

Cannabis and Pain

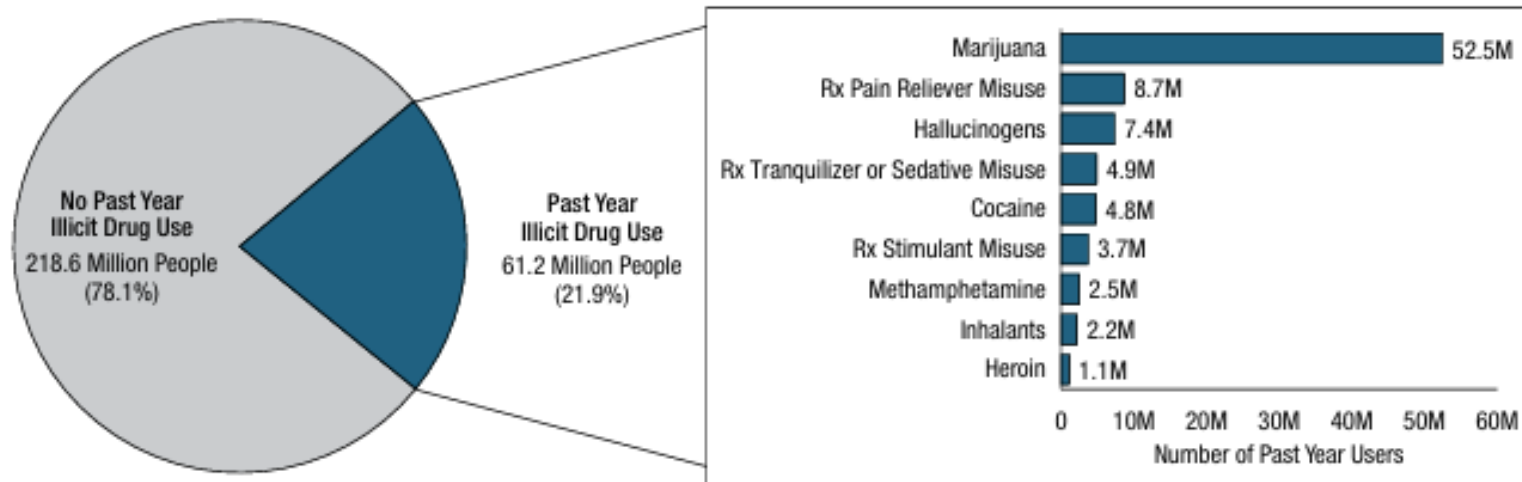
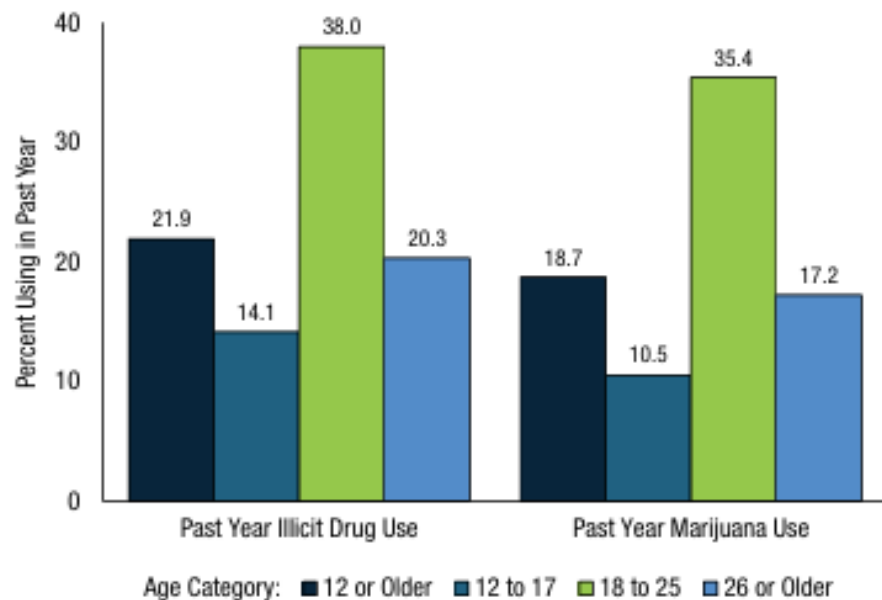
Julia H. Arnsten, MD, MPH
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, NY

“Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.”

Outline

- Widespread use of cannabis
- Unregulated, regulated, and medical cannabis
- Pharmaceutical and botanical (herbal) cannabinoids
- Cannabis and pain
 - Does cannabis work for acute pain
 - Does cannabis work for chronic pain?
 - Does cannabis affect opioid use and overdoses?
- Cannabis use disorder (CUD) and other adverse events

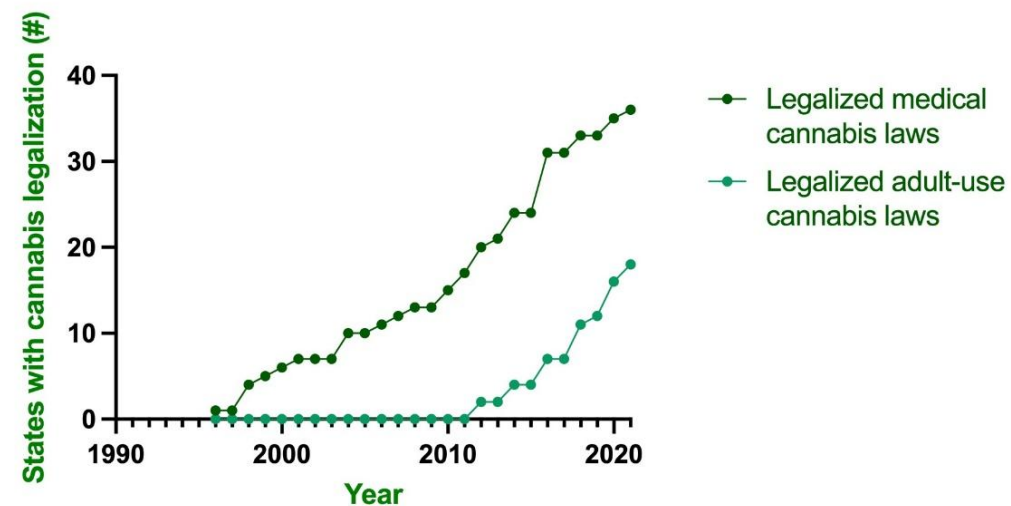
Widespread use of cannabis



Rx = prescription.

Note: The estimated numbers of past year users of different illicit drugs are not mutually exclusive because people could have used more than one type of illicit drug in the past year.

Number of states with cannabis legalization in each year



Sources:

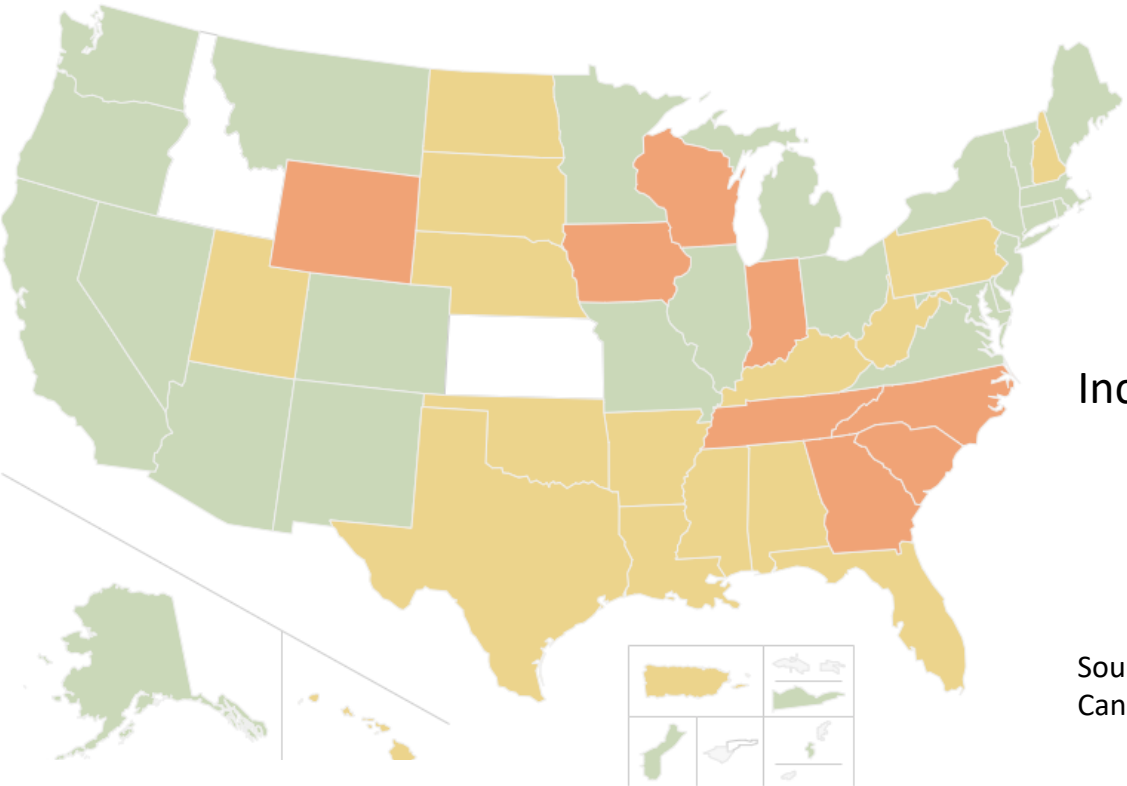
1. Substance Abuse and Mental Health Services Administration, 2022. Key Substance Use and Mental Health Indicators in the United States: Results from the 2021 National Survey on Drug Use and Health
2. National Conference of State Legislatures



