

Clinical Trials of Cannabinoids for Insomnia, Pain, Anxiety, Depression

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Disclosures

- Jazz Pharmaceuticals is providing CBD (Epidiolex) for a clinical trial

Today's Talk

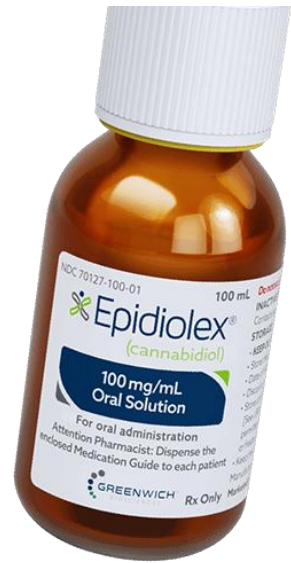
- Cannabis as a Medicine
- Ongoing Research on Cannabis and Pain
 - Cannabis for Pain, Depression, Anxiety, and Insomnia
 - CBD and Neuroinflammation
 - Cannabis and Opioid Taper Support

Cannabis- Based Medicine



THC-Based Treatments:

- **Marinol (Dronabinol)**
 - Used for nausea and vomiting associated with chemotherapy and for appetite stimulation in patients with HIV/AIDS-related anorexia.
 - Synthetic THC
 - Approval Year: 1985.
 - Mechanism: Activates CB1 receptors in the brain, stimulating appetite and reducing nausea.
- **Cesamet (Nabilone)**
 - Used for chemotherapy-induced nausea and vomiting in patients who do not respond to standard treatments.
 - Active Ingredient: Synthetic cannabinoid similar to THC (nabilone).
 - Approval Year: 1985.
 - Mechanism: Binds to CB1 receptors, acting as a potent antiemetic.



Cannabis- Based Medicine

CBD-Based Treatments:

- **Epidiolex (Cannabidiol - CBD)**
 - Used to treat seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome, and tuberous sclerosis complex (TSC) in patients 1 year and older.
 - Active Ingredient: Purified cannabidiol (CBD).
 - Approval Year: 2018.
 - Key Fact: This is the first FDA-approved drug derived directly from cannabis.

THC/CBD-Based Treatments:

- **Nabiximols (Sativex®)** THC/CBD mouth spray for pain relief, muscle spasms; currently being investigated by FDA
- Not available in U.S.(but approved in 29 countries):

Side Effects and Safety

THC Side Effects:

- **Cognitive impairment, anxiety, paranoia, tachycardia.**
- **Addiction potential** with chronic use.
- Can induce **psychotic symptoms** in susceptible individuals.

CBD Side Effects:

- Generally **well tolerated.**
- Possible **drowsiness, diarrhea, stomach upset, changes in appetite.**
- **Potential drug interactions** (e.g., blood thinners).
- Liver enzyme elevation

Now let's talk about **dispensary** **cannabis...**

- Gold standard: double-blind, placebo-controlled clinical trials
- Few exist for dispensary cannabis products
- Clinical trials have been small, largely unsuccessful



Edible

Retro Peach Rings - Fast Acting - (4000mg)

Retro Gummy Rings

4000mg 20pk

\$89.43

Add to bag



CBD ratio edible

***High Dose* Peach 1:1 CBD + Hybrid Enhanced...**

WYLD Gummies

1000mg CBD/1000mg THC 20...

\$39.74

Add to bag



Indica edible

Berry Relaxed [20pk] (1000mg THC/500mg...)

Robhots Gummies

1000mg THC/500mg CBN 20...

\$39.74

Add to bag



Hybrid flower

Sour Grapes

Viola

THC 23.90%

\$11.92/1g - \$159/28g

Select weight



Sativa flower

Blockberry

Cherry

THC 23.90%

\$11.92/1g - \$159/28g

Select weight



Edible

Honey Peanut Butter [10pk] (1000mg)

Nové Luxury Chocolates

1000mg 10pk

\$39.74

Add to bag

<https://lifeflowerdispensary.com/shop-all/store/1570/featured>

FDA Approval Process

- Medicines go through a rigorous process of testing in human subjects for
 - safety
 - efficacy
 - long term effects
 - side effects
 - *Testing for a single medical condition,*
 - many other standards, including:
 - measuring shelf life, gauging manufacturing and labeling practices, inspections of the cleanliness of the facilities in which the drug is manufactured, etc.

