The Systematically Testing the Evidence on Marijuana Project

Devan Kansagara, MD MCR
MIRECC
May 18, 2022
No financial conflicts of interests to disclose

The STEM project is funded by a grant from the VA Office of Rural Health
Outline

- STEM overview
- Cannabis and mental health
  - Psychosis and psychotic spectrum disorders
  - PTSD
  - Mood disorders
  - Withdrawal and CUD
  - Cannabis and alcohol
- Harm reduction strategies
- Tour of the STEM website (www.cannabisevidence.org)
Marijuana is probably the most dangerous drug in America today.

— Ronald Reagan —
“Two of my favorite things are sitting on my front porch smoking a pipe of sweet hemp, and playing my Hohner harmonica.”

-Abraham Lincoln
STEM

“STEM is an independent, methodologically rigorous, and updated cannabis evidence resource for the health care sector that synthesizes what is known from research and what is left to learn about the health effects of cannabis.”
STEM

- Funded by Veteran Rural Health Research Center/Office of Rural Health
- Collaboration with Center for Evidence-based Policy at OHSU
STEM team

- Devan Kansagara
- Chelsea Ayers
- Robin Paynter
- Ben Morasco
- Jamie Lo

- Curtis Harrod
- Shawna Chapman
- Shauna Durbin
- Shannon Robalino
- Beth Shaw
- Landon Donsbach
- Nicole Thompson
- Jacqui Krawetz
- Morgan Reeder
- Sneha Yeddala
Why are we doing this

- Cannabis is more accessible than ever and is increasingly used
  - 10-15% of US adults have used in the last year
  - 4% of all adults use daily
- Potency has increased markedly over time
- Cannabis can be both a medicinal or recreational drug, and many people use it for both reasons
- It is a multi-billion dollar industry, and it is growing
Why are we doing this

- Cannabis may have some benefits, probably is associated with harms in some groups
  - Some harms may be of particular concern among Vets
    - Prevalence of CUD among rural Vets 32%
    - CUD is associated with substantially increased risk of suicidal behavior among Vets
- More organizations are supporting cannabis research, there are congressional bills to support more research, and it is likely to become easier to do more research
- Cannabis policy has rapidly outpaced the evidence and there is a need for more research in many areas
- There are mixed messages about the existing evidence
Many providers don’t feel comfortable discussing cannabis with their patients

- No training
- Lack of knowledge
- Paucity of evidence
Themes:

- Clinicians view cannabis through a traditional pharmacotherapeutic lens
- Clinicians described ambivalence about the medicinal role of cannabis, but raise concerns about its potential harms
- Clinicians feel unprepared when discussing cannabis specifics with patients
- Federal policy complicates VA clinicians’ engagement in conversations about cannabis
- Clinicians had differing views on cannabis in the context of the opioid crisis
Clinician Knowledge, Attitudes, and Practice Regarding Cannabis: Results from a National Veterans Health Administration Survey

Devan Kansagara, MD, MCR,* † Benjamin J. Morasco, PhD,* † Megan O. Iacocca, MS,* Matthew J. Bair, MD, MS,§ Elizabeth R. Hooker, MS, MPH,* and William C. Becker, MD† ||

Table 2. Provider knowledge of cannabis and VA provider rules

<table>
<thead>
<tr>
<th>Survey Question</th>
<th>Correct Responses N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edible forms of cannabis take effect more quickly than smoked cannabis. [false = correct]</td>
<td>198 (79.5)</td>
</tr>
<tr>
<td>Dabbing refers to the transcutaneous application of cannabis. [false = correct]</td>
<td>104 (41.8)</td>
</tr>
<tr>
<td>Preparations containing high CBD content (minimal THC) are effective for treating chronic pain. [false = correct]</td>
<td>84 (33.7)</td>
</tr>
<tr>
<td>CBD, an ingredient in cannabis, causes euphoria. [false = correct]</td>
<td>172 (69.1)</td>
</tr>
<tr>
<td>As a VA clinician, I am permitted to endorse the use of medical cannabis for my patients. [false = correct]</td>
<td>214 (85.9)</td>
</tr>
<tr>
<td>As a VA clinician, I am permitted to discuss the use of medical cannabis with my patients. [true = correct]</td>
<td>175 (70.3)</td>
</tr>
</tbody>
</table>

