The Benefits and Harms of Cannabis Use in Chronic Pain or PTSD: A Systematic Review

VA Portland Health Care System
Evidence-based Synthesis Program

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Presentation Overview

• Background
  – Changing culture of cannabis in the U.S.

• Methods

• Results
  – Chronic pain, PTSD, Harms

• Panel Discussion
  – Clinical considerations and implications

• Participant Questions
VA Evidence-based Synthesis Program

Overview

• Sponsored by VA Office of Research and Development and the Quality Enhancement Research Initiative (QUERI)

• Established to provide timely and accurate syntheses/reviews of healthcare topics identified by VA clinicians, managers, and policy-makers, as they work to improve the health and healthcare of Veterans
VA Evidence-based Synthesis Program:

Evidence syntheses on important clinical practice topics relevant to Veterans help:

• develop clinical policies informed by evidence the implementation of effective services
• support VA clinical practice guidelines and performance measures
• guide future research to address clinical knowledge gaps

Topic Nomination:
Background: Cannabis is increasingly available for the treatment of chronic pain and PTSD, yet its efficacy remains uncertain

Purpose: To systematically review the benefits and harms of cannabis for treating chronic pain or PTSD in adults

Poll Question #1

• What is your primary role (pick one)?
  – VA Clinician
  – VA Researcher
  – VA Administrator, manager or policy maker
  – Non-VA Employee
  – Other
Poll Question #2

• Have you encountered a patient who uses cannabis for chronic pain or PTSD?
  – I have encountered one or more patients who use cannabis for chronic pain only.
  – I have encountered one or more patients who use cannabis for PTSD only.
  – I have encountered patients who report using cannabis for both chronic pain and PTSD.
  – I have never encountered a patient who reported using cannabis for pain or PTSD.
  – I am not a clinician.
Poll Question #3

Do you recommend the medicinal use of cannabis for chronic pain or PTSD?

— Yes, for both.
— Yes, for chronic pain, but not PTSD
— Yes for PTSD, but not chronic pain
— Uncertain

See Alder & Colbert (2013) for a similar NEJM poll related to medicinal cannabis
States That Have Legalized Marijuana
After Nov. 8, these states now allow some form of legalized marijuana.

- Legalized for Adult Recreational & Medical Use
- Legalized for Medical Use Only
- Expected to Legalize in 2017
- Illegal

Sources: Money Morning Staff Research
Cannabis in the U.S.

• Greater proportions of the U.S. population view cannabis as acceptable (Pew Research Center, 2015)
Background on Cannabis

Cannabis has 3 major species:

– Sativa – most common
– Indica
– Ruderalis
Background on Cannabis

• Delta-9-tetrahydrocannabinol (THC)
  – Most studied
  – Considered the major active molecule of cannabis

• Cannabidiol (CBD)
  – Believed to have some medical benefits, but without the euphoria produced by THC

• Potency
  – Recent increase in the potency of cannabis (Pierre, 2017)
  – Labeling inaccuracies (Vandrey et al., 2015)
Background on Cannabis

• Numerous routes of administration
  • Smoking, edibles, tinctures, transdermal patch, suppository, topical cream, eat the raw plant, beverage, dabbing

• Different routes of administration have different effects

• ~40% of medical cannabis users use “vaping” as a route of administration (Cranford et al., 2016)
Cannabis Use for Chronic Pain

• Of patients seeking state-sanctioned medical marijuana, the most common reason is for chronic pain (~80%) (Ilgen et al., 2013)

• 20-40% of patients prescribed opioids report concurrent use of cannabis (Degenhardt et al., 2015; Reisfeld et al., 2009)
Cannabis Use for PTSD

• Over one-third of patients seeking state-sanctioned medical cannabis list PTSD as the primary reason (Bowles, 2012)

• 15% of Veterans who are treated in VA outpatient PTSD clinics report recent cannabis use (Boden et al., 2013)
VA Cannabis Policy