The Elephant in the Room Regarding Cannabis Products from Dispensaries

- ***The science to support effectiveness and safety, the dual standards for an approved medicine, does not yet exist.***
- Medical cannabis has been “legalized” by voting on a ballot or by legislatures, not by scientifically testing whether it meets standards for medicinal use.

3 very important review papers in 2026...

Clinical Review & Education

JAMA | Review

Therapeutic Use of Cannabis and Cannabinoids A Review

Michael Hsu, MD; Arya Shah, MD; Ayana Jordan, MD, PhD; Mark S. Gold, MD; Kevin P. Hill, MD, MHS

- Major clinical review of the evidence across indications.
- Key message: cannabis/cannabinoids have evidence for a relatively narrow set of indications, while evidence is insufficient or unfavorable for many of the conditions for which people commonly use medical cannabis

3 very important review papers in 2026...



The efficacy and safety of cannabinoids for the treatment of mental disorders and substance use disorders: a systematic review and meta-analysis



Jack Wilson, Olivia Dobson, Andrew Langcake, Palkesh Mishra, Zachary Bryant, Janni Leung, Danielle Dawson, Myfanwy Graham, Maree Teesson, Tom P Freeman, Wayne Hall, Gary C K Chan, Emily Stockings

- Reviewed **54 randomized trials involving 2,477 participants**
- Found little evidence of efficacy for most psychiatric and substance-use indications, including **anxiety, PTSD, psychotic disorders, and OUD**.
- There were some signals for specific conditions, but the overall conclusion was that the evidence does not support routine use for most of these disorders.

3 very important review papers in 2026...

REVIEW

Annals of Internal Medicine

Cannabis-Based Products for Chronic Pain

An Updated Systematic Review

Roger Chou, MD; Rongwei Fu, PhD; Azrah Y. Ahmed, BA; and Benjamin J. Morasco, PhD

- Across randomized placebo-controlled trials, some THC-containing products produced **small improvements in pain**, but these came with increased adverse events, and evidence for many products and longer-term outcomes remained inadequate.
- Even for **chronic pain, arguably the flagship indication for medical cannabis**, the evidence is much less impressive than public perception would suggest.

Our current studies...



5R01DA042043

PI: Gilman

Medical Marijuana, Neurocognition, and Subsequent Substance Use

What is the best way to test the efficacy of dispensary cannabis as a medicine?

- We designed a naturalistic/pragmatic RCT, and randomized participants to get a medical marijuana card or to be in a waitlist control condition (WLC).
- Participants could choose their own products and doses.
- Designed to **test the system we have in place for the regulation and distribution of medical cannabis.**

RCT of Medical Cannabis Card- holders (MCC)



