# Using cannabinoids to manage chronic pain

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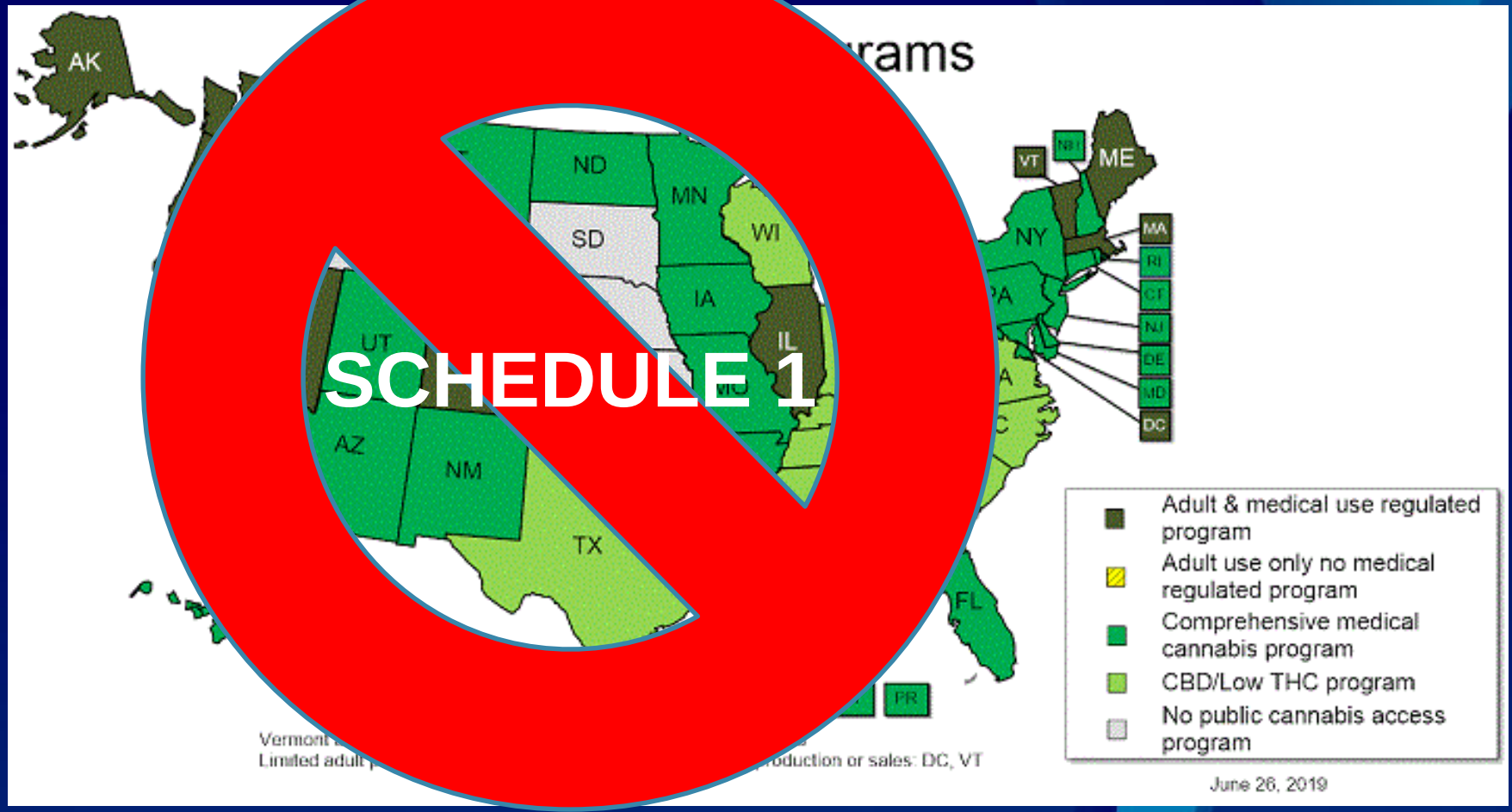
Chronic Pain and Fatigue Research Center
The University of Michigan

# Disclosures

- None

# Medical cannabis in US



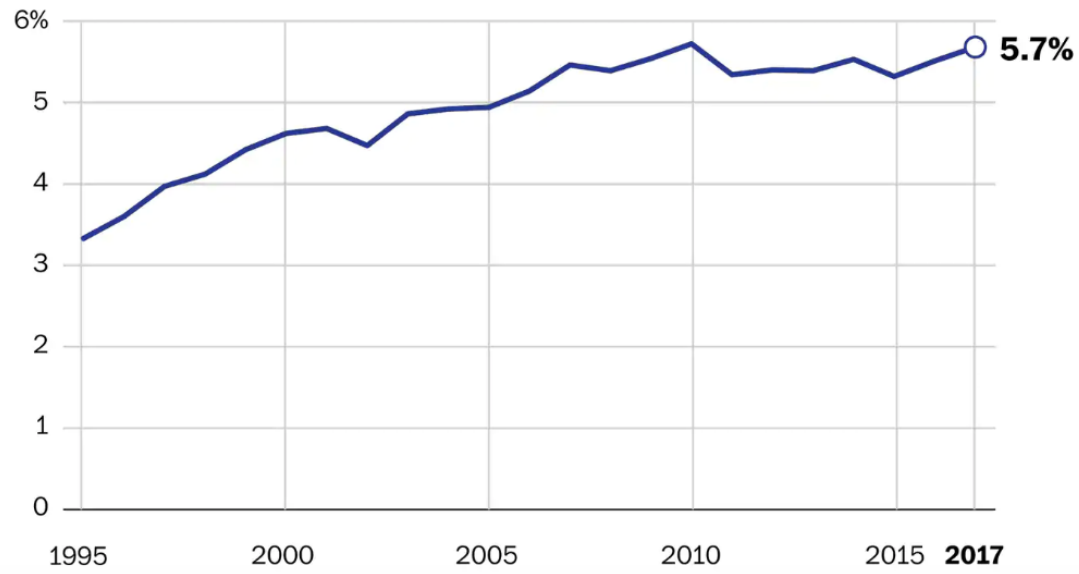

http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx#Table%202

# Where the war on weed still rages

In some U.S. counties, more than 40 percent of all arrests are for marijuana possession