State Regulated Cannabis Programs

Switch View ▾

-  No public cannabis access program
-  Adult & medical use regulated program
-  Adult use only, no medical regulated program
-  Comprehensive medical cannabis program
-  CBD/low THC program



Increasing prevalence of cannabis use in older adults

- 10% of veterans report past 30d use
- 4% of adults >65 yo report past year use
- 12% of adults 50-80 yo report past year use

Sources: Pravosud et al JAMA Network Open 2025; Han et al JAMA IM 2020; Fernandez et al Cannabis and Cannabinoid Research 2024

Outline

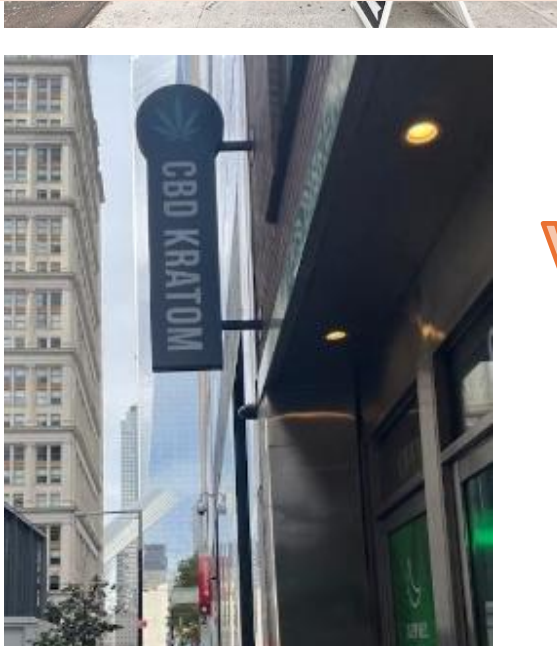
- Widespread use of cannabis
- Unregulated, regulated, and medical cannabis
- Pharmaceutical and botanical cannabinoids
- Cannabis and pain
 - Does cannabis work for acute pain
 - Does cannabis work for chronic pain?
 - Does cannabis affect opioid use and overdoses?
- Cannabis use disorder (CUD) and other adverse events

Unregulated, regulated, and medical cannabis

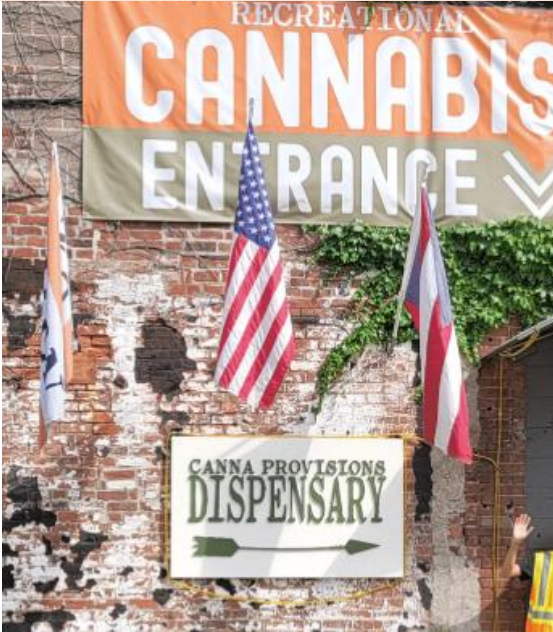
Unregulated cannabis vs. legal regulated cannabis vs. medical cannabis



Patients are using different products of differing strengths



VS.



VS.



Unregulated vs. regulated cannabis

Unregulated	Regulated
<i>Usually</i> bred to have HIGH (>20%) THC content	Available with different THC levels and different ratios of THC and CBD; levels tested for accuracy
Unknown/untested doses of cannabinoids, despite package claims	Exact cannabinoid dosing confirmed by state-certified labs (most states)
Unknown pesticide, heavy metal, or microbial content	Content tested; failures removed from market
Risk of contamination w/other drugs (e.g. K2/spice, cocaine)	Content tested; failures removed from market
Inconsistent availability of different routes of administration	Tinctures, edibles, other non-smoked options available

Cannabis policies vary across states and the federal government

- ▶ Cannabis is an **illegal** Schedule 1 drug under U.S. Federal law, but policies differ by state
 - ▶ Schedule 1: no currently accepted medical use, high abuse potential, lack of accepted safety
 - ▶ While the president has signaled favoring a change to Schedule 3, this has only happened so far for state-regulated medical cannabis products
- ▶ Despite federal **illegality**, 40 states + D.C. + 3 territories allow medical cannabis
 - ▶ Qualifying conditions are different from state to state but most states include:

- ▶ *Amyotrophic lateral sclerosis*
- ▶ *Cachexia/wasting syndromes*
- ▶ *Cancer*
- ▶ *Crohn's disease/IBD*
- ▶ *Epilepsy/seizures*

- ▶ *HIV/AIDS*
- ▶ *Multiple sclerosis/muscle spasticity*
- ▶ *Severe/chronic pain*
- ▶ *PTSD*

Any condition deemed clinically appropriate by your health care provider

Medical cannabis: different states, different laws

State	Year	Possession limit	Home cultivation?	Chronic pain indication?
California	1996	8 oz usable; 6 mature or 12 immature plants	Yes	Yes

Medical products (as well as laws) differ between states

Hawaii	2000	4 oz usable, 7 plants	Yes	Yes
Maine	1999	2.5 oz usable, 7 plants	Yes	Yes
Massachusetts	2012	60 day supply (10 oz) for personal use	Yes	Yes
Connecticut	2012	2.5 oz usable/month	No	Selected
New Jersey	2010	2 oz usable/month	No	No
New York	2014	30-day supply non-combustible marijuana	No	Yes

Outline

- Widespread use of cannabis
- Unregulated, regulated, and medical cannabis
- Pharmaceutical and botanical cannabinoids
- Cannabis and pain
 - Does cannabis work for acute pain
 - Does cannabis work for chronic pain?
 - Does cannabis affect opioid use and overdoses?
- Cannabis use disorder (CUD) and other adverse events

Pharmaceutical and botanical (herbal) cannabinoids

Pharmaceutical cannabinoid products

- Two FDA-approved cannabinoids (pills)
 - Dronabinol (trade name: Marinol®)
 - Synthetic chemical form THC
 - Used for nausea, appetite stimulation
 - Nabilone (trade name: Cesamet® or Canemes®)
 - Synthetic cannabinoid agonist, similar to THC
- Non-U.S. approved (used in 29 countries)
 - Nabiximols (trade name: Sativex®)
 - Oromucosal spray 1:1 THC:CBD
 - Derived from herbal cannabis
 - Many studies conducted in Europe
 - Most common use is MS-associated neuropathy
- Epidiolex (CBD from cannabis) is approved for severe childhood epilepsy



NDC 0591-3591-60

Dronabinol Capsules

2.5 mg

**PRESCRIPTION PREPACK
UNIT-OF-USE**

60 Capsules



Herbal (non-pharmaceutical) routes of cannabis administration

Smoking (joints, pipes)	Vaporization (plant or oil)	Oromucosal and oral digestive	Other
Most common <i>but not recommended</i>	Increasingly common, <i>also not recommended</i>	Oils, capsules, “edibles”	Topicals, suppositories
Combustion at high heat produces toxic byproducts (e.g. polycyclic aromatic hydrocarbons, CO)	Moderate heat, still some release of toxic byproducts	No toxic byproducts	No byproducts
Chronic use associated w/pulm sx (cough, bronchitis); patients may mix with tobacco elevating risk of tobacco-related illness	Fewer pulmonary symptoms	No pulmonary symptoms	?
Rapid onset (<5 min), short duration of action (2-4 hr)	Rapid onset (5-10 min), short duration of action (2-4 hr)	Oromucosal: short onset (15-30 min) Capsules: Longer onset (1-3 hr), longer duration of action (6-8 hr)	?
Up to 50% of cannabis lost to “side-stream” smoke, bioavailability 20-40%, often unknown ratio of components	Bioavailability likely similar to smoked (20-40%) but varies widely, often unknown ratio of components	Can assure standardized ratio and quantity of THC and CBD components through regulated market; bioavailability likely 10-20%; hepatic metabolism	?