![Graph showing responses to survey questions](Image)

CBD = cannabidiol; THC = tetra-hydrocannabinol; VA = Veterans Administration.
Health care providers need to become more involved in discussions about cannabis

- Most patients are getting advice about cannabis from stores/budtenders
- Dispensaries may not be the best place to get medical advice
Dispensary workers most often use personal and past customer experience to guide recommendations about medical cannabis

Often counsel about safe storage and common adverse effects

Rarely counseled about other risks such as CUD, withdrawal, MVAs, psychosis

We should not expect non-medical personnel in a retail establishment to counsel patients about health effects

Clinicians need to fill this gap
VHA directive

“It is VHA policy that VHA providers and/or pharmacists discuss with the Veteran marijuana use, due to its clinical relevance to patient care, and discuss marijuana use with any Veterans requesting information about marijuana”
STEM Mission

- Empower clinicians to have evidence-informed discussions about cannabis with their patients
- Spur research by identifying key gaps and facilitating network
- Be transparent and evidence-based
- Be user friendly
Cannabis and PTSD
Cannabis may not be effective for PTSD, but there is much to learn.
The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: A randomized cross-over clinical trial

Marcel O. Bonn-Miller¹, Sue Sisley², Paula Riggs³, Berra Yazar-Klosinski⁴, Julie B. Wang⁴, Mallory J. E. Loflin⁵,²,⁶, Benjamin Shechet⁷,³, Colin Hennigan⁴, Rebecca Matthews⁴, Amy Emerson⁴, Rick Doblin⁴

- 3 active arms:
  - High THC:low CBD
  - Equal THC:CBD
  - Low THC:high CBD
- Placebo

Bonn-Miller M, PlosOne, 2021
Cannabis in Veterans with PTSD

- > 40% of Veterans with PTSD and recent cannabis use screen positive for cannabis use disorder (CUD)
- Compared with Veterans without PTSD, those with PTSD experience greater cannabis craving and withdrawal symptoms

Hill ML, Addict Behav, 2021
Livne O, Drug Alcohol Depend, 2019
Depression and anxiety

- Nearly all trials enrolled patients with other primary conditions (chronic pain, MS) and measured these as secondary outcomes.
- Very low certainty evidence that pharmaceutical THC, with or without CBD, is associated with small magnitude improvements in anxiety among patients with other medical conditions.
- Little to no effect on other outcomes, but increase in risk of withdrawal due to adverse events.

Black N, Lancet Psych, 2019
## Other mental health effects

<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>Suicidal Behaviors</td>
<td>Insufficient evidence Meta-analysis suggests increased risk of suicidal ideation, attempt, death</td>
<td>Meta analysis</td>
<td>No data on acute cannabis use. Inconsistent results. Inadequate exposure ascertainment and adjustment for confounding.</td>
</tr>
<tr>
<td>Mania</td>
<td>Low strength evidence for 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</td>
<td>Small # of studies, but included one large community-based cohort study showing dose-response effect.</td>
</tr>
</tbody>
</table>

Nugent S, Ann Int Med, 2017
Cannabis and psychosis
Can you overdose on cannabis?
However....

Compton W, JAMA Psych, 2017
“THC, 134 and 201 mcg/kg, usually sedated our subjects without causing unconsciousness. They appeared partly dissociated from surrounding activity. They seemed calm and occasionally talked inappropriately...two of ten subjects dropped out...each of these subjects worried about losing control over his mind.”