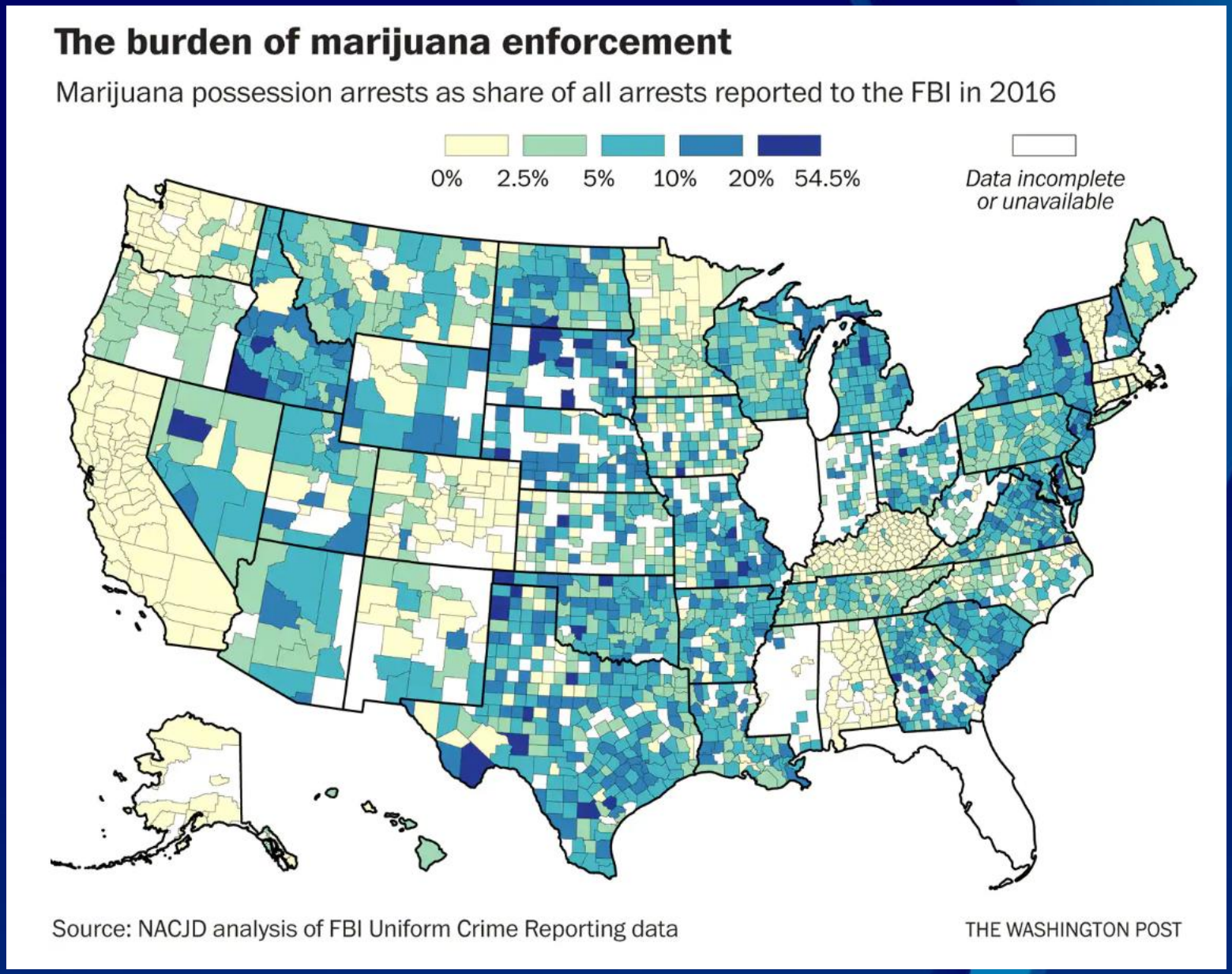
**The burden of marijuana enforcement**

Marijuana possession arrests as share of all arrests reported to the FBI, 1995 to 2017






Source: Washington post https://www.washingtonpost.com/us-policy/2019/04/15/where-war-weed-still-rages/?utm_term=.4ddead2b1eef


The burden of marijuana enforcement
Marijuana possession arrests as share of all arrests reported to the FBI in 2016
0%
2.5%
5%
10%
20%
54.5%
Data incomplete or unavailable
Source: NACJD analysis of FBI Uniform Crime Reporting data
THE WASHINGTON POST

PHARMACEUTICALS & MEDICAL TECHNOLOGY

By Kevin F. B

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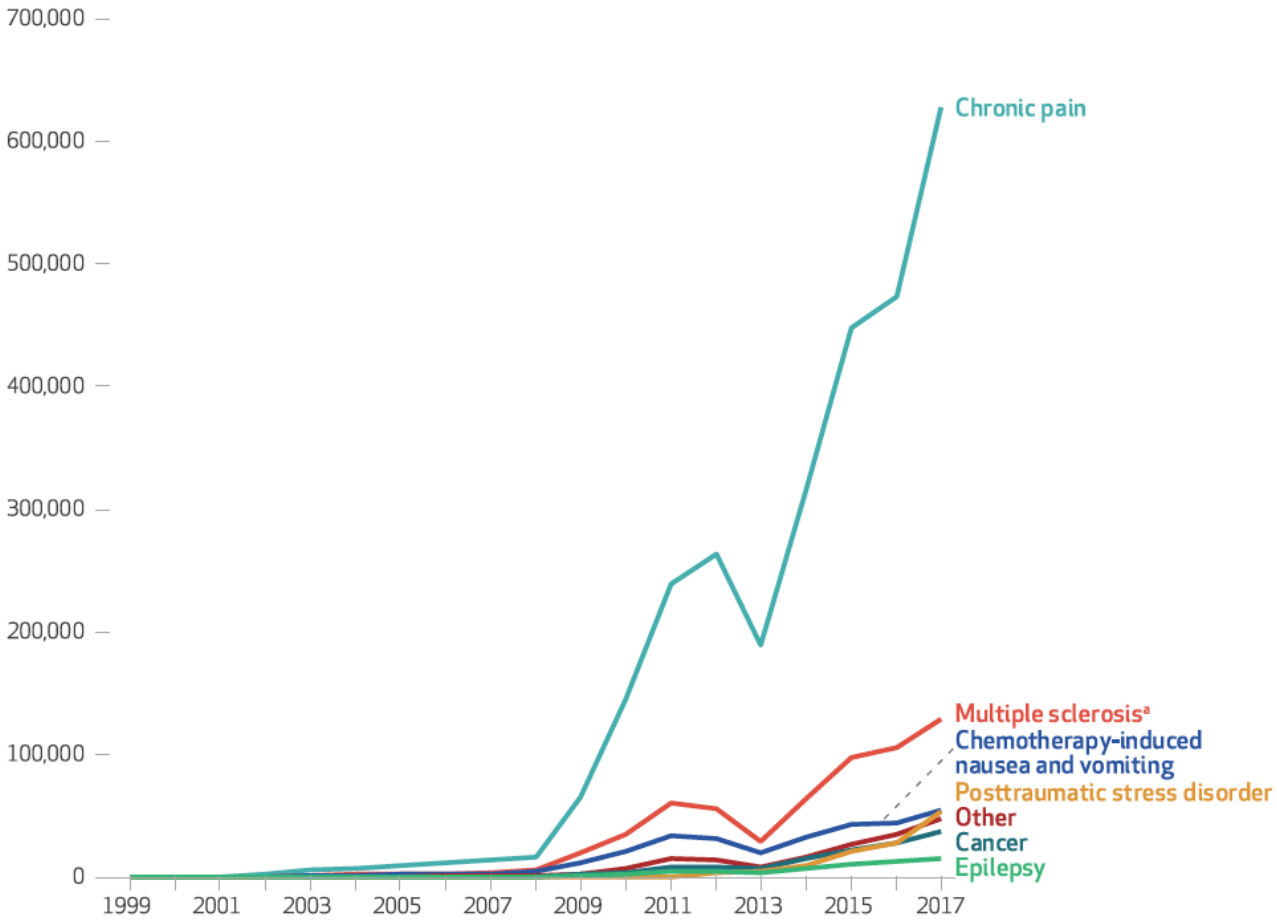
**EXHIBIT 2**

**Numbers of patient-reported qualifying conditions for medical cannabis licenses, 1999–2017**




**SOURCE** Authors' analysis of data from state medical cannabis registries. **NOTES** Data were missing for Michigan for 2010 and 2013 and for Rhode Island for 2007, 2009, 2011, 2013, 2015 and 2016. The sharp dip in patient-reported qualifying conditions in 2013 is attributable to the large number of patients in Michigan who were not accounted for in that year. [a]Spasticity symptoms.

Boehnke, Kevin F., et al. "Qualifying Conditions Of Medical Cannabis License Holders In The United States." *Health Affairs* 38.2 (2019): 295-302.

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# Big Decline in Opioid Use by Marijuana Users

March 23, 2016

RollingStone Medical Pot Is Our Best Hope to Fight the Opioid Epidemic

# Medical Pot Is Our Best Hope to Fight the Opioid Epidemic

"There are direct reasons why [cannabis] could actually help people get off of opioids," says one leading marijuana researcher

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It's time we start talking seriously about medical marijuana as a way to end the opioid epidemic

Vox EXPLAINERS POLITICS & POLICY WORLD

# One way to fight the opioid epidemic? Medical marijuana.

An innovative, but evidence-based, idea.

By German Lopez | @germanrlopez | german.lopez@vox.com | Updated Jan 18, 2017, 1:10pm EST

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# Patients Are Ditching Opioid Pills for Weed

Can marijuana help solve the opioid epidemic?