Smoking (joints, pipes)

Most common **but not recommended**

Combustion at high heat produces toxic byproducts (e.g. polycyclic aromatic hydrocarbons, CO)

Chronic use associated w/pulm sx (cough, bronchitis); patients may mix with tobacco elevating risk of tobacco-related illness

Rapid onset (<5 min), short duration of action (2-4 hr)

Up to 50% of cannabis lost to “side-stream” smoke, bioavailability 20-40%, often unknown ratio of components

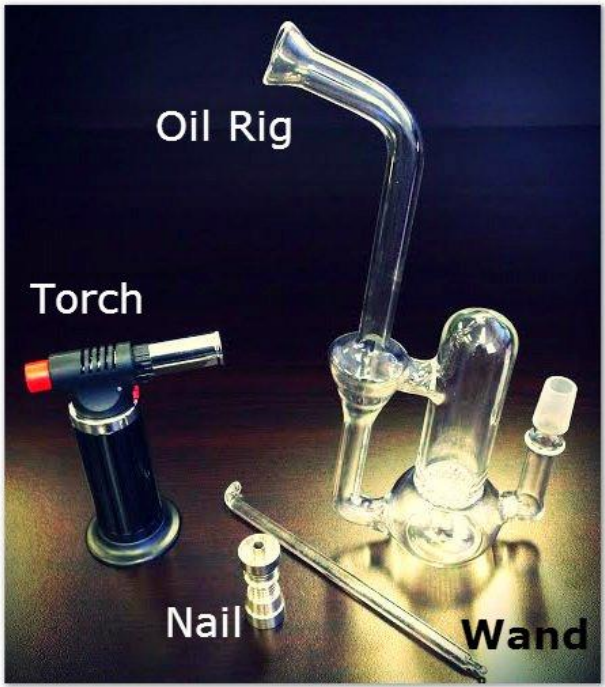


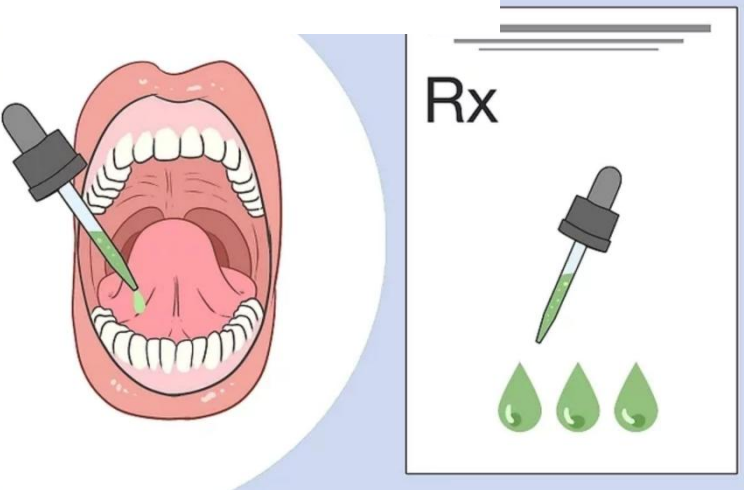
Rapid onset (5-10 min), short duration of action (2-4 hr)

Bioavailability like smoked (20-40%), often unknown ratio of components



Smoking (joints, pipes)	Vaporization	Dromedary Digestive
Most common but not recommended	Increased recom	Oils, cap
Combustion at high heat produces toxic byproducts (e.g. polycyclic aromatic hydrocarbons, CO)	Mode of tox	No toxic
Chronic use associated w/pulm sx (cough, bronchitis); patients may mix with tobacco elevating risk of tobacco-related illness	Fewer pulmoner symptoms	No pulmonary symptoms
Rapid onset (<5 min), short duration of action (2-4 hr)	Rapid c duration	?
Up to 50% of cannabis lost to “side-stream” smoke, bioavailability 20-40%, often unknown ratio of components	Bioavai smoked widely, compo	bioavailability likely 10-20%; hepatic metabolism



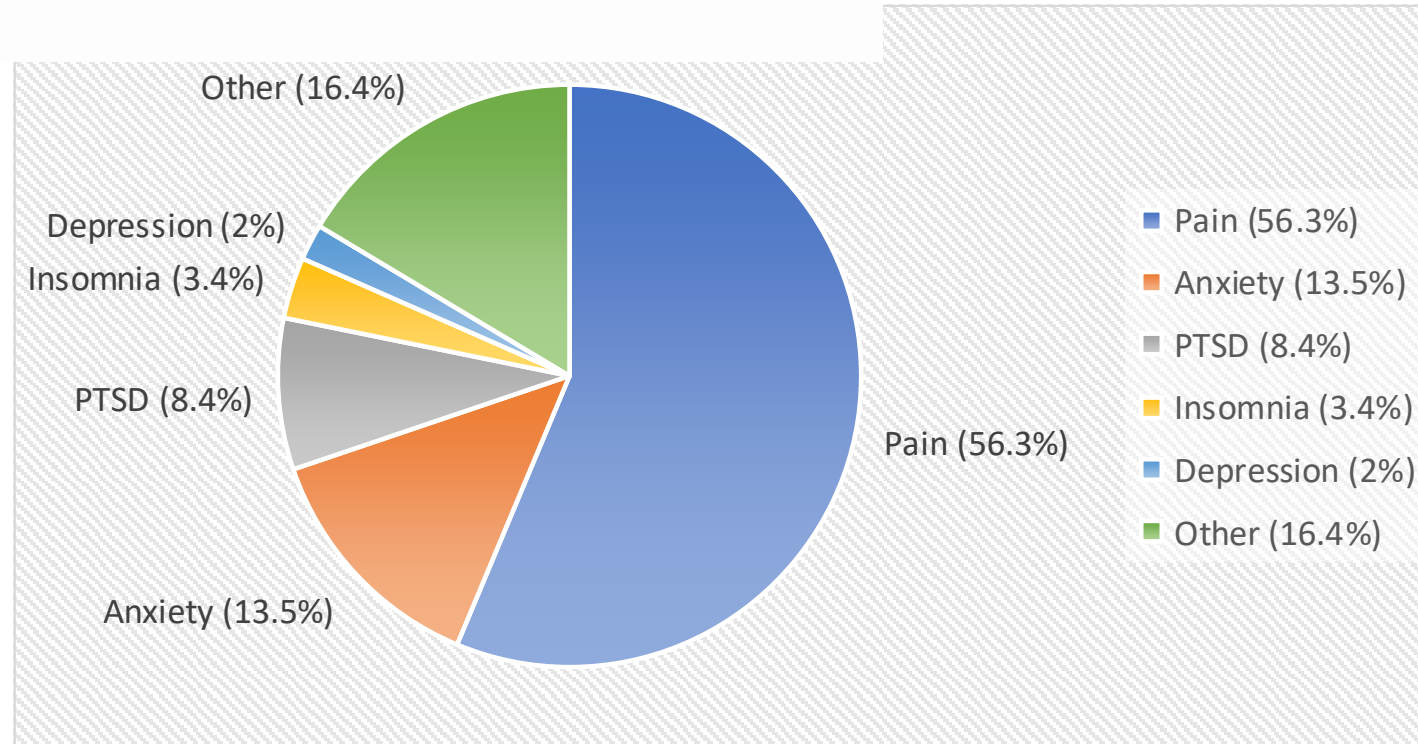
Smoking (joints, pipes)	Vaporization (plant or oil)	Oromucosal and oral digestive	Other
	Increasingly common, also not recommended	Oils, capsules, “edibles”	Topicals, suppositories
	Moderate heat, still some release of toxic byproducts	No toxic byproducts	No byproducts
	Lower pulmonary symptoms	No pulmonary symptoms	?
		Oromucosal: short onset (15-30 min) Capsules: Longer onset (1-3 hr), longer duration of action (6-8 hr)	?
		Can assure standardized ratio and quantity of THC and CBD components through regulated market; bioavailability likely 10-20%; hepatic metabolism	?