- H.R. 2577
  - Would allow federally-employed physicians working for the Veterans Health Administration to recommend cannabis for medical purposes to Veterans if appropriate in states that have legalized its use.
ESP Methods

**Topic Development**
- Key Questions.

**Data Sources and Search**
- Clinical trial registries; technical advisors; reference lists.

**Study Selection**
- English-language intervention trials.
- Rigorously designed observational studies with control group.
- Plant-based cannabis preparations.
PICOTS

• Population
  – Non-pregnant adults with chronic pain or PTSD (effectiveness)
  – Chronic pain, PTSD, and general population (harms)

• Intervention
  – Plant-based cannabis preparations
  – Included pharmaceutically prepared products

• Comparator
  – Placebo, non-users
PICOTS

• Outcomes
  – Chronic Pain: Pain intensity and function, spasticity
  – PTSD: Symptom severity
    • Mood, sleep, quality of life, health care utilization
  – Harms: medical and mental health harms

• Time
  – Any length of follow-up time

• Study Design
  – Systematic reviews, RCTs, rigorously designed observational studies with control group, case series
ESP Methods

Data Abstraction
- Study design, setting, patient population, intervention, follow-up, important co-interventions, health outcomes, healthcare utilization, and harms.
- Dual investigator abstraction process.

Quality Assessment
- Risk of Bias (ROB) assessed utilized published assessment tools:
  - Trials (Cochrane), Observational (Newcastle-Ottawa).
  - ROB rated as High, Low, or Unclear.

Data Synthesis
- Could not combine findings in meta-analysis.
- Strength of Evidence (SOE) for each outcome classified as high, moderate, low, or insufficient.
  - Consistency, coherence, and applicability of the body of evidence; internal validity of individual studies.
**Literature Flow**

10,831 Citations identified from electronic database searches

44 Citations identified from other sources

10,875 Citations compiled for review of titles and abstracts

9,801 Non-relevant titles and abstracts excluded

1,074 Potentially relevant articles retrieved for further review

1,016 Excluded publications

60 Included publications

Chronic Pain:
- 2 Systematic Reviews (34 RCTs)
- 5 RCTs
- 3 Observational studies

PTSD:
- 1 Systematic Review (0 RCTs)
- 2 Observational studies

Harms:
- 10 Systematic reviews
- 38 Observational studies
<table>
<thead>
<tr>
<th>Pain Condition</th>
<th>Number of studies/ROB</th>
<th>SOE</th>
<th>Primary Intervention of Low ROB studies</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis</td>
<td>- 4 Low ROB (N=1017)</td>
<td>Low – Pain, spasticity, and sleep</td>
<td>- Nabiximols (2.7 mg THC/2.5 mg CBD)</td>
<td>Inconsistent results; restrictive entry criteria</td>
</tr>
<tr>
<td></td>
<td>- 3 Unclear ROB</td>
<td></td>
<td>- THC (2.5mg) capsules</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 7 High ROB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>- 2 Low ROB (N=62)</td>
<td>Insufficient</td>
<td>- Smoked: % THC = 0, 2.5, 6, 9</td>
<td>Small N; inconsistent results below clinical threshold</td>
</tr>
<tr>
<td></td>
<td>- 4 Unclear ROB</td>
<td></td>
<td>- Vaporized: % THC = 1.29, 3.55</td>
<td></td>
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<tr>
<td></td>
<td>- 12 High ROB</td>
<td></td>
<td></td>
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<tr>
<td>Other/mixed</td>
<td>- 2 Low ROB (N=465)</td>
<td>Insufficient</td>
<td>- 12.5% ± 1.5% THC</td>
<td>One small (n=34) trial; observational study, high attrition</td>
</tr>
<tr>
<td></td>
<td>- 3 Unclear ROB</td>
<td></td>
<td>- 1:1 THC/CBD, CBD only, THC only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 3 High ROB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>- 2 Unclear ROB</td>
<td>Insufficient</td>
<td>N/A</td>
<td>Use of non-validated measures, high attrition</td>
</tr>
</tbody>
</table>
Ongoing Studies: Chronic Pain