Participants

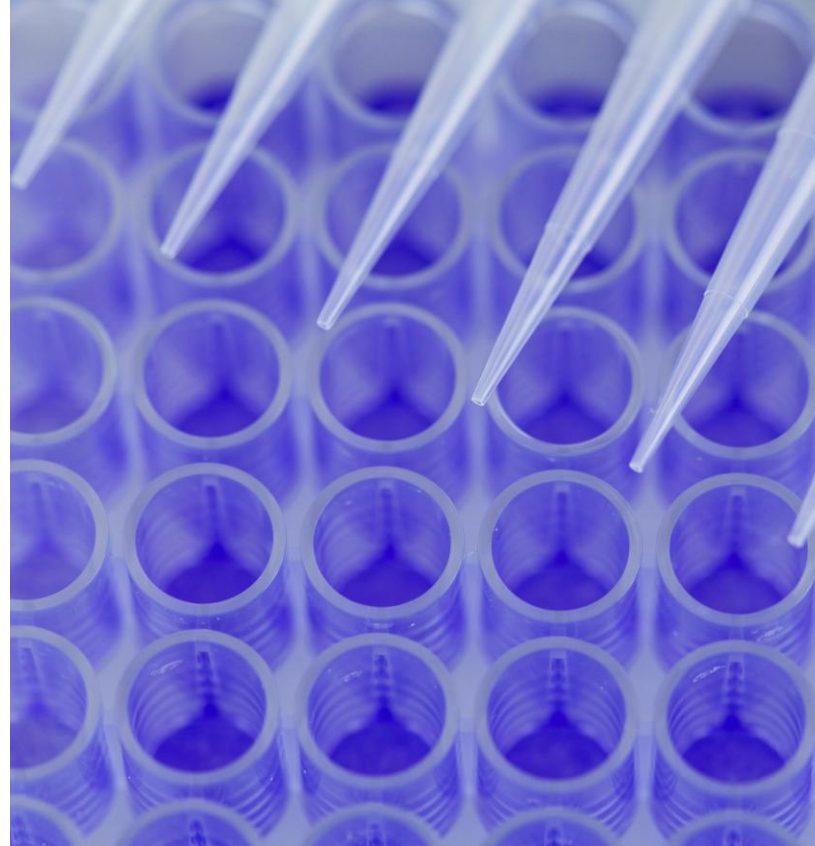
- Age 18-65
- Seeking MCC for pain, insomnia, depression or anxiety symptoms.
- Exclusionary: Daily cannabis use, CUD at screening or baseline, cancer, psychosis and current substance use disorders (except for mild or moderate AUD)
- In keeping with the pragmatic nature of the trial, participants assigned to MMC were responsible for arranging for and paying the costs of obtaining MMCs and cannabis products.

Outcomes

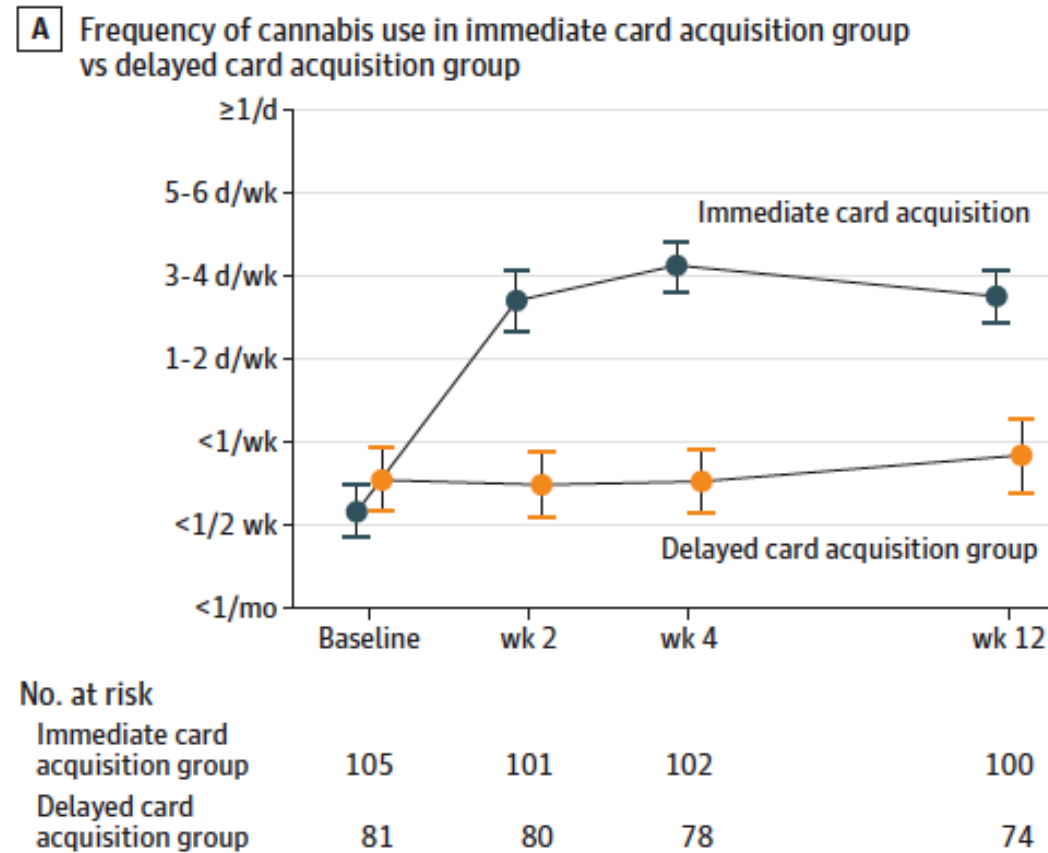
1. Cannabis use itself (how much do people use?
What sort of patterns emerge)?
- 2. Cannabis Use Disorder**
3. Symptom scores of Pain (BPI), Insomnia (AIS),
Depression and Anxiety (HADS)
4. Cognition (Memory, Attention, Executive Function)