Outline

- Widespread use of cannabis
- Unregulated, regulated, and medical cannabis
- Pharmaceutical and botanical cannabinoids
- Cannabis and pain
 - Does cannabis work for acute pain
 - Does cannabis work for chronic pain?
 - Does cannabis affect opioid use and overdoses?
- Cannabis use disorder (CUD) and other adverse events

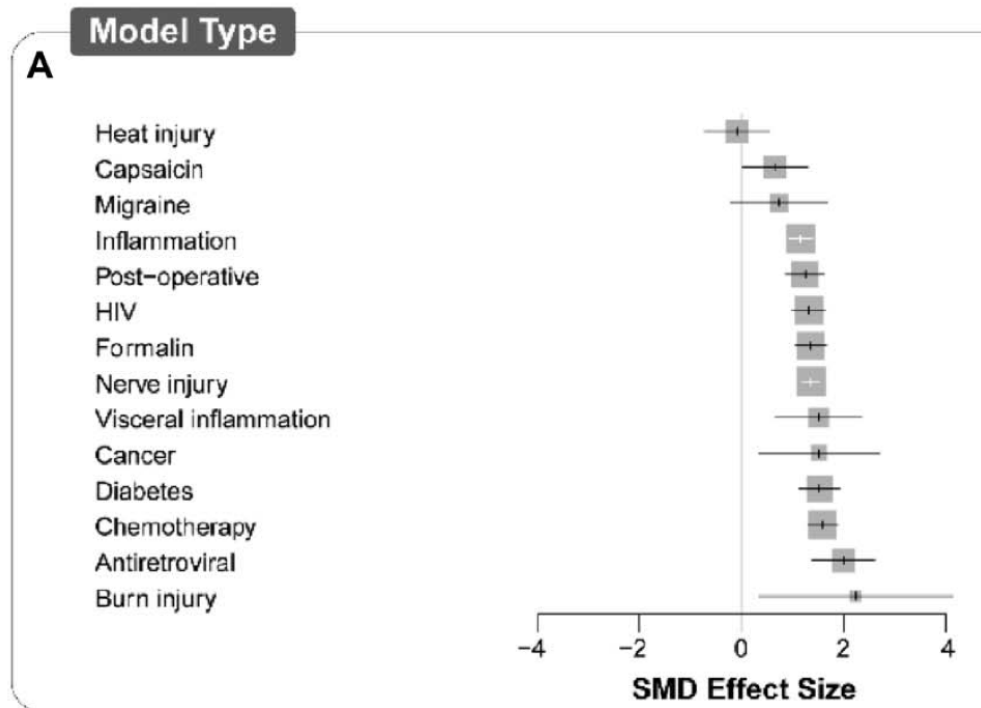
Why do patients seek medical cannabis certification?

- Electronic medical record data from CB2 Insights Clinical network
- 12 states
- n=61,379



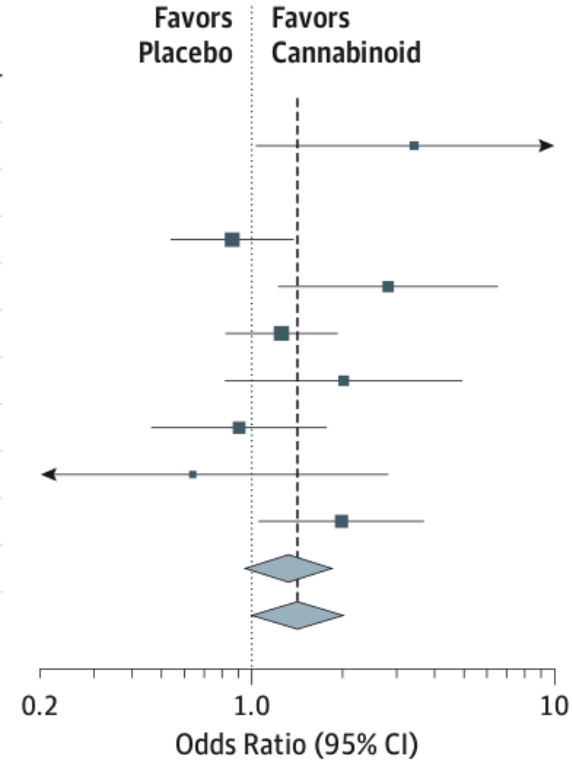
Source: Mahabir et al Journal of Cannabis Research 2020

Impact of cannabis on pain



Cannabis improves pain in animal models
(meta-analysis of 374 studies)

Source: Soliman et al Pain 2021



Cannabis improves pain in humans
(meta-analysis of 28 studies)

Source: Whiting et al JAMA 2015

Acute and chronic pain are not the same phenomenon

Duration matters—but the deeper difference is function, mechanism, and treatment goal.

ACUTE PAIN

Seconds to ≤ 3 months

- **Primary role**
A protective warning of actual or threatened tissue injury
- **Typical course**
Tracks injury and healing; usually diminishes as the cause resolves
- **Treatment goal**
Treat the cause and provide short-term symptom relief

CHRONIC PAIN

>3 months or recurrent

- **Primary role**
May no longer be protective; pain can become the dominant clinical problem
- **Typical course**
May persist beyond healing and reflect nociceptive, neuropathic, or nociplastic mechanisms
- **Treatment goal**
Restore function and quality of life through individualized, multimodal care

WHY THIS MATTERS

A drug's effect on brief, experimentally induced pain does not establish effectiveness for chronic clinical pain.

- International Association for the Study of Pain. Pain Management Center, Chapter 1: What is pain? <https://www.iasp-pain.org/resources/toolkits/pain-management-center/chapter1/>
- International Association for the Study of Pain. Definitions of Chronic Pain Syndromes. <https://www.iasp-pain.org/advocacy/definitions-of-chronic-pain-syndromes/>
- De Vita MJ, Moskal D, Maisto SA, Ansell EB. Association of Cannabinoid Administration With Experimental Pain in Healthy Adults. JAMA Psychiatry. 2018;75(11):1118–1127. <https://doi.org/10.1001/jamapsychiatry.2018.2503>

Outline

- Widespread use of cannabis
- Unregulated, regulated, and medical cannabis
- Pharmaceutical and botanical cannabinoids
- **Cannabis and pain**
 - **Does cannabis work for acute pain**
 - Does cannabis work for chronic pain?
 - Does cannabis affect opioid use and overdoses?
- Cannabis use disorder (CUD) and other adverse events

Dronabinol versus smoked cannabis for experimental pain

30

daily cannabis smokers

Randomized • placebo-controlled
double-blind • double-dummy

Cold pressor test at 4 °C

Threshold = time until pain is first reported

Tolerance = time until the hand is withdrawn

Intensity = subjective pain rating



Cooper, Comer, Haney.
Neuropsychopharmacology 38, 1984–1992, 2013

THE CLINICAL QUESTION

How do oral THC and smoked cannabis differ in their analgesic effects?

Smoked cannabis

Fast onset
Shorter duration
Greater subjective effects

Dronabinol

Slower onset
Longer duration
Lower abuse-related ratings

Remember: acute experimentally induced pain in cannabis-tolerant, otherwise healthy participants is not equivalent to chronic pain.

Cooper, Comer, Haney
Neuropsychopharmacology 38, 1984–1992, 2013

Rigorous laboratory design compared matched active and placebo routes

Double-blind • double-dummy • randomized • placebo-controlled

Population

30 healthy adults
15 women, 15
men
Daily cannabis
smokers

Cannabinoids

Smoked cannabis
0.00%, 1.98%,
3.56% THC

Dronabinol
0, 10, 20 mg

Pain model

Cold pressor test
Left hand in 4 °C
water

Repeated
assessments over
time

Outcomes

Pain sensitivity
Pain tolerance
Pain intensity
Subjective drug
effects
Cardiovascular
effects

Cooper, Comer, Haney.
Neuropsychopharmacology 38, 1984–1992, 2013

Outcome	Smoked cannabis vs placebo	Dronabinol vs placebo
Pain sensitivity (time to first pain)	✓ Improved at 3.56% THC	✓ Improved at 20 mg
Pain tolerance (time to withdrawal)	✓ Improved at 1.98% THC	✓ Improved at 20 mg
Pain intensity (subjective rating)	✓ Lower at 1.98% and 3.56%	✓ Lower at 20 mg

Cooper, Comer, Haney.
Neuropsychopharmacology 38, 1984–1992, 2013

Strong internal control; limited clinical generalizability

Strengths

- Randomized, double-blind, double-dummy design
- Active and placebo comparisons for both routes
- Validated experimental pain model
- Repeated time-course assessment
- Balanced enrollment by sex

Limitations

- Small sample (N=30) of daily cannabis smokers (tolerance and expectancy matter)
- Acute dosing of cold pressor pain, not a chronic pain syndrome
- No evidence about long-term function, disability, or safety

Cooper, Comer, Haney.
Neuropsychopharmacology 38, 1984–1992, 2013

Systematic review and meta-analysis of acute cannabinoid exposure in experimental pain

Evidence base

18 placebo-controlled studies
442 healthy adults
Studies published 1974–2016
89% crossover designs
Mean participant age about 27 years