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PUBLIC HEALTH

# Could Medical Cannabis Break the Painkiller Epidemic?

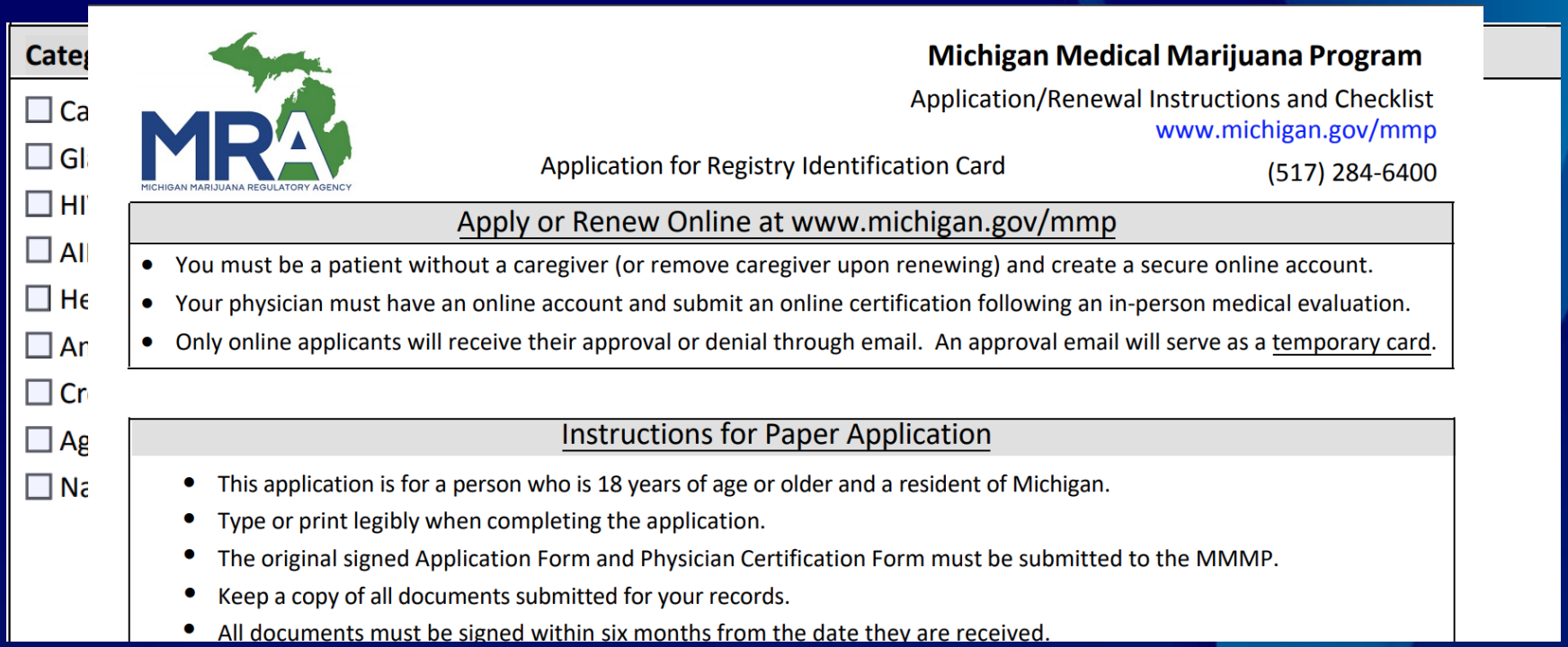
A body of research suggests yes, but scientists are having to fight red tape to study whether medical marijuana could substitute for opioid drugs

# Cannabis as an opioid substitute for chronic pain?

- Cannabis as a synergist with opioids[1,2]
- State-wide analyses[3-5]
  - Importance of Dispensaries in these studies (Powell et al, 2018)
- Cross-sectional[6-8] and longitudinal support[9-11]

1. Abrams et al, *Clinical Pharmacology and Therapeutics*, (2011) 2. Cooper, Ziva D., et al. *Neuropsychopharmacology* (2018) 3. Bachhuber MA et. al. JAMA Int Med (2014). 4. Bradford and Bradford *Health* Affairs, (2016) 5. Bradford and Bradford, *Health* Affairs (2017). 6. Boehnke, Kevin F., Evangelos Litinas, and Daniel J. Clauw. *The Journal of Pain* (2016). 7. Lucas et al, *Journal of International Drug Policy* (2017) 8. Reiman et al, *Cannabis and Cannabinoid Research* (2017). 9. Haroutounian et al,. *Clinical Journal of Pain* (2016). 10. Stith et al, *PLOSone* (2017) 11. Abuhasira et al, *European Journal of Internal Medicine*, (2018)

# Michigan Medical Marihuana Act



**Michigan Medical Marijuana Program**

Application/Renewal Instructions and Checklist

www.michigan.gov/mmp

(517) 284-6400

MICHIGAN MARIJUANA REGULATORY AGENCY

Application for Registry Identification Card

**Apply or Renew Online at www.michigan.gov/mmp**

- You must be a patient without a caregiver (or remove caregiver upon renewing) and create a secure online account.
- Your physician must have an online account and submit an online certification following an in-person medical evaluation.
- Only online applicants will receive their approval or denial through email. An approval email will serve as a temporary card.

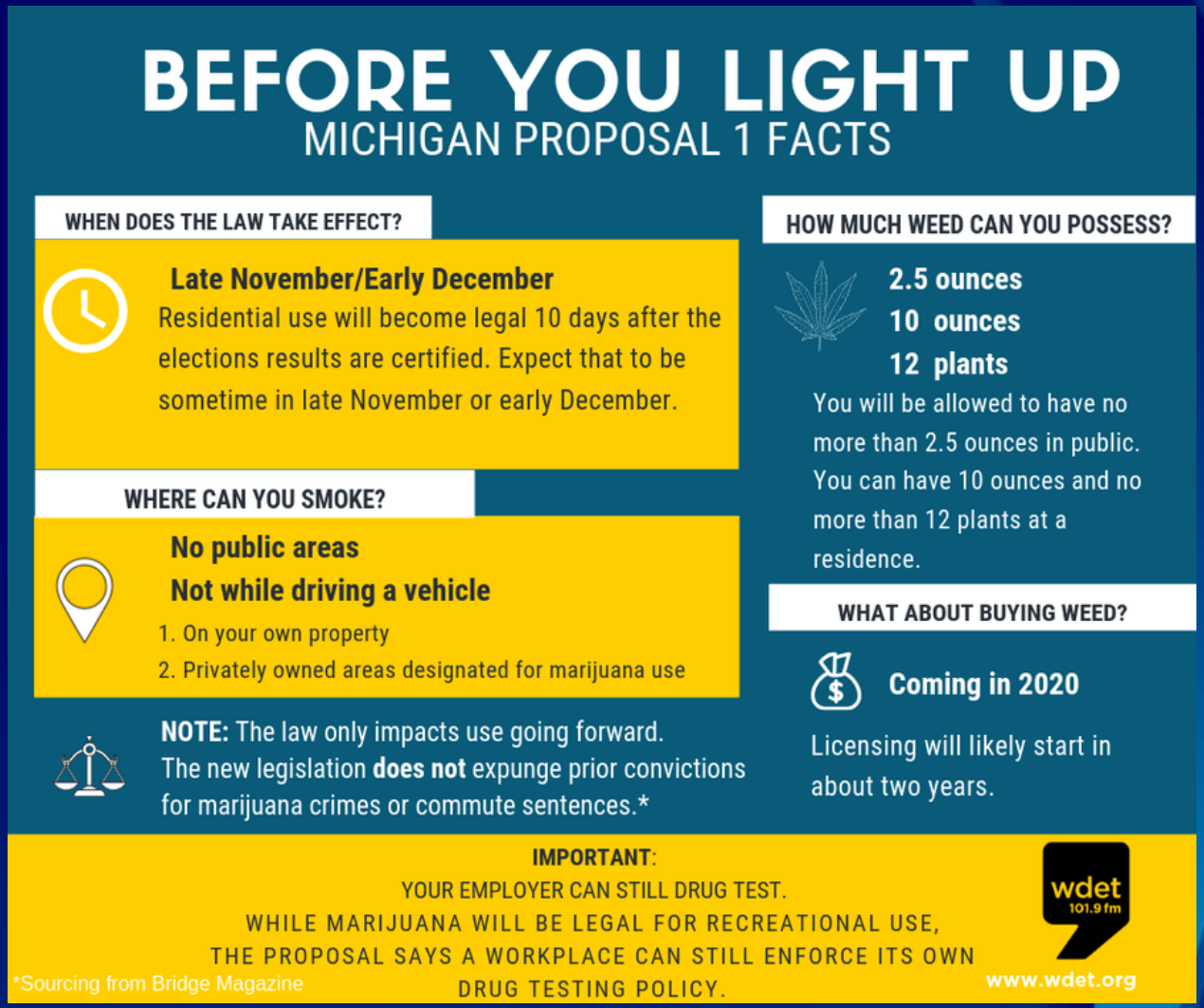
**Instructions for Paper Application**

- This application is for a person who is 18 years of age or older and a resident of Michigan.
- Type or print legibly when completing the application.
- The original signed Application Form and Physician Certification Form must be submitted to the MMMP.
- Keep a copy of all documents submitted for your records.
- All documents must be signed within six months from the date they are received.