Cannabis Metabolites in Urine

- At each visit, participants provided urine, reported whether their products were THC-dominant, CBD-dominant, or approximately equal CBD and THC.
- Tested for 17 metabolites.
 - THC
 - 11OH-THC
 - THC-COOH
 - THC-glucoronide
 - CBC
 - CBD
 - CBDV
 - CBN
 - CBG
 - THCV
 - THCV-COOH



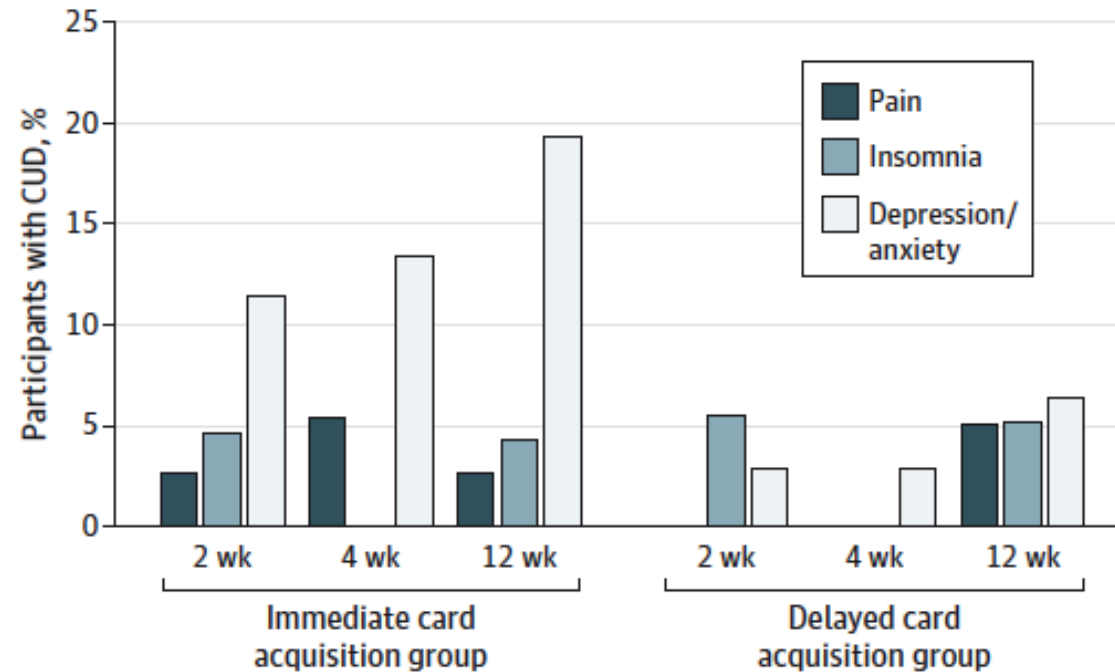
Cannabis Use Patterns



Gilman et al., 2022, JAMA Network Open

Cannabis Use Disorder increased by 3x in the MMC group

B Incidence of CUD by randomization group and primary complaint



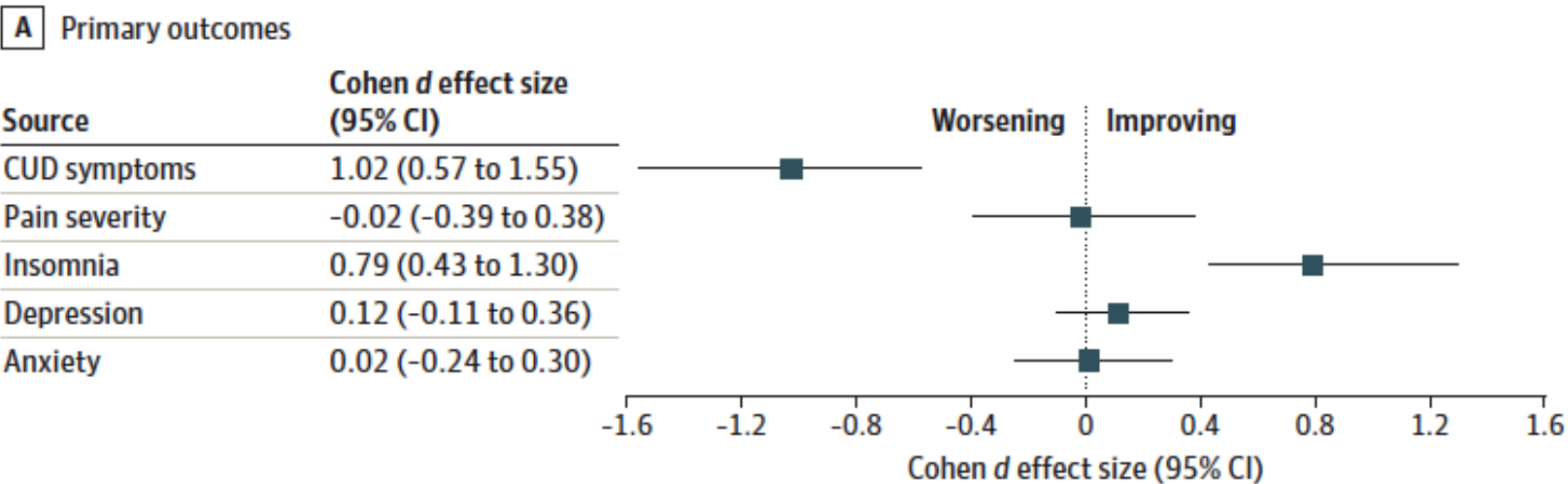
-The MMC group had **3x** odds of CUD diagnoses as the WLC group (**10% in MMC, 5.4% in WLC**; OR=2.9; 95% CI, 1.17 - 7.07; p=0.02)

-Most common CUD symptoms: tolerance and continued use despite problems with use

Gilman et al., 2022, JAMA Network Open

No Effect of Cannabis on Pain, Depression, or Anxiety but Improved Self-reported Sleep

Figure 3. Effect Sizes for Primary, Secondary, and Exploratory Outcomes



Gilman et al., 2022, JAMA Network Open

Cannabinoid Assay: Buyer Beware

- Among participants who reported using CBD-dominant products, there was no detectable CBD metabolite 30% of samples.
- Among samples from participants reporting THC-dominant or equal CBD-THC products, no THC metabolites were present in 35% of samples.
- **Vaping was the most common method of administration, but 20% of samples contained no measurable cannabinoid whatsoever.**

Gilman et al., 2021, JAMA Network Open

Poor regulation has real-life consequences

'I was taking what I thought was CBD oil, and apparently it wasn't what I thought it was. I started feeling the effects when I was driving, which was really scary. I got home as quickly as I could. I felt so high I didn't know where I was and couldn't focus, and the only way I got home was the noises from GPS. I was paranoid that I might have hit someone or something, but I checked my car and there was no damage.'

Take home points

- Healthcare providers and patients should be cautious about using cannabis, especially those with mood disorders.
- More research is needed to better understand the risks and benefits of cannabis for specific medical conditions and to see how the risk of developing CUD changes with longer use.
- This information will help doctors and patients make better decisions about using cannabis for specific health problems.