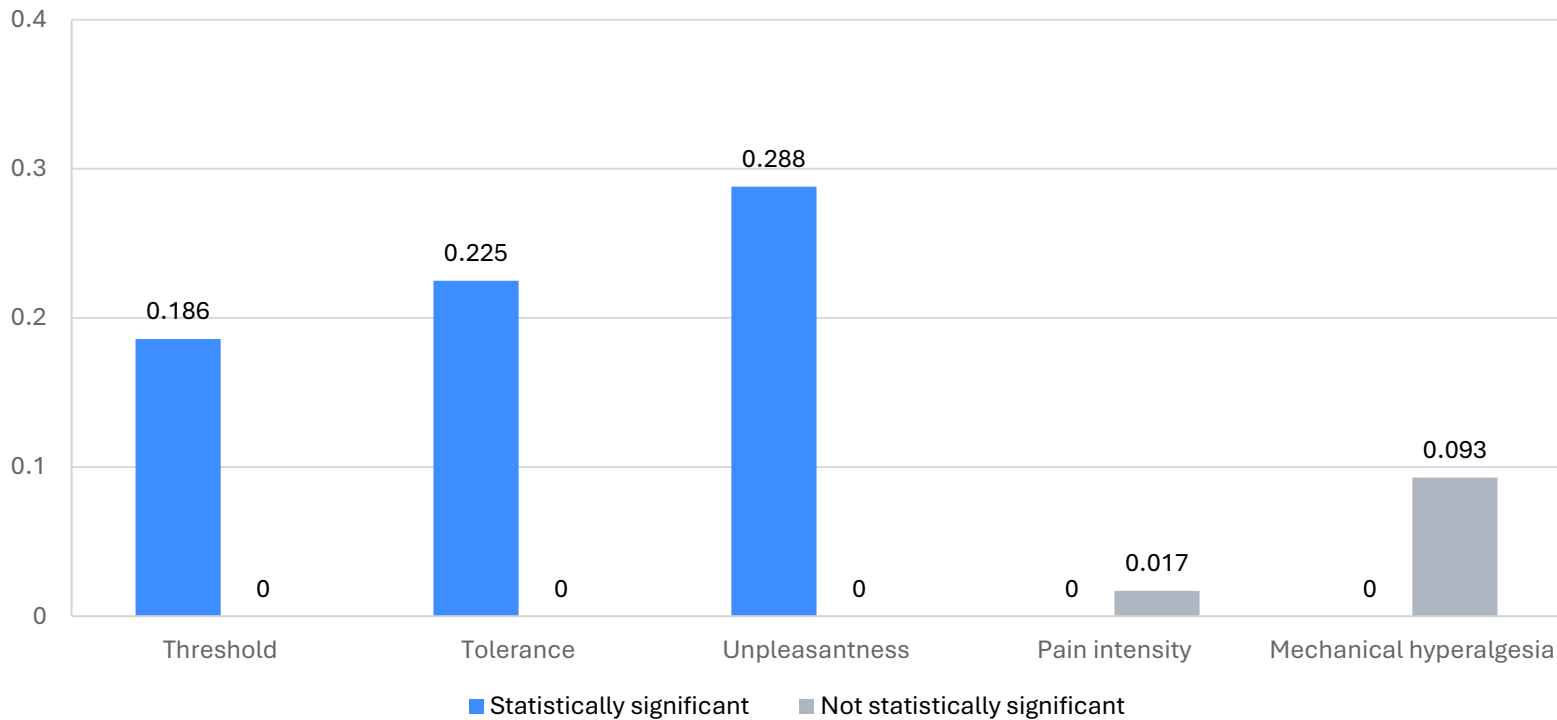
Five distinct outcomes

Pain threshold: when pain begins
Pain tolerance: how long it is endured
Pain intensity: sensory magnitude
Pain unpleasantness: affective response
Mechanical hyperalgesia: sensitization

De Vita MJ, Moskal D, Maisto SA, Ansell EB. Association of Cannabinoid Administration With Experimental Pain in Healthy Adults: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2018;75(11):1118–1127

The clearest pooled effect was reduced pain unpleasantness

Standardized effect size (Hedges g)



Pooled estimates

Pain unpleasantness
g 0.288 (0.104 to 0.472)

Pain tolerance
g 0.225 (0.015 to 0.436)

Pain threshold
g 0.186 (0.054 to 0.318)

Intensity and hyperalgesia: null

De Vita MJ, Moskal D, Maisto SA, Ansell EB. Association of Cannabinoid Administration With Experimental Pain in Healthy Adults: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2018;75(11):1118–1127

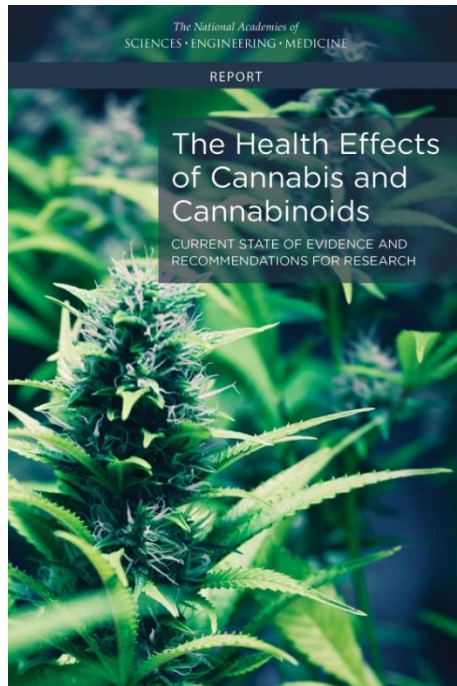
Outline

- Widespread use of cannabis
- Unregulated, regulated, and medical cannabis
- Pharmaceutical and botanical cannabinoids
- Cannabis and pain
 - Does cannabis work for acute pain
 - **Does cannabis work for chronic pain?**
 - Does cannabis affect opioid use and overdoses?
- Cannabis use disorder (CUD) and other adverse events

Burden of chronic pain

- Chronic pain (pain lasting >3 m or past the normal time for tissue healing) is common and a major cause of decreased quality of life and disability
- Existing meds provide modest relief with many side effects
- Opioids *in particular* cause constipation, impaired sleep, & respiratory depression
- No good quality clinical randomized trials support efficacy of opioid medications for pain lasting more than 90 days
- Despite this, opioid prescriptions for chronic pain increased dramatically in past two decades, and this trend has been accompanied by greatly increased levels of prescription opioid overdoses and opioid-related deaths
- ***Pain relief is the most frequent condition reported by medical cannabis patients, nearly 70% of NYS medical cannabis patients***

Does cannabis work in chronic pain?



The National Academies of
SCIENCES • ENGINEERING • MEDICINE

- ▶ 2017 report summarizing health impacts of cannabis and cannabis-derived products
- ▶ Cannabis- or cannabinoid-treated patients more likely to have significant **reduction in pain symptoms**
- ▶ *Conclusive or substantial evidence* that **cannabis is effective for treating chronic pain**
- ▶ “While the use of cannabis for the treatment of pain is supported by well-controlled clinical trials.... very little is known about the efficacy, dose, routes of administration or side effects of commonly used and commercially available cannabis products in the U.S.”
- ▶ Also noted substantial evidence of effect in
 - ▶ Chemotherapy-induced nausea/vomiting
 - ▶ Spasticity associated with multiple sclerosis

Smoked cannabis for chronic HIV-associated neuropathic pain, using an experimental model

Five-day inpatient randomized, double-blind, placebo-controlled trial

Study design

55 adults randomized; 50 completed
Painful HIV-associated sensory neuropathy
Stable pain and HIV medications
Prior cannabis experience required
Primary outcome: daily 100-mm pain VAS

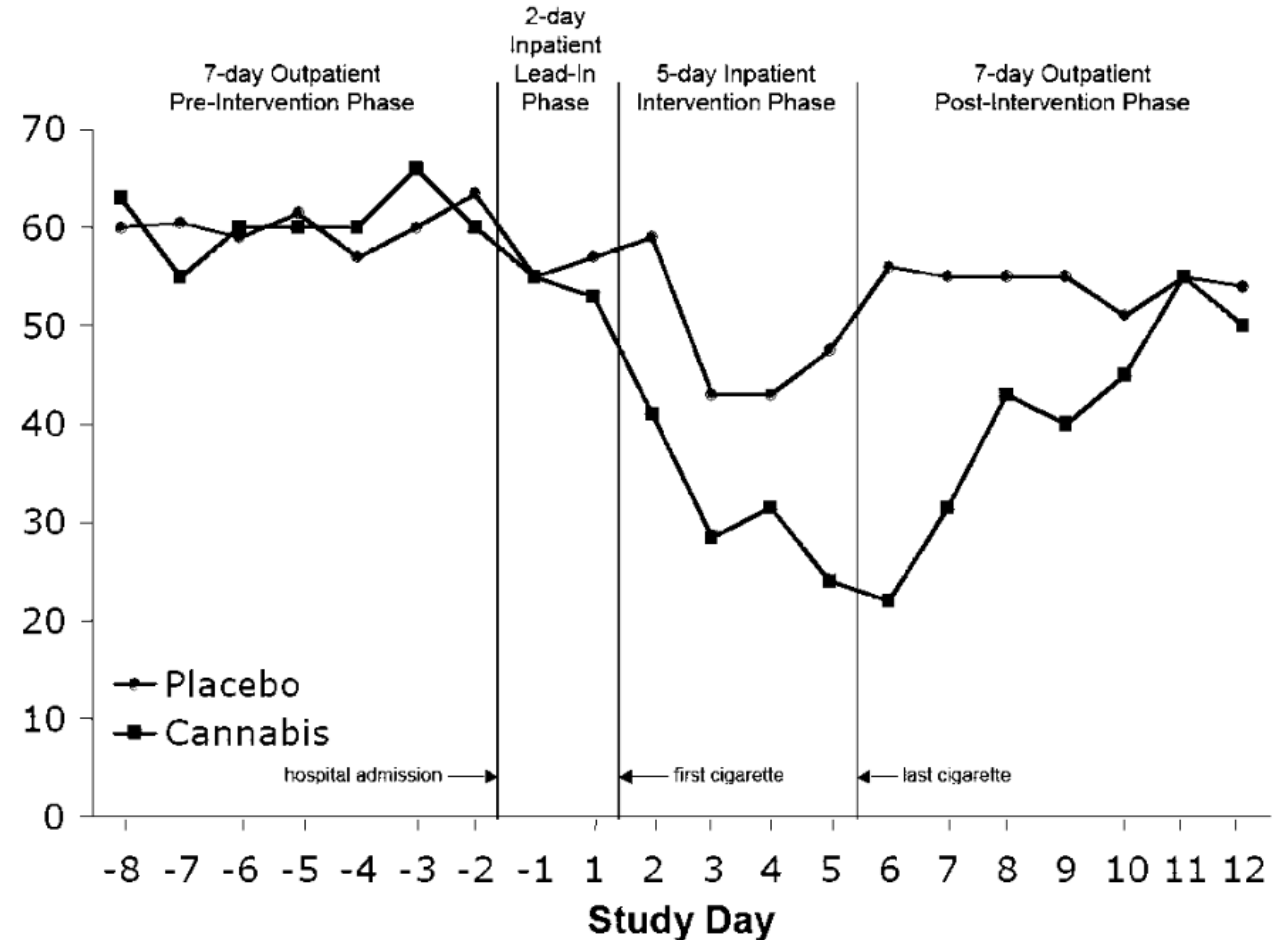


(Abrams DI et al *Neurology* 2007)