- In 2019: 276,970 medical cannabis patients in Michigan.
  - 63.6% severe and chronic pain
  - 49.7% chronic pain
  - 19.5% arthritis
- Doctor certifies that patient has condition: NOT PRESCRIPTION
- 2.5 ounces, 12 plants per patient
- Dispensaries: now must sell regulated products (mostly)

1: 2019 Medical Marihuana Act Statistical Report, Michigan

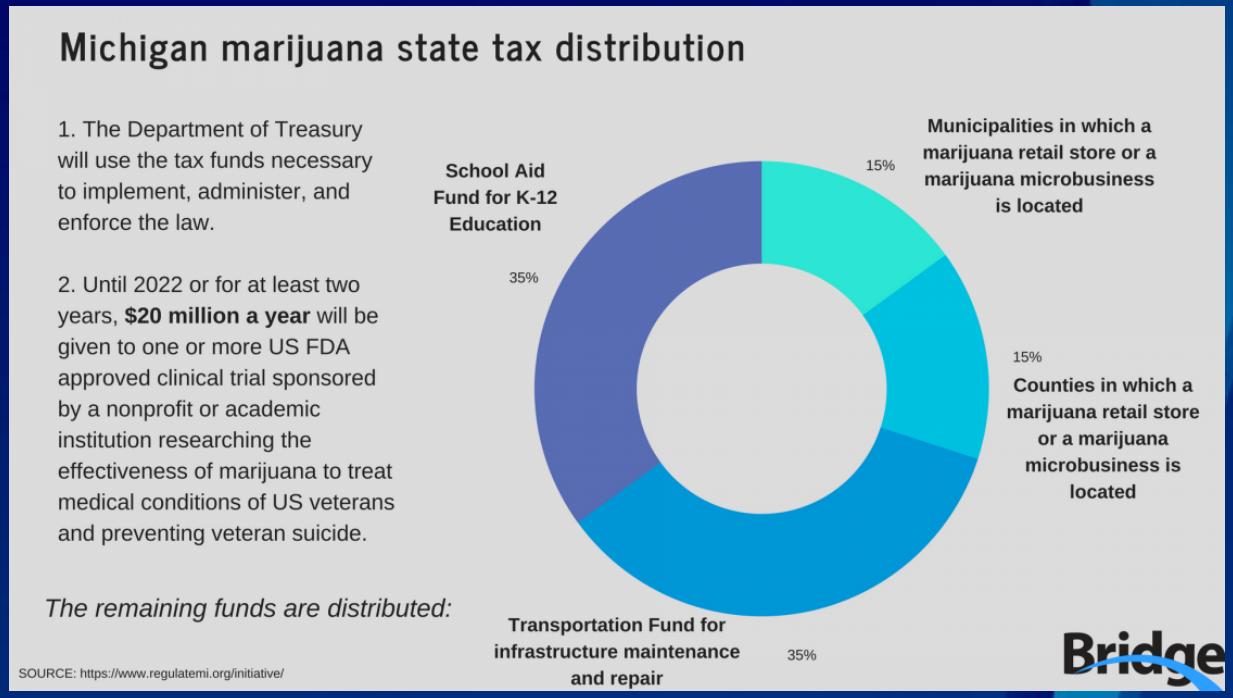
# Adult-use cannabis (Proposal 1)




https://detroit.cbslocal.com/2020/02/03/heres-a-list-of-42-active-adult-use-marijuana-licenses-in-michigan/

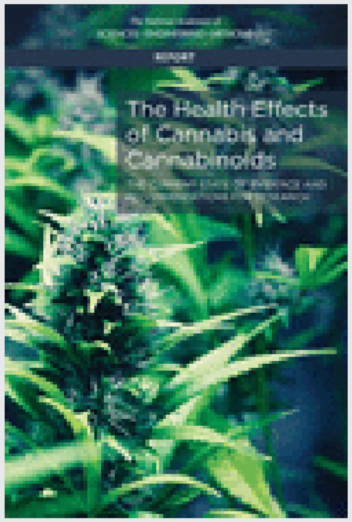
# Dispensaries, taxes

- Dispensaries:
  - 47 currently, up from 27 in January 2020.
    - 10 in Ann Arbor
  - Municipalities can opt in or out of hosting cannabis businesses: (~80% have opted out)
  - Taxes: 10% excise tax in addition to 6% sales tax



# Cannabis and Cannabinoids

- Definitions and Background
- Overview of Risks and Benefits of Cannabinoids
- Role in Pain Management
- Summary

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# The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research

## DETAILS

486 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-45304-2 | DOI: 10.17226/24625

## CONTRIBUTORS

Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda; Board on Population Health and Public Health Practice; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine

# Definitions

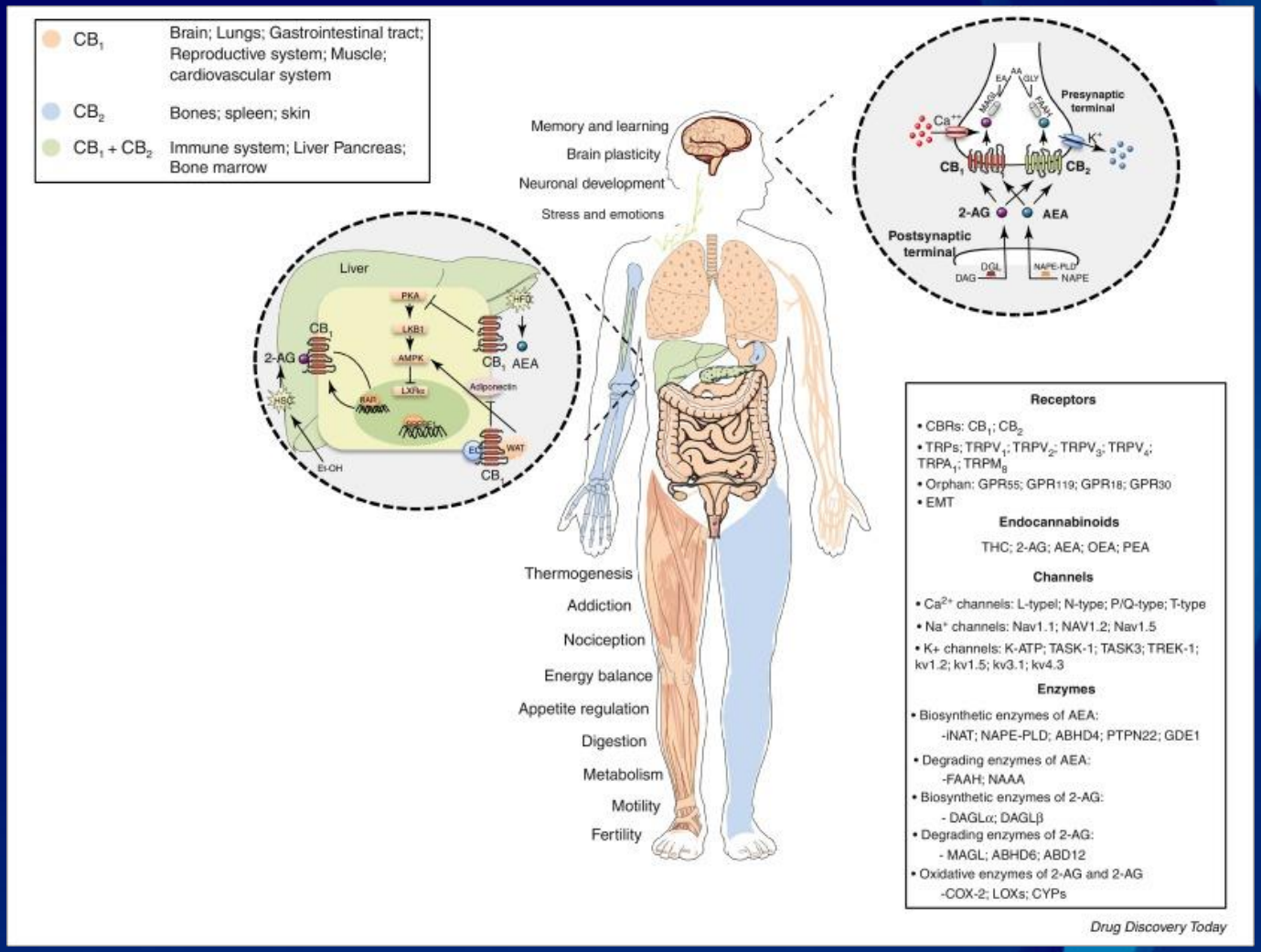
- Cannabis - indica, sativa, and ruderalis
- Cannabinoids:
  - Endocannabinoids
  - Phytocannabinoids – plant origin
  - Synthetic cannabinoids – e.g. dronabinol and Nabilone

https://upload.wikimedia.org/wikipedia/commons/2/23/Marijuana-Cannabis-Weed-Bud-Gram.jpg

https://en.wikipedia.org/wiki/Cannabis#/media/File:Cannabis_sativa_Koehler_drawing.jpg

# Endocannabinoid system - I

**A set of receptors and their naturally occurring ligands (endocannabinoids) and enzymes regulating control**




Aizpurua-Olaizola, Oier, et al. "Targeting the endocannabinoid system: future therapeutic strategies." *Drug discovery today*22.1 (2017): 105-110. Fonseca et al, *Prostaglandins & other lipid mediators* 102 (2013): 13-30.