Cannabis, Pain, and Opioid Use in Patients with Chronic Non- Cancer Pain

R01DA051540

MPIs: Gilman and Evins



Why are we doing this study?

- Approximately 40 million adults in the United States suffer from CNCP, a debilitating medical condition that is complex to manage.
- Because of the complex medical needs of this patient group, there has been enthusiasm over the potential to treat CNCP with cannabis.
- However, evidence to support the effectiveness of cannabis to either treat chronic pain or to reduce opioid use is weak, and there are risks associated with cannabis.
- *There have been no randomized studies that have directly addressed this question.*

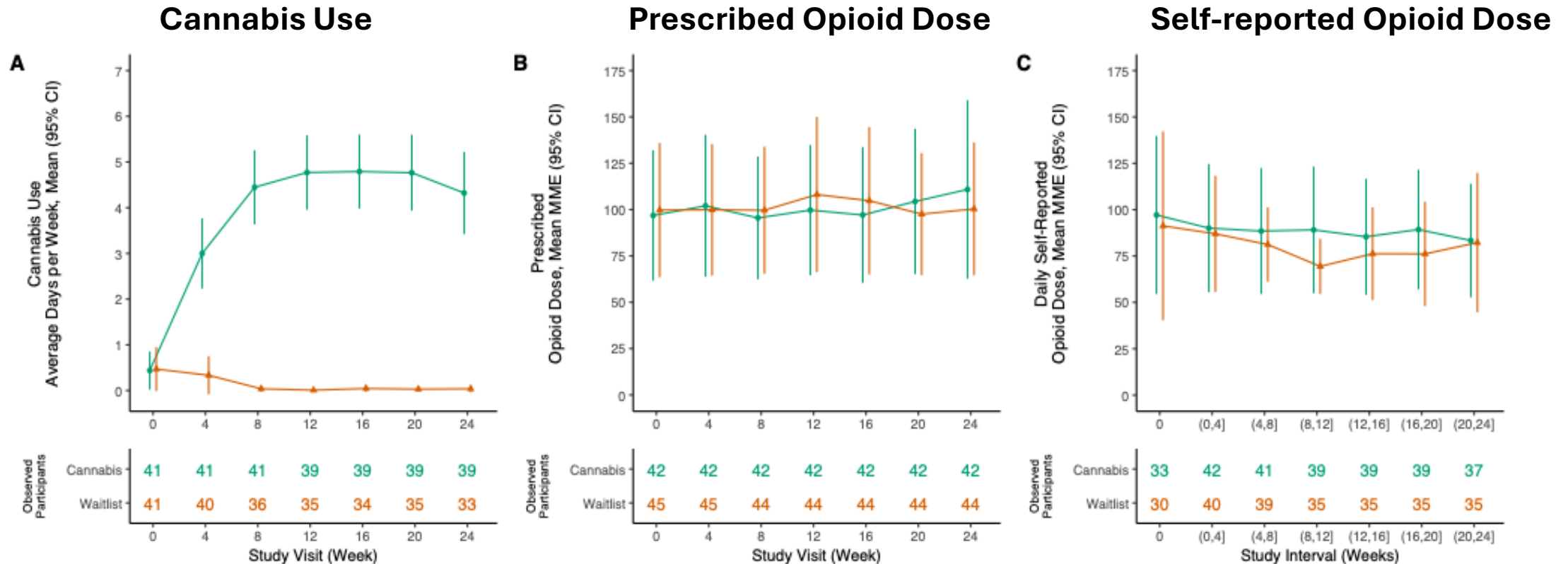
Study Design

- 26-week Prescription Opioid Taper Support (POTS) program, which is a combination of CBT, MI, and pain management techniques
- Goal is 10% taper per month, ~50% taper by Week 26.
- Participants were randomized to cannabis without delay vs waiting to use cannabis until the end of the 26-week intervention
- Primary outcomes: Pain Intensity/Interference and prescription opioid dose (MME/day), verified by the Prescription Monitoring Program
- Secondary outcomes: Quality of life, depression, anxiety, symptoms of opioid and cannabis use disorders