Malit LA, Anesthesiology, 1975
• Ingestion produces a particularly potent metabolite of THC
• Onset of action is longer for edibles: 1-3 hours
• In a case series of edible-induced psychosis, patients took up to 100 mg THC
  • Didn’t feel anything
  • Ate the whole cookie, rather than 10 mg dose
  • Felt odd not eating the whole cookie given familiarity with baked products
• ? Greater risk in cannabis-naïve individuals

Cannabis and psychosis

- In studies of participants with no psychotic symptoms at baseline:
  - Those who had ever used had an increased likelihood of psychotic symptoms
  - Frequency of use correlated with the likelihood of a psychotic outcome
- In a 30-year study of young adults regular (> weekly) cannabis use was associated with subsequent development of schizotypal signs
  - OR 2.29 (1.32-3.97)
  - Regular cannabis use was more strongly associated with this outcome than other drug or alcohol use
- Experimental studies show cannabis administration assoc with acute psychotic symptoms
  - Less risk in THC plus CBD preparations, than THC alone

Kuepper R, BMJ, 2011
Nugent S, Ann Int Med, 2017
Rossler W, Addiction, 2012
Some of the increase in schizophrenia incidence in Denmark may be attributed to CUD.

Hjorthoj C, JAMA Psych, 2021
Dose-response between THC and psychotic disorders

DiForti M, Lancet Psych, 2019
Cannabis and schizophrenia

- Unclear whether cannabis increases the risk of schizophrenia
- More data that cannabis associated with increased risk of schizophrenia in patients with genetic predisposition
  - Shared genetic predisposition for psychotic spectrum disorders and cannabis use
- Very preliminary data suggesting that CBD may actually reduce psychotic symptoms

Henquet C, BMJ, 2005
Wainberg M, Translational Psych, 2021
Cannabis induced psychosis may be an early manifestation of schizophrenia.

**Figure.** Cumulative incidence of schizophrenia spectrum disorder diagnoses in 894 individuals born in Denmark between January 1, 1955, and July 1, 1990, and treated because of cannabis-induced psychosis. Of these, 309 developed a schizophrenia spectrum disorder during follow-up between January 1, 1995, and July 1, 2005.

Arendt M, Arch Gen Psych, 2008
Cannabis withdrawal
Cannabis withdrawal

- Overall, prevalence 47%
  - 17% in population based studies
  - 54% in studies of outpatient clinics
  - 87% in inpatient studies
- Can develop up to a week after cessation
- Can last up to several weeks
- Anxiety, restlessness, insomnia, depression

Bahji A, JAMA Network Open, 2020
Hasin D, Neuropsychopharmacology, 2017
Cannabis use disorder
### CUD definitions

<table>
<thead>
<tr>
<th>DSM-IV Abuse&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DSM-IV Dependence&lt;sup&gt;b&lt;/sup&gt;</th>
<th>DSM-5 SUD&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazardous use (e.g., driving under the influence)</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Social/interpersonal problems related to use</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Neglected major roles to use</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Legal problems</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Withdrawal&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tolerance</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Used larger amounts/longer</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Repeated attempts to quit/control use</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Much time spent using</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Physical/psychological problems related to use</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Activities given up to use</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Craving&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> One or more abuse criteria within a 12-month period

<sup>b</sup> Three or more dependence criteria within a 12-month period

<sup>c</sup> Two or more SUD criteria within a 12-month period

<sup>d</sup> New criterion added in DSM-5

Hasin D, Neuropsychopharm Rev, 2018
Cannabis use disorder

**NESARC**
- 2012-2013
- In person, interviews
- Past year use: 9.5%
- CUD total: 2.9%
- CUD among users: 31%

**NSDUH**
- 2017
- Anonymous, survey
- Past year use: 15.3%
- CUD total: 1.4%
- CUD among users: 9.3%

Hasin D, JAMA Psych, 2015

Compton W, DAAD, 2019
America’s Invisible Pot Addicts

More and more Americans are reporting near-constant cannabis use, as legalization forges ahead.