# Endocannabinoid system - II

Some known functions of the endocannabinoid system:

- Functions: “Relax, eat, sleep, forget, protect”
- Memory
- Neurogenesis
- Analgesia
- Immune function
- Stress
- Appetite

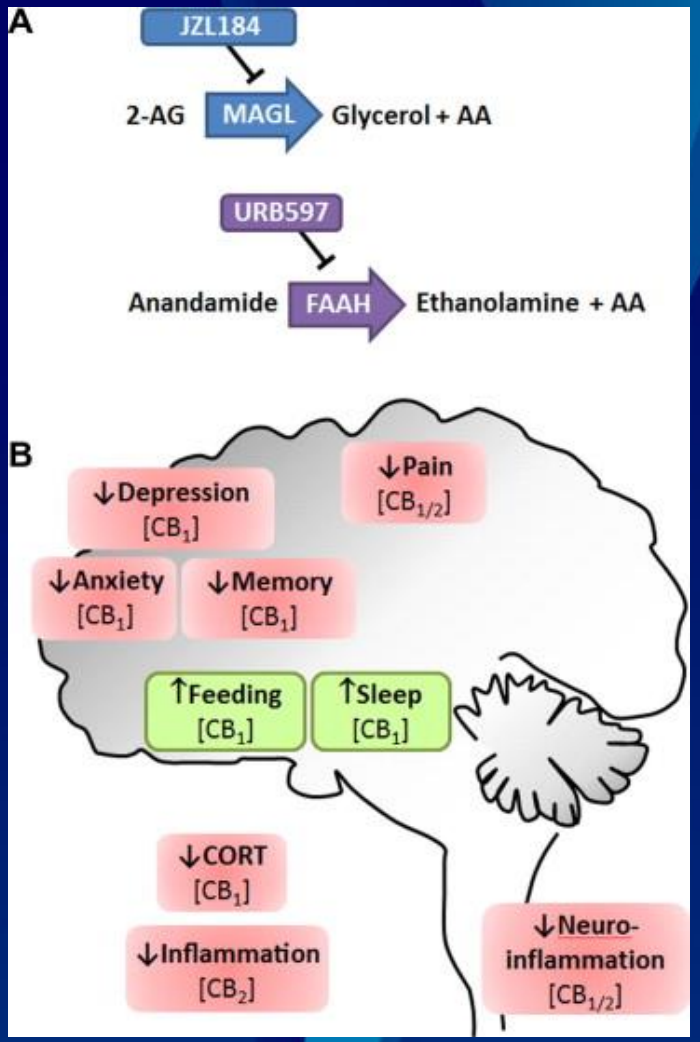



Figure from Crowe et al, 2014.

1. Rom S. Journal of Neuroimmune Pharmacology. 2013; 8(3): 608-620. 2. Hill et. al. PNAS 2010; 107(20) 9406–9411. 3. Crowe S et. al. Brain, Behavior, and Immunity, Volume 42, 2014, 1 - 5

# Cannabis-derived cannabinoids

**>100 known**

- **Tetrahydrocannabinol (THC)**
  - Analgesic, mood-altering, appetite stimulating
  - Partial agonist of CB1 and CB2
- **Cannabidiol** (CBD)
  - Does not bind with significant affinity to CB receptors
  - Non-intoxicating, potentially protective against anxiogenic effects of THC
  - Anti-inflammatory, anxiolytic[1], anti-convulsant[2]
- **Other cannabinoids:** CBN, CBG, CBC, etc. **–The "Entourage Effect"**[3]

By Indirectantagonist - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=1853423

By Cannabis Training University - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=21152729

1. Hurd, Yasmin L., et al. *American Journal of Psychiatry* 176.11 (2019): 911-922. 2. Devinsky, Orrin, et al. *New England Journal of Medicine* 376.21 (2017): 2011-2020. 3. Russo, Ethan B. *British journal of pharmacology* 163.7 (2011): 1344-1364.

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## CBD Biscuits

*For small to medium dogs (9-44lbs)*

*For medium to large dogs (45-120lbs)*

## CBD Extracts

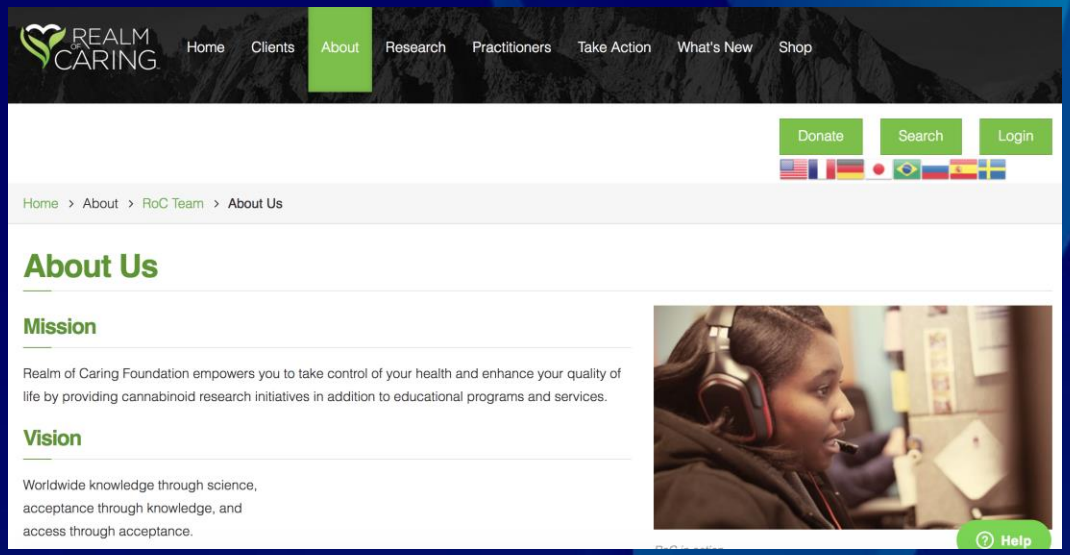
# Verifiable products, Hemp vs. Marijuana-derived cannabinoids

## Letters

RESEARCH LETTER

### Labeling Accuracy of Cannabidiol Extracts Sold Online

There is growing consumer demand for cannabidiol (CBD), a constituent of the cannabis plant, due to its purported medicinal benefits for myriad health conditions.[1] Viscous plant-derived extracts, suspended in oil, alcohol (tincture), or vaporization liquid, represent most of the retail market for CBD. Discrepancies between federal and state cannabis laws have resulted in inadequate regulation and oversight, leading to inac-




https://www.theroc.us/

Table 1. Label Accuracy by Cannabidiol Extract Type

| | Cannabidiol Extract Products | | | |
|---|---|---|---|---|
| | Oil (n = 40) | Tincture (n = 20) | Vaporization Liquid (n = 24) | Total (N = 84) |
| Label accuracy, No. of products (%) [95% CI] | | | | |
| Accurate[a] | 18 (45.00) [30.71-60.17] | 5 (25.00) [11.19-46.87] | 3 (12.50) [4.34-31.00] | 26 (30.95) [22.08-41.49] |
| Under[b] | 10 (25.00) [14.19-40.19] | 8 (40.00) [21.88-61.34] | 18 (75.00) [55.10-88.00] | 36 (42.85) [32.82-53.53] |
| Over[c] | 12 (30.00) [18.07-45.43] | 7 (35.00) [18.12-56.71] | 3 (12.50) [4.34-31.00] | 22 (26.19) [17.98-36.48] |
| Labeled concentration, mg/mL | | | | |
| Mean (95% CI) | 56.15 (14.23-98.07) | 11.14 (5.60-16.60) | 26.15 (12.50-39.74) | 36.86 (16.21-57.51) |
| Median (range) | 22.26 (2.50-800.00) | 8.33 (1.33-50.00) | 18.33 (2.00-160.00) | 15.00 (1.33-800.00) |
| Deviation of labeled content from tested value, mg/mL | | | | |
| Mean (95% CI) [% of deviation] | 10.34 (4.95-15.74) [29.01] | 3.94 (2.74-5.14) [220.62] | 11.52 (8.10-14.94) [1098.70] | 9.16 (4.96-13.36) [380.26] |
| Median (range) [% of deviation] | 2.76 (0.13-144.73) [12.11] | 1.48 (0.01-22.30) [19.12] | 4.62 (0.14-66.07) [67.34] | 3.17 (0.10-144.73) [20.42] |

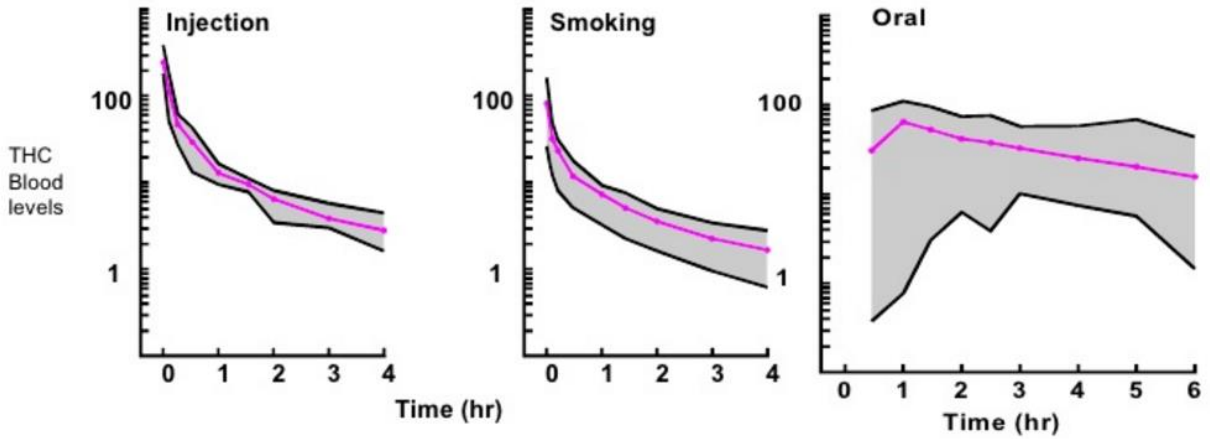
[a] Cannabidiol content tested within 10% of labeled value.
[b] Cannabidiol content exceeded labeled value by more than 10%.
[c] Cannabidiol content tested more than 10% below labeled value.