- 7 RCTs
  - Musculoskeletal pain (2), cancer (2), spinal cord injury (1), ulcerative colitis (1), mixed conditions (1)
  - Various routes of administration: oral capsule or vaporized
  - Examine various potencies and ratios of CBD:THC
PTSD Results

• Included studies were limited to those that included a non-cannabis using comparison group

• 1 Systematic review and 2 observational studies provided insufficient evidence related to the effectiveness of cannabis for treating PTSD
None of the studies included in the Wilkinson et al., 2016 systematic review met our inclusion criteria even though it included a broader range of preparations including synthetics. Their findings:

- “The strength of evidence for the use of medical marijuana for psychiatric indications of PTSD... is very low at the present time.”

- “The consequences of chronic cannabinoid exposure includes tolerance, dependence, and withdrawal. Early and persistent marijuana use has been associated with the emergence of psychosis. Marijuana impairs attention, memory, IQ, and driving ability.”
<table>
<thead>
<tr>
<th>Study, setting, design, N, Risk of bias</th>
<th>Sample description</th>
<th>Description and duration of cannabis use and comparators</th>
<th>Primary findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilkinson 2015 Retrospective cohort study N=2276 Medium ROB</td>
<td>All Veterans referred for intensive PTSD treatment. Excluded those with prior drug or alcohol use. Mean age 51.7 96.7% male</td>
<td>Self-reported cannabis use, 4-month follow-up: • 850 never users • 299 stoppers (use at admission, not follow-up) • 296 continuing users (admission and follow-up) • 831 starters (no use at admission, use at follow-up) Usual medical care including psychotropic medications and psychotherapy provided to all participants</td>
<td>Continuing users and starters had significantly worse PTSD symptoms than never users and stoppers: F=21.47, P&lt;.0001</td>
</tr>
<tr>
<td>Johnson 2016 Matched case control cross sectional study N=700 High ROB</td>
<td>All Veterans with a probable PTSD diagnosis referred for a primary care/mental health integration program based on clinical need following mental health screening or clinical judgment. Mean age 47.1 91.0% male</td>
<td>Self-reported cannabis use within 3 months of the assessment (n=350) Compared to no lifetime cannabis use reported at the time of assessment (n=350) Users were matched to non-users on age and gender</td>
<td>Users had significantly worse PTSD symptoms than non-users: t (349) = 0.11, P=.91</td>
</tr>
</tbody>
</table>
PTSD Ongoing Studies

• 3 RCTs: Effectiveness of cannabis for treating PTSD, effects of CBD vs. THC content, and effects of CBT-Insomnia on cannabis use
• 4 observational studies: Cannabis use and exposure therapy, PTSD, other clinical outcomes, functional outcomes, and sleep
• Will provide stronger evidence related to effectiveness and harms in the next few years
Harms Associated with Cannabis Use

• Cannabis use is associated with a higher likelihood of adverse events, but not serious adverse events (Ware et al., 2015)

• General adverse events among patients with chronic pain
  – AEs: dizziness, lightheadedness, fatigue, muscle spasms, dry-mouth, short-term memory impairment
  – SAEs: suicide attempts, paranoia, and agitation
# Mental Health Harms in General Population

<table>
<thead>
<tr>
<th>Mental Health Harm</th>
<th>Findings/ Strength of Evidence (SOE)</th>
<th>Data Source</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis</td>
<td>Low strength evidence that a history of cannabis use was associated with an increase in risk of developing psychotic symptoms.</td>
<td>Systematic Review (Moore et al., 2007) -7 additional studies</td>
<td>Magnitude of risk uncertain.</td>
</tr>
<tr>
<td>Mania</td>
<td>Increased incidence of new-onset mania symptoms among populations without a diagnosis of bipolar disorder, (OR 2.97; 95% CI, 1.80 to 4.90)</td>
<td>Meta-analysis/ Systematic Review (Gibbs et al., 2015)</td>
<td>Small # of studies.</td>
</tr>
<tr>
<td>Suicide related behaviors</td>
<td>Suicide ideation (pooled OR 1.43; 95% CI, 1.13 to 1.83) Suicide attempt (pooled OR 2.23; 95% CI, 1.24 to 4.00) Death by suicide (OR 2.56; 95% CI, 1.25 to 5.27)</td>
<td>Meta analysis (Borges et al., 2016)</td>
<td>No data on acute cannabis use. Heterogeneity of exposure measurement.</td>
</tr>
</tbody>
</table>
## Mental Health Harms Associated with Cannabis Use