Intervention and testing

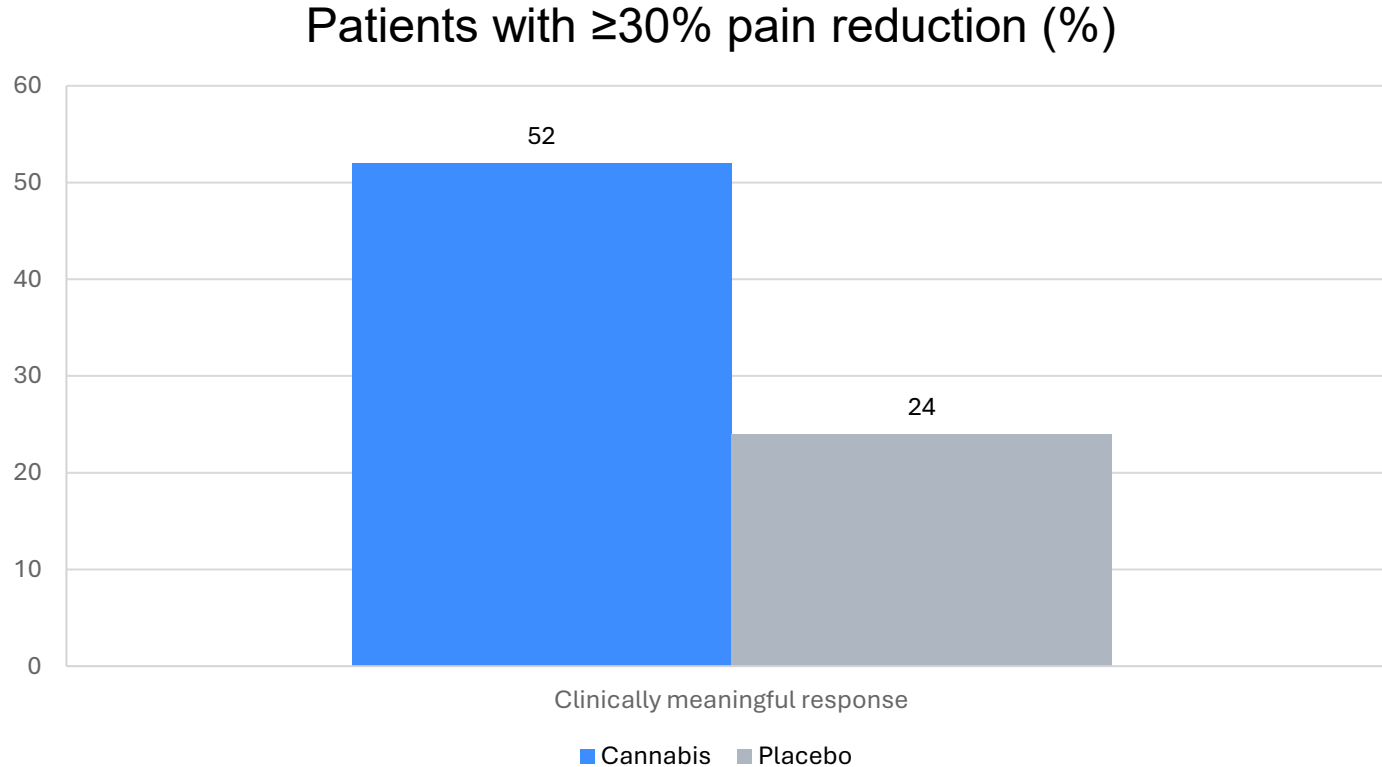
Smoked cannabis: 3.56% THC
Cannabinoid-extracted placebo
One cigarette three times daily for 5 days
Observed, standardized puff procedure
Embedded heat and capsaicin pain models

- Prospective, blinded placebo RCT
- 55 PLWH with painful sensory neuropathy
 - Smoked cannabis (4% THC) 3x/day (n=27)
 - Placebo cigarette 3x/day (n=28)
- Primary outcome: daily pain diary visual analog scale
- Cannabis group: 34% reduction in pain
- Placebo group: 17% reduction in pain (p= 0.03)



(Abrams DI et al *Neurology* 2007)

Smoked cannabis doubled the clinically meaningful response rate



Primary outcomes

$\geq 30\%$ pain reduction
52% cannabis vs 24% placebo
Risk difference 28%
95% CI 2% to 54%; $P = 0.04$

Median pain reduction
34% vs 17%; $P = 0.03$

NNT ≈ 3.6

(Abrams DI et al *Neurology* 2007)

Systematic review and meta-analysis of RCTs of cannabinoids for chronic pain

Evidence base

32 randomized trials
5,174 adults
29 placebo-controlled trials
28 non-cancer pain; 4 cancer pain
Follow-up: 1 to 5.5 months

thebmj Research ▾ Education ▾ News & Views ▾ Campaigns ▾ Jobs ▾

Yvgeniy Oparin, resident¹, Chris J Hong, resident⁴, Brian Y Hong, resident², Mahmood Aminilari, doctoral student^{2,3}, Lucas Gallo, resident⁸, Aika Kaushal, family physician⁹, Samantha Craigie, research coordinator², Rachel J Couban, librarian², Elena Kum, masters student³, Harsha Shanthanna, anesthesiologist and associate professor¹, Ira Price, assistant clinical professor¹⁰, Suneel Upadhye, associate professor^{3,11}, Mark A Ware, pain specialist and associate professor¹², Fiona Campbell, anesthesiologist and professor¹³, Rachelle Buchbinder, rheumatologist and professor¹⁴, Thomas Agoritsas, general internist and assistant professor^{3,15}, Jason W Busse, associate professor^{1,2,3,16,17}

Author affiliations ▾

Correspondence to: Li Wang wangli1@mcmaster.ca, Twitter: @liwang246

Accepted 5 March 2021

Abstract

Objective To determine the benefits and harms of medical cannabis and cannabinoids for chronic pain.

Design Systematic review and meta-analysis.

Data sources MEDLINE, EMBASE, AMED, PsycInfo, CENTRAL, CINAHL, PubMed, Web of Science, Cannabis-Med, Epistemonikos, and trial registries up to January 2021.