MARIJUANA MOMENT

## Hemp is officially legalized with President Trump's signature on the Farm Bill

# Pharmacokinetics

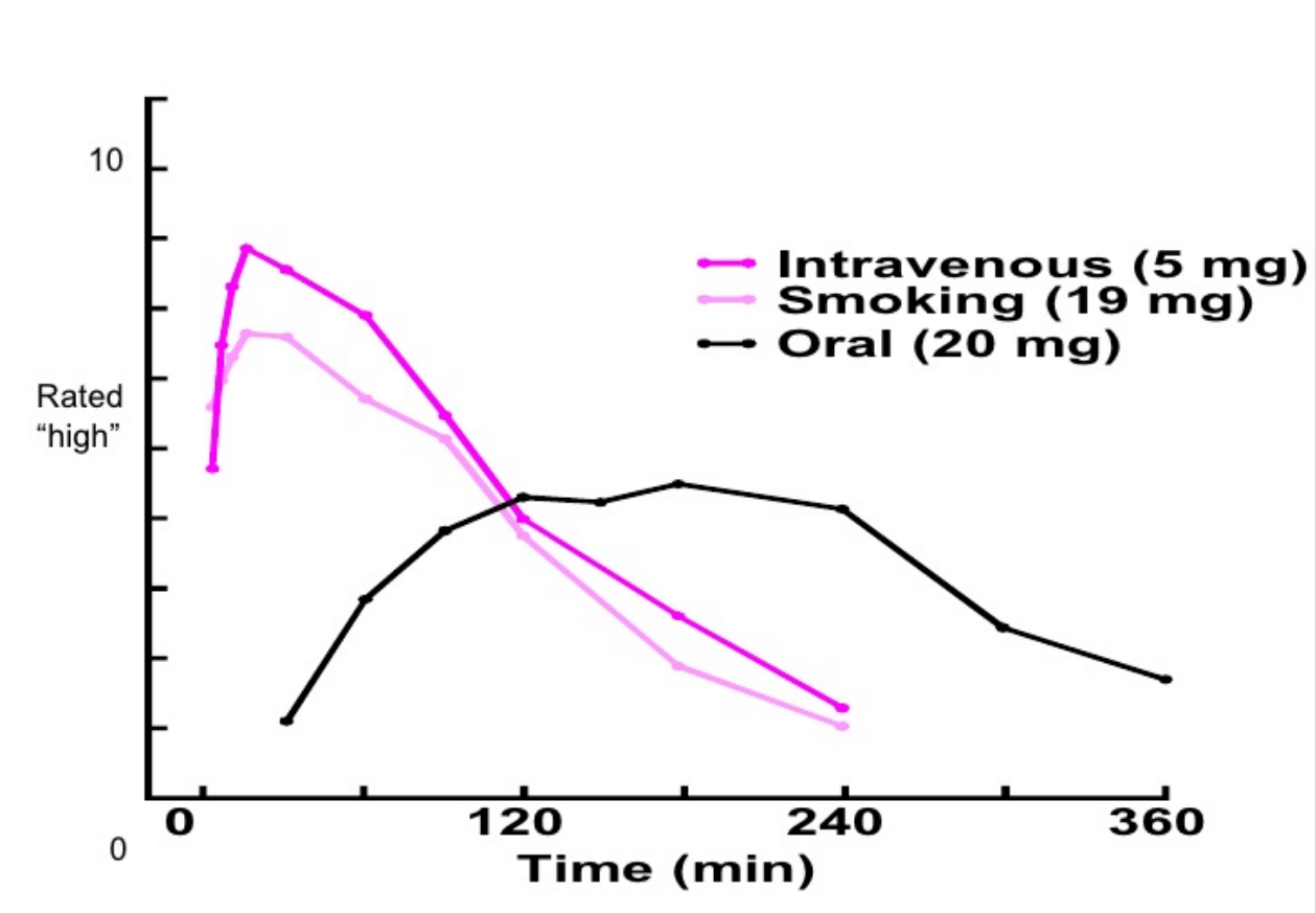
## Pharmacokinetics




Route of administration influences THC pharmacokinetics, left = 5 mg i.v. injection, center = smoking 13.0 mg, or right =consuming cookie with 20 mg (Agurell et al. 1986).

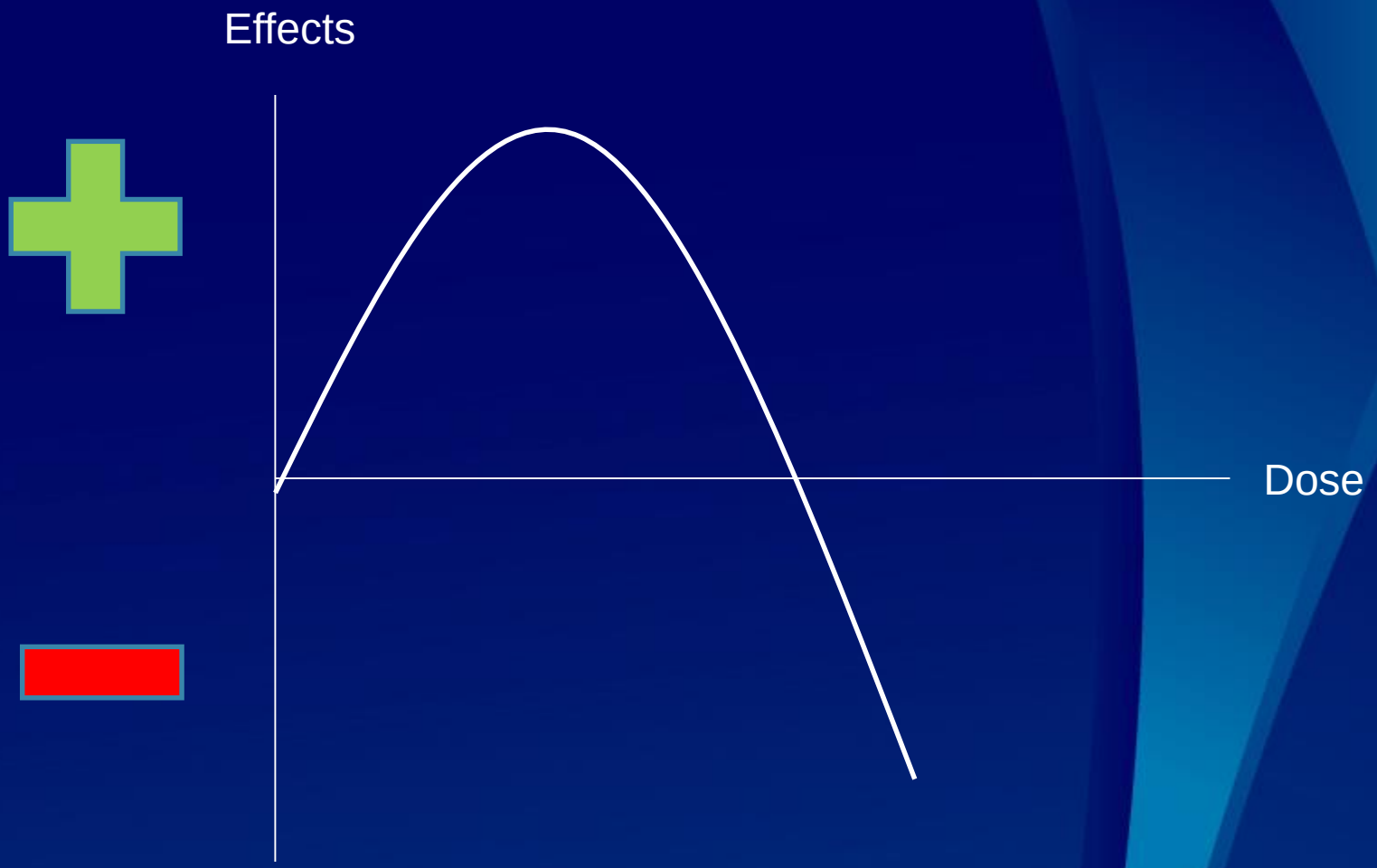
Agurell, Stig, et al. *Pharmacological Reviews* 38.1 (1986): 21-43.

