54 to 12.67)</td>
</tr>
</tbody>
</table>

Discussion

Stimulants activate NE levels in the CNS increasing re-experiencing symptoms.

Increased risk for incident PTSD with prolonged use of stimulants.

Pharmacologic Action: Cannabinoids

- **Nabiximols (Orexim)**: exercises effects on cannabinoid receptor 1 (CB1) within the central nervous system.
  - FDA indications: Refractory chemotherapy-induced nausea and vomiting
  - Schedule II control substance
  - Disease related concerns

- **Δ9-Tetrahydrocannabinol (THC)** natural derivative from marijuana plant, a selective CB1 agonist
  - Shown increase release of DA from nucleus accumbens and PFC
  - Exerts anxiolytic, sedative, analgesic, and euphoric effects

Cannabinoid Use in PTSD

Current literature review

Cameron et al. (2016)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective chart review</td>
<td>Mean age=52.7 years (SD=8.0)</td>
<td>Determine the efficacy of powdered NAB in patients with mental morbidities and PTSD-related insomnia, nightmares, and chronic pain</td>
</tr>
<tr>
<td>NAB treated with single-dose or more</td>
<td></td>
<td>Included: Cannabis experienced and naïve patients, patients with &gt; 1 Axis 1 diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary outcome: Improvement in PCL-C, GAF, nightmares per week, and hours of sleep obtained per night</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep (hours)</td>
<td>101 ± 1.4</td>
<td>7.2 ± 1.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nightmares (per week)</td>
<td>90 ± 2.2</td>
<td>0.9 ± 1.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GAF</td>
<td>103 ± 6.9</td>
<td>58.2 ± 8.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Cameron et al. (2016) - Results
Cameron et al. (2016)

- **Limitations**
  - Retrospective design
  - Other concurrent use of psychotropic medications, effects on PCL and GAF scores
  - NAB only demonstrated efficacy for two PTSD symptom clusters

- **Conclusions**
  - NAB offers promise for use in nightmares and insomnia associated with PTSD
  - NAB demonstrated improvement of symptoms (i.e., sleep and nightmares) occurred within 1-2 weeks of initiation
  - Treatment should be considered based on patient-specific diagnosis, caution use in patients with pre-existing psychopathology.

Jetly et al. (2016)

- **Study Design**
  - Randomized, double-blind, placebo-controlled trial
  - Evaluate the efficacy of NAB vs placebo in reducing the frequency and intensity of nightmares in PTSD patients

- **Population**
  - Canadian military trauma clinic
  - n=10, Caucasian males
  - Mean age: 43.6 ± 8.2

- **Outcomes**
  - Primary: Mean reduction in CAPS Recurring and Distressing Dream Scores
  - Secondary: CGI and WBQ improvements

Jetly et al. (2016)

- **Discussion**
  - First double-blind, placebo-controlled trial using nabilone
  - Applicable to military population
  - This study replicated positive results in reduction of PTSD nightmares from comparable trials

- **Limitations**
  - Results are statistically and clinically significant, but from a very small sample
  - Further exploration is needed on effect of nabilone for other PTSD symptoms such as re-experiencing, hyperarousal, and insomnia

Roitman et al. (2014)

- **Study Design**
  - Open-label, adjusted-dose trial
  - Evaluate tolerance, safety, and preliminary clinical efficacy of ∆9-THC as adjunct therapy for unremitting chronic PTSD patients

- **Population**
  - Hadassah University Hospital Outpatient Clinic in Jerusalem, Israel
  - n=10
  - Mean age: 52.3 ± 8.3
  - All patients received Song ∆9-THC twice a day as add-on treatment

- **Outcomes**
  - Evaluated 17 DSMIV PTSD and associated symptoms on frequency and intensity using CAPS
  - Measured severity of illness with CGI-S, sleep with PSQI, and nightmares with NFQ and NES surveys

Roitman et al (2014)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 1</th>
<th>Week 4</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPS intrusion</td>
<td>24.2</td>
<td>18.7</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>CAPS avoidance</td>
<td>37.5</td>
<td>35.0</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>CAPS insomnia</td>
<td>37.5</td>
<td>35.0</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>NDS frequency of nightmares</td>
<td>0.61</td>
<td>0.94</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NDS score</td>
<td>32.2</td>
<td>22.9</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>PSQI Score</td>
<td>17.33</td>
<td>13.9</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>CGI-S</td>
<td>6.0</td>
<td>2.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Roitman et al. (2014)

- Limitations
  - Very small sample size
  - Patients predominantly men - 70%
  - Study location

- Discussion
  - Results of this pilot study provide preliminary evidence on the safety and tolerance of THC as an adjunct therapy for nightmares, hyper arousal, and sleep disturbances associated with PTSD.
  - First study to use fixed concentrations of THC and THC, in comparison to the variability in other studies.
  - Dosage form and route eliminates adverse effects associated with smoking and variability of doses.

Wilkinson et al. (2015)

<table>
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<tr>
<th>Study Design</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal Observational Study</td>
<td>n=2,276</td>
<td>Compliant, follow-up measures of PTSD symptoms, drug and alcohol use, violent behavior, and relapse (hypothetical)</td>
</tr>
<tr>
<td>Conducted from 1992 to 2011</td>
<td>Specified into 4 groups: never users, recent users, continuing users, stoppers</td>
<td></td>
</tr>
<tr>
<td>Examine the association between marijuana use and PTSD symptom severity</td>
<td>Initiating marijuana use after treatment demonstrated increasing symptoms of PTSD, violent behavior, and alcohol use</td>
<td></td>
</tr>
<tr>
<td>Conducted at Veterans Affairs treatment programs</td>
<td>Assistance and cessation of use remains an important goal of PTSD treatment</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Consideration

- Do stimulants and cannabinoids provide viable treatment for patients with PTSD?
- What are associated risks for utilizing these agents in patients with PTSD?

Conclusion

- Novel studies for unconventional use of stimulants and cannabinoids have demonstrated:
  - Relevant efficacious findings in the reduction of some PTSD cluster symptoms
- However, the limited data does not dispel potential consequences:
  - Stimulant and cannabinoid have abuse potential
  - Some target symptoms may improve, but cause detriment or exacerbation of other cluster symptoms
  - Use and dosing strategies lack consistent methodology
  - Existing literature supports the abuse and adverse effects
- Need for larger RCTs to strengthen current data to emerge in PTSD treatment

References