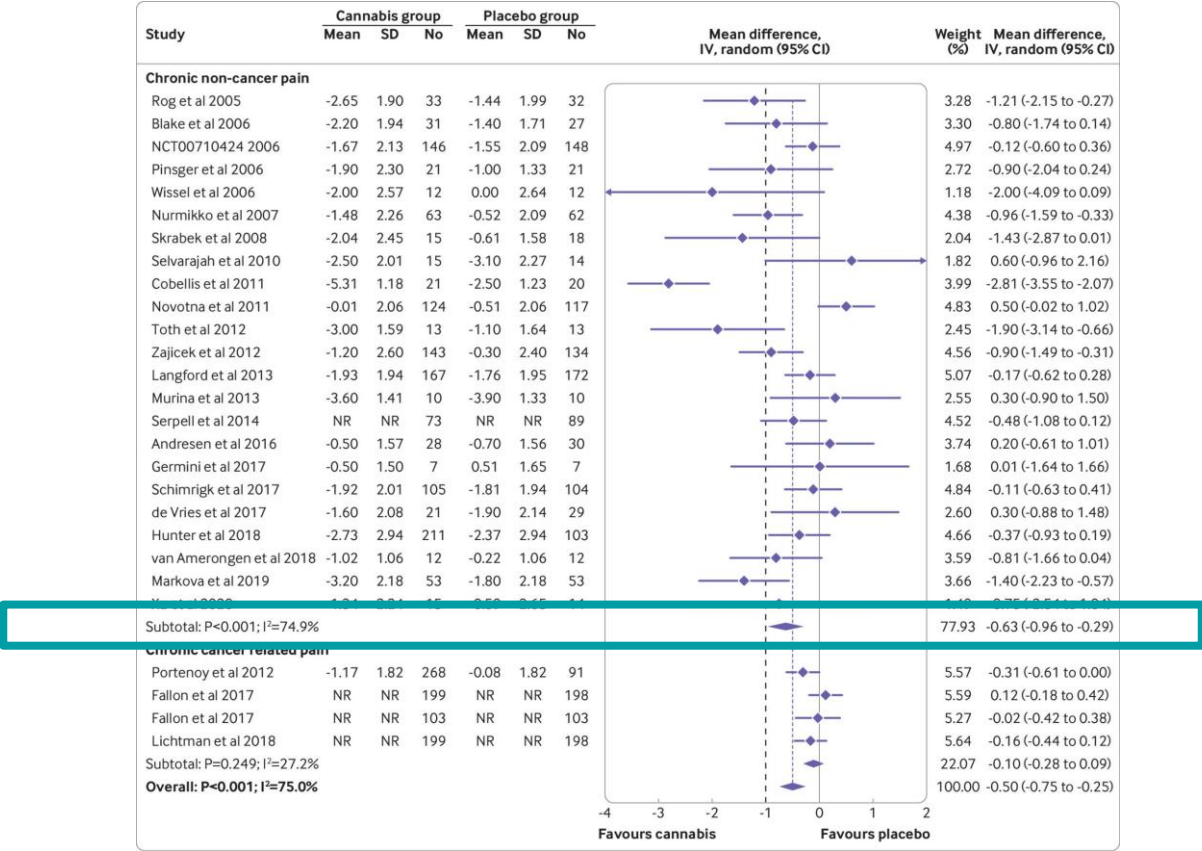
Study selection Randomised clinical trials of medical cannabis or cannabinoids versus any non-cannabis

What the evidence actually covers

30 trials used oral products
2 trials used topical products
No inhaled cannabis trials
Chronic pain defined as ≥ 1 month
GRADE assessed certainty
Effects translated to meaningful-change thresholds

Wang L, Hong PJ, May C, et al. "Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials." *BMJ*. 2021;374:n1034

Pain relief on a 10 cm visual analogue scale (VAS) among people living with chronic pain who received non-inhaled medical cannabis or cannabinoids versus placebo.



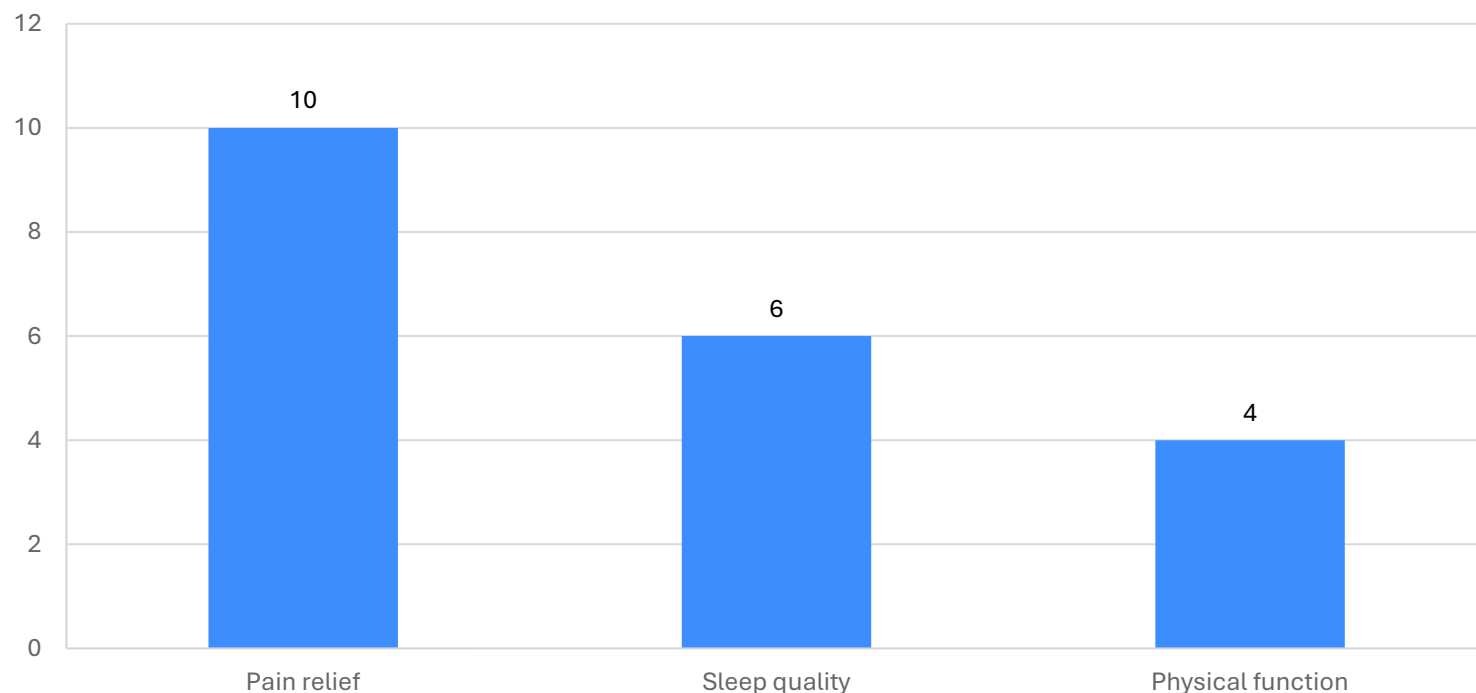
Li Wang et al. BMJ 2021;374:bmj.n1034



About 1 in 10 more patients achieved meaningful pain relief

Absolute benefit was smaller for sleep and physical functioning

Additional patients achieving MID (%)



Compared with placebo

Pain relief
RD +10% (5% to 15%)
WMD -0.50 cm on 10-cm VAS
Moderate certainty

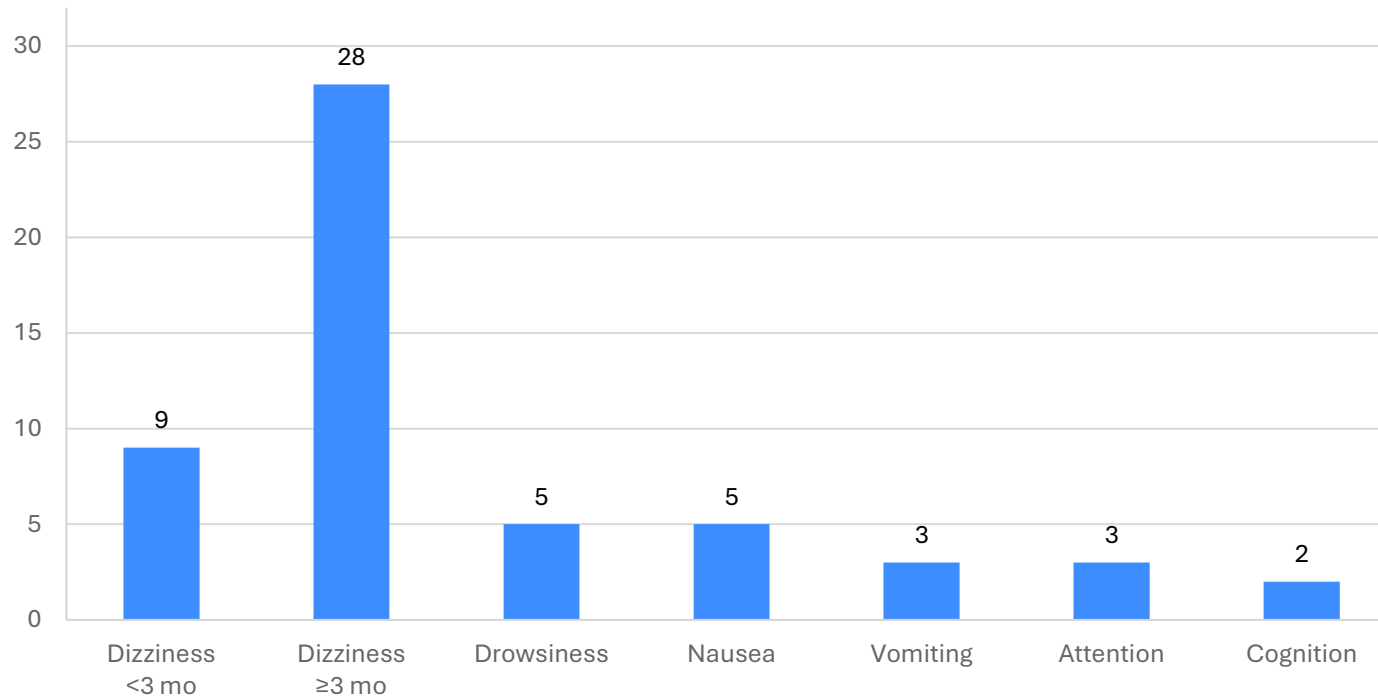
Sleep quality
RD +6% (2% to 9%)
High certainty

Physical function
RD +4% (0.1% to 8%)
High certainty

Wang L, Hong PJ, May C, et al. "Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials." *BMJ*. 2021;374:n1034

Dizziness was the largest harm—and rose with longer exposure

Risk difference versus placebo (%)



Absolute excess risk

Dizziness

<3 months: +9% v placebo

≥3 months: +28%

Other transient harms

Drowsiness

Nausea

Vomiting

Impaired attention

Cognitive impairment

Wang L, Hong PJ, May C, et al. "Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials." *BMJ*. 2021;374:n1034

Review



Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis

Herman Johal¹, Tahira Devji², Yaping Chang ², Jonathan Simone³, Christopher Vannabouathong ², and Mohit Bhandari^{1,2}

Johal et al. • 36 randomized trials • 4,006 participants

Cannabinoids modestly reduce chronic non-cancer pain

The review asked a clinically direct question

Benefits and harms of cannabinoids versus placebo for chronic non-cancer pain?