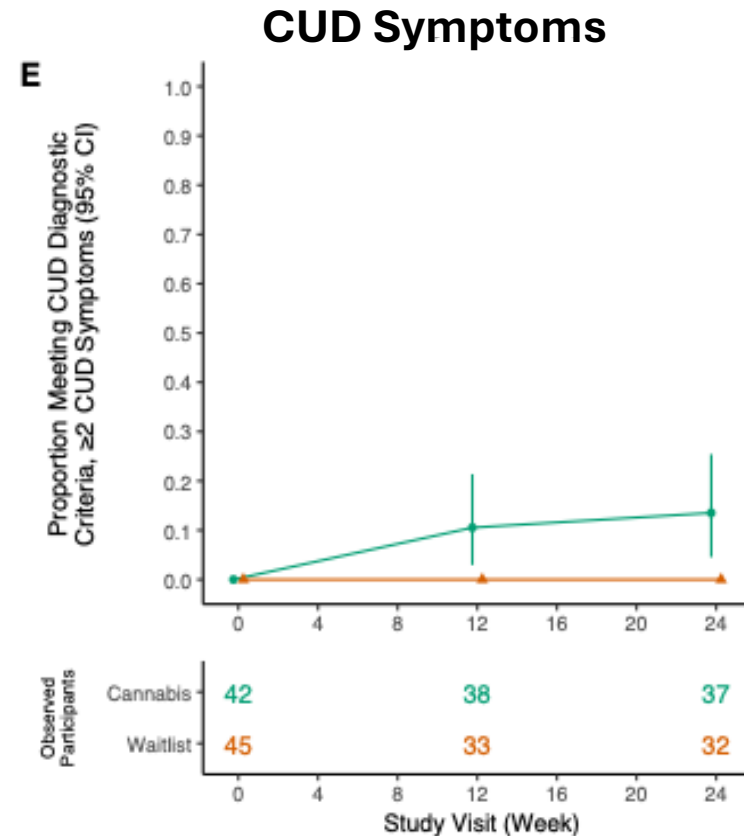
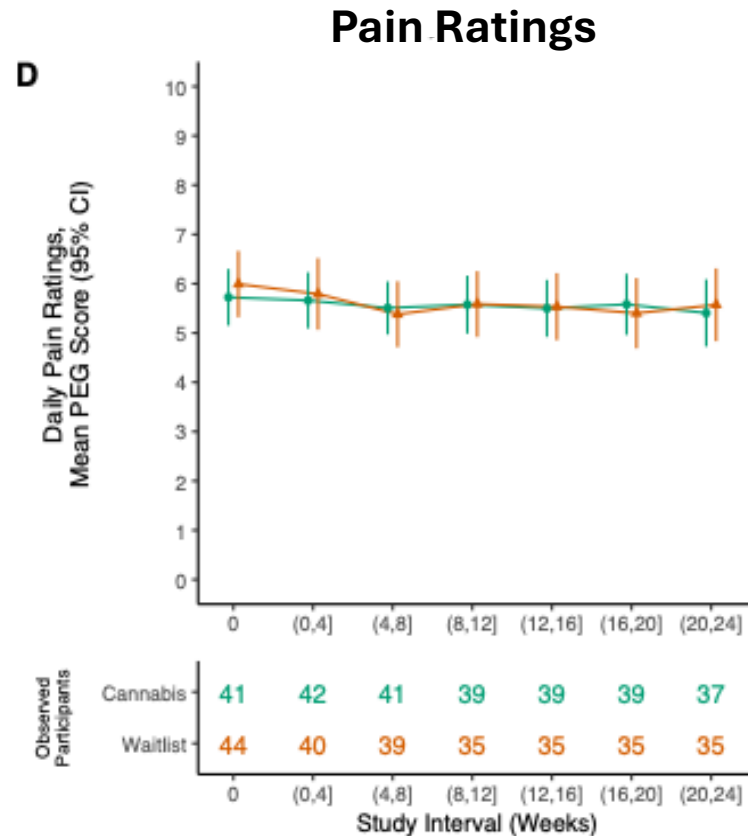
Participant Characteristics