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<td>Cognitive effects</td>
<td>Moderate SOE that active, long-term cannabis use is associated with small negative effects on all domains of cognitive function; Insufficient evidence of long-term cognitive effects in past users.</td>
<td>Systematic Review (Schreiner et al., 2012)</td>
<td>Inconsistent data about past use.</td>
</tr>
<tr>
<td>Cannabis Use Disorder (Pain pts)</td>
<td>No evidence.</td>
<td>Observational (Fleming et al., 2007)</td>
<td>Data are cross-sectional.</td>
</tr>
<tr>
<td></td>
<td>Prevalence of cannabis misuse = 2.4% and dependence = 0.9%</td>
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</tbody>
</table>
## Medical Harms Associated with Cannabis Use

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<tr>
<td>Pulmonary Function</td>
<td>Moderate strength of evidence that there is <strong>no adverse</strong> effect for low levels of smoking among young adults.</td>
<td>- 2 Low ROB prospective, cohort (N = 6053)</td>
<td>No data on heavy use or on older, chronically ill patients.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 systematic review (N = 851)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Insufficient evidence of cardiovascular harms in short or long term light cannabis use.</td>
<td>- 2 High ROB observational</td>
<td>Recall bias, no data about longitudinal exposure.</td>
</tr>
</tbody>
</table>
# Medical Harms Associated with Cannabis Use

<table>
<thead>
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<tbody>
<tr>
<td>Lung Cancer</td>
<td>Low SOE that there is no association between light cannabis use and lung cancer.</td>
<td>- 1 patient-level meta-analysis of 6 case-control studies (2150 cases)</td>
<td>Recall bias, light users.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 High ROB cohort study (N = 49,231)</td>
<td></td>
</tr>
<tr>
<td>Head and Neck Cancer</td>
<td>Low SOE that there is no association between head and neck cancer and cannabis use.</td>
<td>- Meta-analysis of 9 case-control studies (5732 cases)</td>
<td>Imprecise exposure measurement, recall bias.</td>
</tr>
</tbody>
</table>
## Medical Harms Associated with Cannabis Use

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<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular Cancer</td>
<td>Insufficient evidence of association.</td>
<td>- Meta-analysis of 3 High ROB case-control studies</td>
<td>Recall bias and potentially confounded by tobacco use.</td>
</tr>
<tr>
<td>Transitional Cell Cancer</td>
<td>Insufficient evidence of an increased risk among those with &gt;40 joint years.</td>
<td>- 1 High ROB case-control study (52 cases)</td>
<td>Small and methodologically limited.</td>
</tr>
</tbody>
</table>
Other Harms Associated with Cannabis Use

• Motor Vehicle Accidents (MVA)
  – Moderate strength evidence that acute cannabis intoxication is associated with increase in collision risk. (Rogeberg et al., 2016)
    • (OR 1.35; 95% CI = 1.15 - 1.61)

• Emerging Harms
  – Cannabis hyperemesis syndrome
  – Exposure to contaminants
  – Exposure to infectious diseases
Summary: Chronic Pain

- Cannabis (nabiximols) may improve pain, spasticity, and sleep in patients with multiple sclerosis (Low SOE).