AUG 20, 2018

Annie Lowrey
Contributing editor at The Atlantic covering economic policy

Users or former users I spoke with described lost jobs, lost marriages, lost houses, lost money, lost time. Foreclosures and divorces. Weight gain and mental-health problems. And one other thing: the problem of convincing other people that what they were experiencing was real. A few mentioned jokes about Doritos, and comments implying that the real issue was that they were lazy stoners. Others mentioned the common belief that you can be “psychologically” addicted to pot, but not “physically” or “really” addicted. The condition remains misunderstood, discounted, and strangely invisible, even as legalization and white-marketization pitches ahead.
- CUD may be more prevalent among adults with chronic pain than those without chronic pain (RR 1.52, 95% CI 1.21-1.87)
CUD and Veterans

- In 2009, overall ICD9 prevalence of CUD among Vets was 1.1%
  - Overall prevalence of CUD without other SUD was 0.6%
- In NESARC III, the prevalence of CUD among those with PTSD was 9.4% (compared with 2.2% among this without PTSD)
- CUD was associated with 3 fold higher odds of suicide attempt among OEF/OIF Vets after adjusting for demographics, combat exposure, trauma, PTSD, TBI, other SUD dx

Bonn-Miller M, Psychol Serv, 2012
Bilivicius E, Depress Anxiety, 2019
Kimbrel N, Suicide Life Threat Beh, 2018
Treatment of CUD: Psychosocial interventions

For patients with cannabis use disorder, we suggest one of the following interventions as initial treatment, considering patient preference and availability:
- Cognitive behavioral therapy
- Motivational enhancement therapy
- Combined cognitive behavioral therapy/motivational enhancement therapy

We suggest against the use of a brief intervention (i.e., 60 minutes or less) for the treatment of cannabis use disorder.

<table>
<thead>
<tr>
<th>Interventions (Alphabetical)</th>
<th>Alcohol</th>
<th>Opioids</th>
<th>Stimulants/</th>
<th>Cannabis</th>
<th>Opioids</th>
<th>Stimulants/</th>
<th>Cannabis</th>
<th>Added Effectiveness as Adjunctive Interventions in Combination with Pharmacotherapy and/or Other First-line Psychosocial Interventions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral couples therapy (BCT)</td>
<td>√</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>?</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Effective for male or female SUB patients and partners; improves marital satisfaction</td>
</tr>
<tr>
<td>Cognitive behavioral therapy (CBT)</td>
<td>√</td>
<td>N/A</td>
<td>√</td>
<td>√</td>
<td>√/?</td>
<td>N/A</td>
<td>√</td>
<td>Added benefit in methadone treatment; unclear added benefit of CBT in some studies of office-based buprenorphine</td>
<td></td>
</tr>
<tr>
<td>Contingency management (CM)/Motivational incentives</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>?</td>
<td>√</td>
<td>√</td>
<td>CM is recommended only as an adjunctive treatment; CM for cannabis may be problematic given slow clearance in urine</td>
<td></td>
</tr>
<tr>
<td>Community reinforcement approach (CRA)</td>
<td>√</td>
<td>N/A</td>
<td>√</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Complex intervention best when including CM</td>
<td></td>
</tr>
<tr>
<td>Individual drug counseling (IDC)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>√</td>
<td>N/A</td>
<td>One study found benefit when combined with group drug counseling</td>
<td></td>
</tr>
<tr>
<td>Motivational enhancement therapy (MET)</td>
<td>√</td>
<td>N/A</td>
<td>√</td>
<td>√</td>
<td>N/A</td>
<td>?</td>
<td>?</td>
<td>Some evidence for those with AUD and low readiness or high anger</td>
<td></td>
</tr>
</tbody>
</table>
### Treatment of CUD: Pharmacotherapy

#### Summary:
There is substantial uncertainty about the effectiveness and harms of examined pharmacotherapies for cannabis use disorder (CUD).