- Participants were on average 57.1 (SD, 10.2) years of age and had longstanding chronic pain and opioid exposure.
- Mean duration of chronic pain was approximately 20 years, and participants had received opioid therapy for a mean of 15.8 (SD, 8.3) years.
- More than 40% of participants were disabled, and an additional 18% were retired.
- Participants had clinically complex chronic pain
 - musculoskeletal and neurologic conditions including arthritis, disc disorders, back pain, neuropathy, and migraine.
 - Most reported pain at multiple anatomical sites.
 - Concomitant medication use was common

Did Cannabis Help People Taper their Opioids?



Did Cannabis Help People Taper their Opioids?



Conclusions

- No reduction in opioid dose with adjunctive cannabis.
- No improvement in pain intensity or pain interference.
- Anxiety symptoms increased in the cannabis group.
- Cannabis use disorder symptoms increased, with ~14% developing incident CUD.
- Findings do not support cannabis as an opioid-sparing strategy for chronic non-cancer pain.

Evaluation of Cannabidiol for Reduction of Brain Neuroinflammation



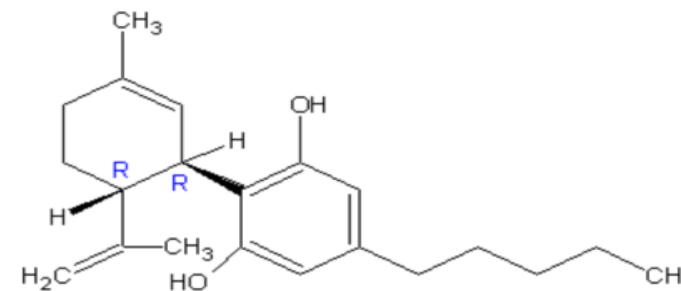
Neuroinflammation and Pain

- In the last ~20 years, animal studies have demonstrated that glial cells (microglia and astrocytes, mainly), as well as neuro-glial interactions, play a key role in the establishment and/or maintenance of persistent pain
- Recently, however, our group has used positron emission tomography (PET) to demonstrate the presence of increased levels of the 18kDa translocator protein (TSPO), a PET marker associated with glial activation/neuroimmune processes, in the brains of patients with chronic low back pain.

STUDY DESIGN

- We randomized patients with chronic low back pain to four weeks of pharmaceutical-grade CBD or placebo.
- Our primary mechanistic hypothesis was that CBD would reduce pain-related neuroinflammation.
- We measured that using PET with [11C]PBR28, which binds to TSPO and gives us an in vivo measure of neuroimmune-related activity.
- Participants underwent imaging before treatment and again after four weeks.

- **Recommended starting dose:** 2.5 mg/kg taken twice daily (5 mg/kg/day)
- **Treatment duration:** 4 weeks
- Titration Schedule
 - Week 1: 5 mg/kg/day
 - Week 2: 10 mg/kg/day
 - Week 3: 15 mg/kg/day
 - Week 4: 20 mg/kg/day



To be continued...

- Ongoing analyses will determine whether CBD reduces chronic low back pain compared with placebo after 4 weeks.
- Ongoing analyses will determine whether CBD produces measurable changes in brain function.

Summary and Future Directions

- Ongoing research is investigating **therapeutic potential and risks of cannabinoids**, especially in **neuropsychiatric disorders, pain management, and inflammation**.
- Future studies will **further explore targeted modulation of the endocannabinoid system** for precision medicine approaches.

Acknowledgments



- A. Eden Evins, MD
- Marco Loggia, PhD
- Gladys Pachas, MD
- Randi Schuster, PhD
- Harrison Reeder, PhD
- Julia Jashinski, MSW
- Cori Cather, PhD
- CRCs who collected the data
- Funding sources
(NIDA)

I'd love to hear from you! For further info, email me at jgilman1@mgh.harvard.edu

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Questions?