- Insufficient data on other secondary outcomes.
- Insufficient data for other chronic pain patient populations.
- Insufficient data on non-nabiximols preparations or other routes of administration for pain.
Summary: PTSD

• Insufficient evidence from two observational studies to draw conclusions about the effectiveness of cannabis in patients with PTSD
• 7 ongoing studies of cannabis to treat PTSD
• No studies of harms of cannabis in patients with PTSD
• Increased risk of some harms in a general population that are potentially relevant for patients with PTSD including cognitive functioning and mental health effects
Summary: Harms

• Cannabis use may be associated with:
  – Increased risk of mental health adverse effects in a general population.
    • Psychosis, mania, suicide related behaviors
  – Strength of evidence on its long term and physical effects is low and inconsistent.
Limitations

• OF EVIDENCE BASE:
  – Few methodologically rigorous trials.
  – Limited or no trials available on musculoskeletal pain, cancer pain, and other pain conditions.
  – Cannabis formulations studied in trials may not reflect what is available in dispensaries.
  – Applicability to heavy users or older, chronically ill populations is limited.
  – Short follow-up duration.

• OF OUR SYSTEMATIC REVIEW:
  – Relied on existing high quality systematic reviews when available.
  – Excluded studies of synthetic, prescription cannabinoids.
Discussion

• Recent cannabis related reviews
• Evidence-based treatment for chronic pain
  – Considerations related to cannabis use and opioid epidemic
• Cannabis Use Disorder diagnosis and treatment
• Evidence-based treatment for PTSD
  – Considerations related to the possibility of mental health and cognitive functioning adverse effects
  – Weighing risks and benefits with patients and discussing alternative evidence-based options
Other Recent Reviews

• Recent systematic reviews:
  – Non-significant trend towards benefit of pain reduction (low to moderate SOE) (Whiting et al., 2015)
  – Insufficient to low SOE for benefit (Butler et al., 2015)

• National Academies of Science, Engineering, and Medicine
  – “There is substantial evidence that cannabis is effective for the treatment of chronic pain in adults.”
Chronic Pain Treatment

- Effective non-pharmacologic therapies: exercise, cognitive behavioral therapy (CBT), interventional procedures
- Effective non-opioid medications: acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, antidepressants

(Dowell et al., 2016)
Clinical Practice Recommendations

Focus Article

Cannabis in Pain Treatment: Clinical and Research Considerations

Seddon R. Savage, * † Alfonso Romero-Sandoval, ‡ Michael Schatman, § Mark Wallace, ¶ Gilbert Fanciullo, * Bill McCarberg, ¶ and Mark Ware ‡

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‡Presbyterian College School of Pharmacy, Clinton, North Carolina.
¶University of California San Diego School of Medicine, La Jolla, California.
‖McGill University Faculty of Medicine, Montreal, Quebec, Canada.
Clinical Practice Recommendations for Pain

- Awareness of federal, state, and institutional policies and laws.
- Establish goals of care for cannabis use.
- Screen for signs of misuse, abuse, and addiction.
- Counsel patients on harms and risks.
- Advise on routes of administration.
- Continually monitor cannabis use/utility, functional status, symptom severity, and use of other medications/substances.
  - Consider use of urine drug tests.
- Monitor for other harms (i.e. MVA, falls).
- Advise on discontinuation or referral to substance use treatment.

Savage et al., 2016
Cannabis Use Disorder

• DSM 5 Criteria for Cannabis Use Disorder (CUD)

• CUD treatment
  – No FDA approved medications to treat CUD
  – Contingency Management, Motivational Enhancement Therapy, Cognitive Behavioral Therapy
PTSD Treatment Considerations

• Possible harms of cannabis use particularly salient for patients with PTSD

• Other evidence-based treatments for PTSD
  – VA/DoD Clinical Practice Guideline for PTSD

• Patient and provider resources available at the National Center for PTSD website: https://www.ptsd.va.gov/

• Currently, the evidence base is insufficient
Discussants

• Karen Drexler, MD, Deputy National Mental Health Program Director
• Paula Schnurr, PhD, Executive Director of the National Center for PTSD
• John Williams, MD, Director of the Durham VA ESP
QUESTIONS/COMMENTS

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