#### Study design:
Living systematic review of randomized and controlled trials (RCTs).

#### Data sources:
Multiple databases searched to May 2021 → 28 RCTs.

#### Comparator:
Placebo, another intervention, or usual care.

#### Population:
Adults with known or suspected CUD.

#### Interventions:
Pharmacotherapies identified as potential treatments for CUD.

#### Outcomes:
Medications for which there were positive, negative, or mixed findings by outcome.

<table>
<thead>
<tr>
<th>Pharmacotherapies</th>
<th>Very low certainty</th>
<th>Low certainty*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abstinence</strong></td>
<td>Antidepressant: Venlafaxine (N=80)</td>
<td>Cannabinoids: Low THC to CBD: synthetic CBD</td>
</tr>
<tr>
<td>Cannabis use</td>
<td>Anticonvulsant: Gabapentin</td>
<td>Cannabinoids: Comparable THC to CBD: nabilominals</td>
</tr>
<tr>
<td></td>
<td>Antipsychotic: Quetiapine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAO Inhibitor: Fluoxetine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glutamatergic modulator: N-acetylcysteine (N=199)</td>
<td></td>
</tr>
<tr>
<td>Treatment retention</td>
<td>Anticonvulsant: Topiramate</td>
<td>Cannabinoids: Low THC to CBD: synthetic CBD: low and high dose</td>
</tr>
<tr>
<td></td>
<td>Antipsychotic: Quetiapine</td>
<td>Cannabinoids: High THC to CBD: nabilominals, dronabinol + haloperidol, nabilominals</td>
</tr>
<tr>
<td></td>
<td>MAO Inhibitor: Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Harms</td>
<td>Anticonvulsant: Topiramate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antipsychotic: Quetiapine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAO Inhibitor: Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Withdrawal symptoms</td>
<td>Anticonvulsant: Gabapentin</td>
<td>Cannabinoids: Low THC to CBD: synthetic CBD: low and high dose</td>
</tr>
<tr>
<td></td>
<td>Antipsychotic: Quetiapine</td>
<td>Cannabinoids: Comparable THC to CBD: nabilominals, dronabinol + haloperidol, nabilominals</td>
</tr>
<tr>
<td></td>
<td>MAO Inhibitor: Fluoxetine</td>
<td></td>
</tr>
</tbody>
</table>

*Significant improvement with intervention. **Increased risk of harm with intervention. #Mixed or conflicting results.

- Outcomes not reported or not assessable.

- Abbreviations: CBD: cannabinol; FAAH: fatty acid amide hydrolase; SNR: serotonin receptors; nabilominal: THC tetrahydrocannabinol

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- No treatments ready for “prime time”
- Cannabinoids hold some promise
Cannabis and alcohol use
Cannabis and alcohol use

- Cannabis use is associated with an increased risk of heavy drinking, and of AUD
- About 60% with CUD also meet criteria for AUD
- In those with AUD, cannabis may trigger an urge to drink
- Some individuals may substitute cannabis use for alcohol use, particularly patients who drink heavily but are without AUD diagnosis
- Some evidence that medical cannabis users may have fewer alcohol related problems relative to those using cannabis for recreational purposes

Metrik J, STEM, 2022
Harm reduction strategies

- Ask patients about their cannabis use: dose, frequency, formulation, route of administration
- Consider assessing for CUD
- Describe cannabis withdrawal syndrome symptoms to patients (restlessness, insomnia, agitation, depression, chills) as some patients may be using cannabis to treat these symptoms
- Avoid daily, prolonged, heavy use; educate about CUD
- If patients choose to use cannabis as a substitute for opioids, be intentional about this
- Caution use in patients with AUD
- Caution with use in patients with or at risk for serious mental illness
- Caution in the still-developing brain - especially those at risk
- Caution with high-potency (ie - high THC) formulations and routes of administration
https://www.cannabisevidence.org/

Twitter: @CannabisEviSyn

Questions: kansagar@ohsu.edu