# Feelings of ‘high’ from different administration routes




Agurell, Stig, et al. *Pharmacological Reviews* 38.1 (1986): 21-43.

# U-Shaped Curve for cannabis effects




1. Hill KP. Jama. 2015;313(24):2474. 2. Wallace M, Schulteis G, Atkinson JH, Wolfson T, Lazzaretto D, Bentley H, et al. Anesthesiology. 2007;107(5):785–96. 3. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. J Pain. Elsevier Ltd; 2012;13(5):438–49.

# Cannabis and Cannabinoids

- Definitions and Background
- Overview of Risks and Benefits of Cannabinoids
- Role in Pain management
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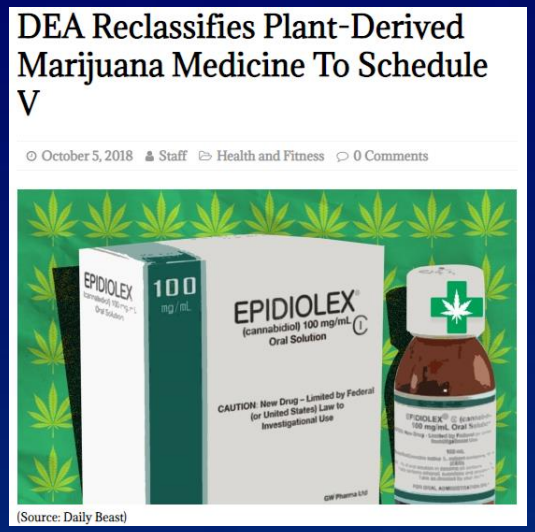
# Known benefits of Cannabinoids

- Antiemetic and anorexia[1-4] – dronabinol and nabilone are FDA-approved (Schedule II + III) in US.[6]
- Nabiximols: Anti-spasticity agent, used for MS[4,5,6]
- Sleep: In context of chronic pain[7]
- Analgesia[6]: Strongest evidence in chronic neuropathic pain
- Epilepsy: CBD found to reduce seizure frequency in Dravet Syndrome, Lennox-Gastaut, and other epileptic disorders

http://www.floridamarijuanainfo.org/marinol-the-prescription-thc-pill/




(Source: Daily Beast)

https://www.medycznamarihuana.com/glejak-kannabidiol-cbd-moze-hamowac-rozwoj-raka-mozgu/


***1.*** Sharkey K. et. al. Eur J Pharm 2014; 722:134-146. 2. Machado Rocha, Francisco C., et al. *European journal of cancer care* 17.5 (2008): 431-443. 3. FDA:http://www.fda.gov/ohrms/dockets/dockets/05n0479/05N-0479-emc0004-04.pdf 4.Collin C, et al. Neurol Res. 2010;32(5):451-459. 5. Collin C et al. Eur J Neurol. 2007;14(3):290-296.128. 6. Whiting, Penny F., et al. *Jama* 313.24 (2015): 2456-2473. 7. National Academies of Sciences, engineering, and medicine. Health effects of cannabis and cannabinoids (2017).

# Contraindications of medical cannabinoids

- Poor data available on herbal cannabis
- Dronabinol contraindications:
  - Disulfiram or Metronidazole use in past 14 days
  - History of substance abuse
  - Pregnancy
  - Psychiactric disorder
  - Cardiovascular disease
  - History of seizures
- Epidiolex contraindications:
  - Hypersensitivity to cannabidiol or any of the ingredients in EPIDIOLEX
  - Potential drug-drug interactions make it important to monitor liver enzymes, especially with anti-convulsants (e.g., valproate)

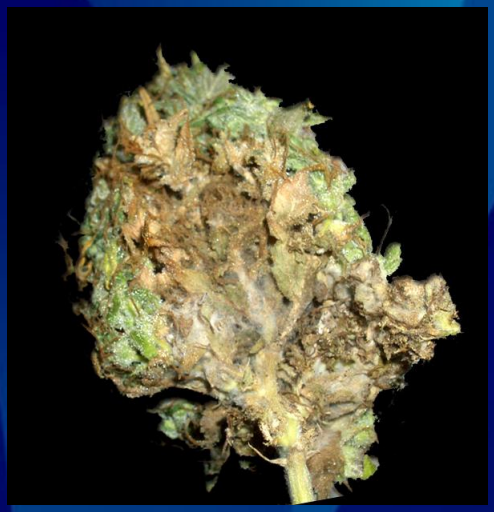
# Risks of cannabinoids (recreational)

Long term:

- Respiratory effects
- Dependence and addiction
- Psychotic illnesses:1.5-2.4x rate developed under age of 25
- Long term effects on memory and brain structure

Acute:

- Common: Dizziness, somnolence, euphoria, light-headedness, anxiety, and others
- Uncommon: Vomiting, hallucinations, paranoia, seizures
- Uncertain quality of herbal preparation[4]
- Vehicle accidents

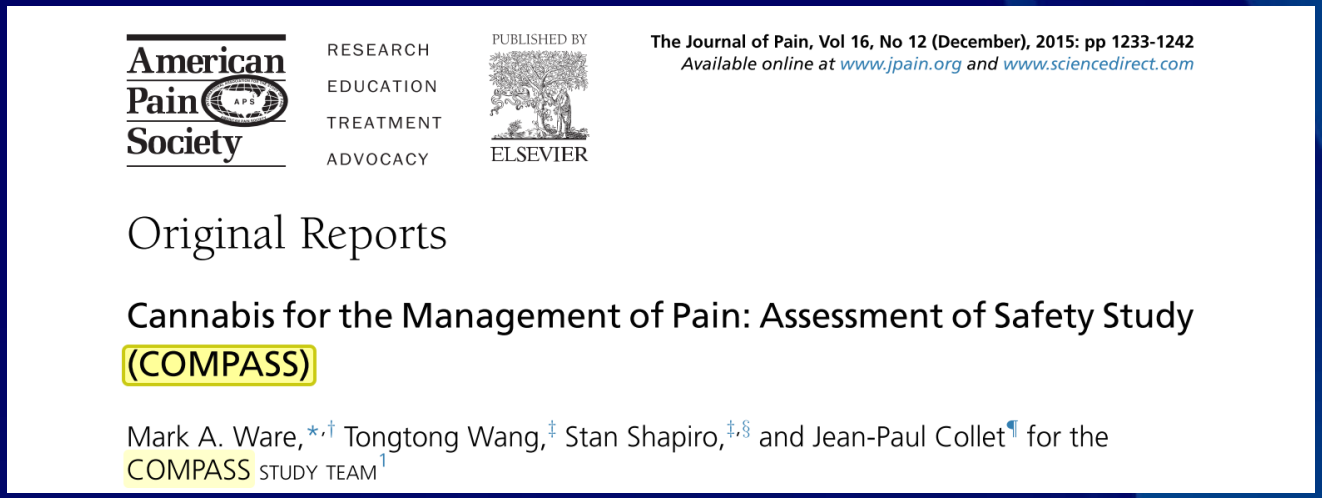


http://arts.bio/en/products/budrot-mildew-rust-control

http://www.clker.com/cliparts/6/4/b/1/13234884051988079243joint-hi.png

1. Hall W. Drug Test Analysis 2014:6:39-45 2. Radhakrishnan R. Frontiers in Psychiatry 2014:5(54):1-6. 3. James et. al. Psychiatry Research: Neuroimaging 2013; 214:181-9. 4. Russo, Ethan B. *Frontiers in Pharmacology* 7 (2016). 5. National Academies of Sciences, engineering, and medicine. Health effects of cannabis and cannabinoids (2017).

# Risks of cannabinoids (medical)



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PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 16, No 12 (December), 2015: pp 1233-1242
*Available online at www.jpain.org and www.sciencedirect.com*

Original Reports

Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS)

Mark A. Ware,*,† Tongtong Wang,‡ Stan Shapiro,‡,§ and Jean-Paul Collet¶ for the COMPASS STUDY TEAM[1]

- Much fewer data on risks of medical use
- In observational trial of smoked medical cannabis: Increased minor adverse events, no increase in serious adverse events [1]
- Similar risk profile in elderly adults as younger medical users. [2,3]

1. Ware, Mark A., et al. *The Journal of Pain*16.12 (2015): 1233-1242. 2. van den Elsen, Geke AH, et al. *Ageing research reviews* 14 (2014): 56-64. 3. Abuhasira, Ran, et al. *European Journal of Internal Medicine* (2018).

# Risks of CBD

Cannabis and Cannabinoid Research
Volume 2.1, 2017
DOI: 10.1089/can.2016.0034

Cannabis and Cannabinoid Research
Mary Ann Liebert, Inc. publishers

REVIEW Open Access

**An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies**

Kerstin Iffland and Franjo Grotenhermen

- Generally well tolerated: multiple studies demonstrate safety of ≥600mg/day CBD in several different conditions[1]
- Drug-drug interactions: Can inhibit or affect liver enzyme activity which can affect CBD plasma concentrations[1,2]
- Epidiolex effects (high doses): Drowsiness, decreased appetite, diarrhea, fatigue, malaise, weakness/lethargy, rash, difficulty sleeping, infections[2]
- Quality control!
  - Pesticides, solvents, heavy metals can be left behind by sloppy manufacturing

Iffland, Kerstin, and Franjo Grotenhermen. "An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies." *Cannabis and cannabinoid research* 2.1 (2017): 139-154. 2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf

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# Role of Cannabinoids in Pain Management

- **Mechanisms of action**
- Clinical trials in chronic pain states
  - Efficacy

# Mechanistic Characterization of Pain

*Any combination may be present in a given individual*

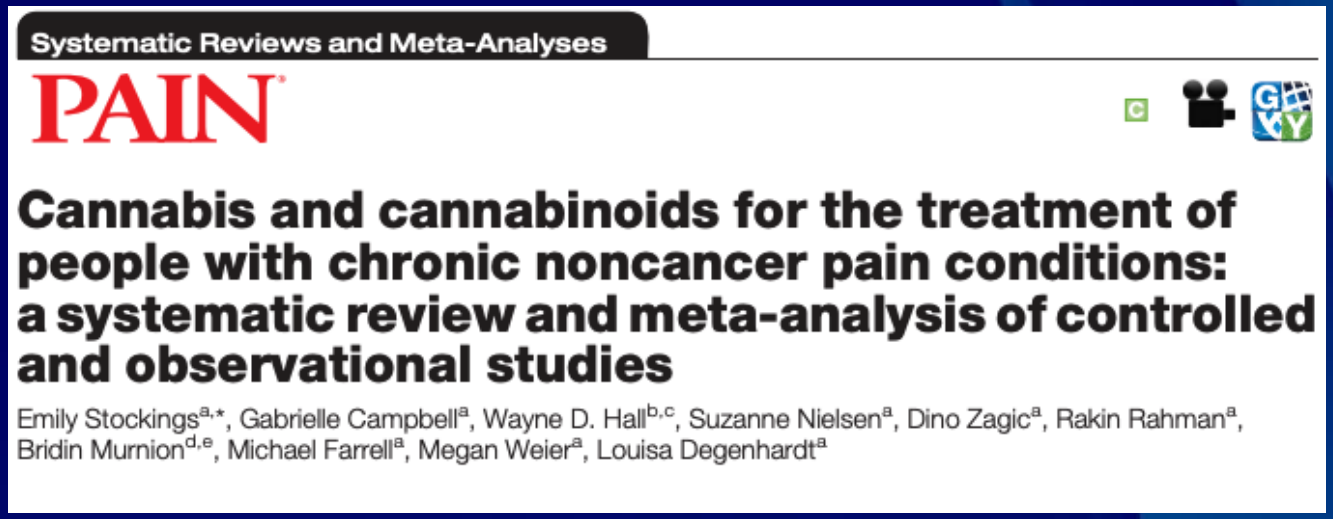
| Peripheral (nociceptive) | Peripheral Neuropathic | Centralized Pain |
|---|---|---|
| ▪ Inflammation or mechanical damage in tissues<br>▪ NSAID, opioid responsive<br>▪ Responds to procedures | ▪ Damage or dysfunction of peripheral nerves<br>▪ Responds to both peripheral (NSAIDs, opioids, Na channel blockers) and central (TCA's, neuroactive compounds) pharmacological therapy | ▪ Characterized by central disturbance in pain processing (diffuse hyperalgesia/allodynia)<br>▪ Responsive to neuroactive compounds altering levels of neurotransmitters involved in pain transmission |
| ▪ Classic examples<br>▪ Acute pain due to injury<br>▪ Osteoarthritis<br>▪ Rheumatoid arthritis<br>▪ Cancer pain | ▪ Classic examples<br>▪ Diabetic neuropathic pain<br>▪ Carpal tunnel<br>▪ Sciatica | ▪ Classic examples<br>▪ Fibromyalgia<br>▪ Irritable bowel syndrome<br>▪ TMJD<br>▪ Tension headache |

Mixed Pain States

# Role of Cannabinoids in Pain Management

- Mechanisms of action
- Clinical trials in chronic pain states
  - **Efficacy**

# Cannabis clinical trials for chronic pain



Systematic Reviews and Meta-Analyses

PAIN

**Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies**

Emily Stockings[a,*], Gabrielle Campbell[a], Wayne D. Hall[b,c], Suzanne Nielsen[a], Dino Zagic[a], Rakin Rahman[a], Bridin Murnion[d,e], Michael Farrell[a], Megan Weier[a], Louisa Degenhardt[a]

- Limited: short length and small sample size
  - Many used THC alone or THC + CBD
- Most support in neuropathic pain (THC+CBD).
- Increased risk of short-term AEs (mostly minor) for study participants
- CBD may be useful in nociceptive pain[2] or neuropathic pain[3]. Less certainty for centralized pain[4]

1. Stockings, Emily, et al. *Pain* 159.10 (2018): 1932-1954. 2. Hunter, D., et al. *Osteoarthritis and Cartilage* 26 (2018): S26. 3. Xu, D. H., et al. *Current pharmaceutical biotechnology* (2019). 4. van de Donk, Tine, et al. *Pain* (2018).

# Cannabis and Cannabinoids

- Definitions and Background
- Overview of Risks and Benefits of Cannabinoids
- Role in Pain Management
- Summary

# Summary

- Cannabinoids and chronic pain: plausibility for therapeutic value at right dose and in right person
  - Risk benefit profile superior to opioids
- If planning to use cannabis/cannabinoids:
  - “Start low, go slow”[1]
  - Use verifiable source with credible third-party testing
  - Minimize harm by avoiding smoking
  - Come up with individualized treatment plan (functional goals, symptom tracking, etc…)
  - Monitor for problematic use, as with any other drug with abuse potential

1. MacCallum, Caroline A., and Ethan B. Russo. "Practical considerations in medical cannabis administration and dosing." *European journal of internal medicine* (2018).

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Review Article

# Practical considerations in medical cannabis administration and dosing

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ABSTRACT

Cannabis has been employed medicinally throughout history, but its recent legal prohibition, biochemical complexity and variability, quality control issues, previous dearth of appropriately powered randomised controlled trials, and lack of pertinent education have conspired to leave clinicians in the dark as to how to advise patients pursuing such treatment. With the advent of pharmaceutical cannabis-based medicines (Sativex/nabiximols and Epidiolex), and liberalisation of access in certain nations, this ignorance of cannabis pharmacology and therapeutics has become untenable. In this article, the authors endeavour to present concise data on cannabis pharmacology related to tetrahydrocannabinol (THC), cannabidiol (CBD) et al., methods of administration

IDEAS AND OPINIONS

Annals of Internal Medicine

## Brief Commentary: Cannabinoid Dosing for Chronic Pain Management

**Kevin F. Boehnke, PhD, and Daniel J. Clauw, MD**

***Editors' Note:*** *This commentary was selected for publication from among 100 submitted manuscripts in response to a call for readers' perspectives on prescribing or recommending marijuana.*

As pain researchers, we are underwhelmed by systematic reviews of clinical trials of cannabinoids, which report modest effect sizes for chronic neuropathic pain but limited or insufficient efficacy in other pain conditions (1). These reviews also report substantial adverse events (1). Nevertheless, we cannot ignore the reality of cannabis's growing use as medicine, especially for chronic pain.

We endorse this paradigm because conservative titration, delayed introduction to THC, and flexible administration allow patients to find their optimal personal dosing strategy without being prematurely pushed into using high-dose THC products–some of which contain more than 100 mg of THC per serving (4). Given the growing understanding of how long-term, high-dose opioid use dysregulates the endogenous opioid system (5), we are concerned that consistent, high doses of THC might do the same to the endogenous cannabinoid system. We are satisfied with how our paradigm mitigates such exposure.

# Questions?