PICO

Adults with persistent or recurrent pain lasting >3 months

Smoked cannabis, oromucosal sprays, and oral cannabinoids

Patient-reported pain and adverse events

Methods

- English-language randomized placebo-controlled trials
- Six databases searched through December 15, 2018
- Pain scales converted to a 0–10 visual analogue scale
- Results pooled at 1–14 days, 2–8 weeks, and 2–6 months
- Cochrane risk-of-bias and GRADE assessment

Johal H, Devji T, Chang Y, et al. Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis. Clin Med Insights Arthritis Musculoskelet Disord. 2020;13

The evidence base was broad— but highly heterogeneous

36 trials generated 43 cannabinoid-versus-placebo comparisons

4,006

participants

Across trials published from 2002–
2018

36

randomized trials

22 parallel-group; 14 crossover

3 routes

of administration

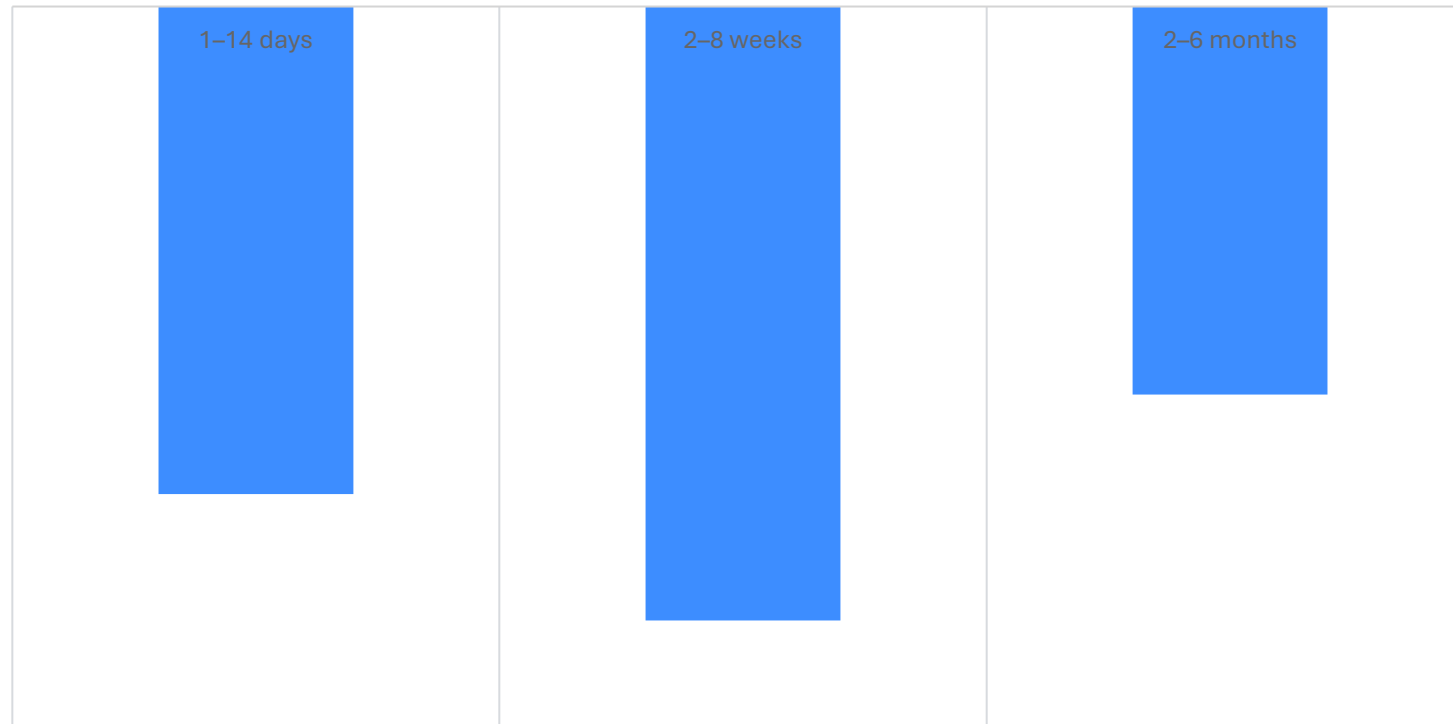
18 oral • 14 oromucosal • 4 smoked

Johal H, Devji T, Chang Y, et al. Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis. Clin Med Insights Arthritis Musculoskelet Disord. 2020;13

Pain improved by about half a point on a 0–10 scale

Weighted mean difference versus placebo; negative values favor cannabinoids

Mean difference on 0–10 pain scale



Interpretation

1–14 days
-0.54 (95% CI -0.76 to -0.31)
Moderate-quality evidence

2–8 weeks
-0.68 (-0.96 to -0.40)
Low-quality evidence

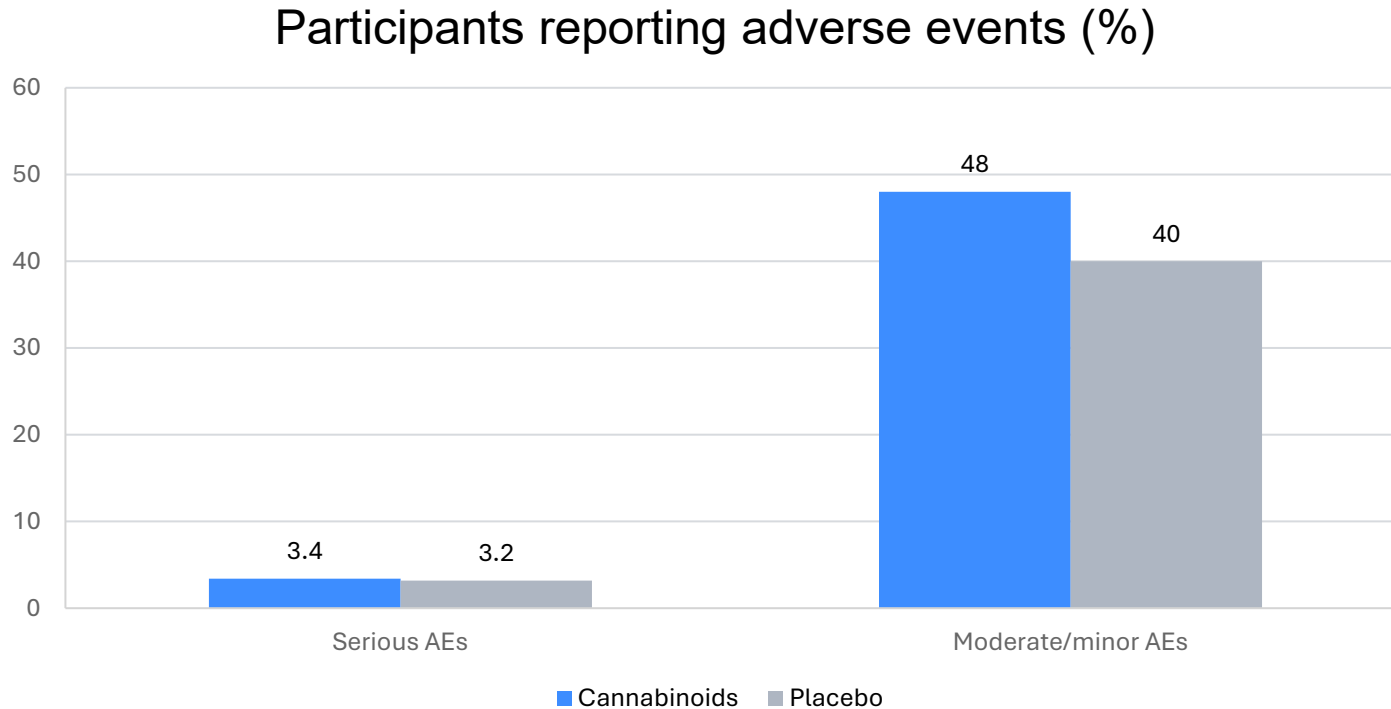
2–6 months
-0.43 (-0.75 to -0.10)
Low-quality evidence

All pooled differences were <1 point.

Johal H, Devji T, Chang Y, et al. Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis. Clin Med Insights Arthritis Musculoskelet Disord. 2020;13

Adverse events: serious similar, others more common

Crude proportions reported across trials



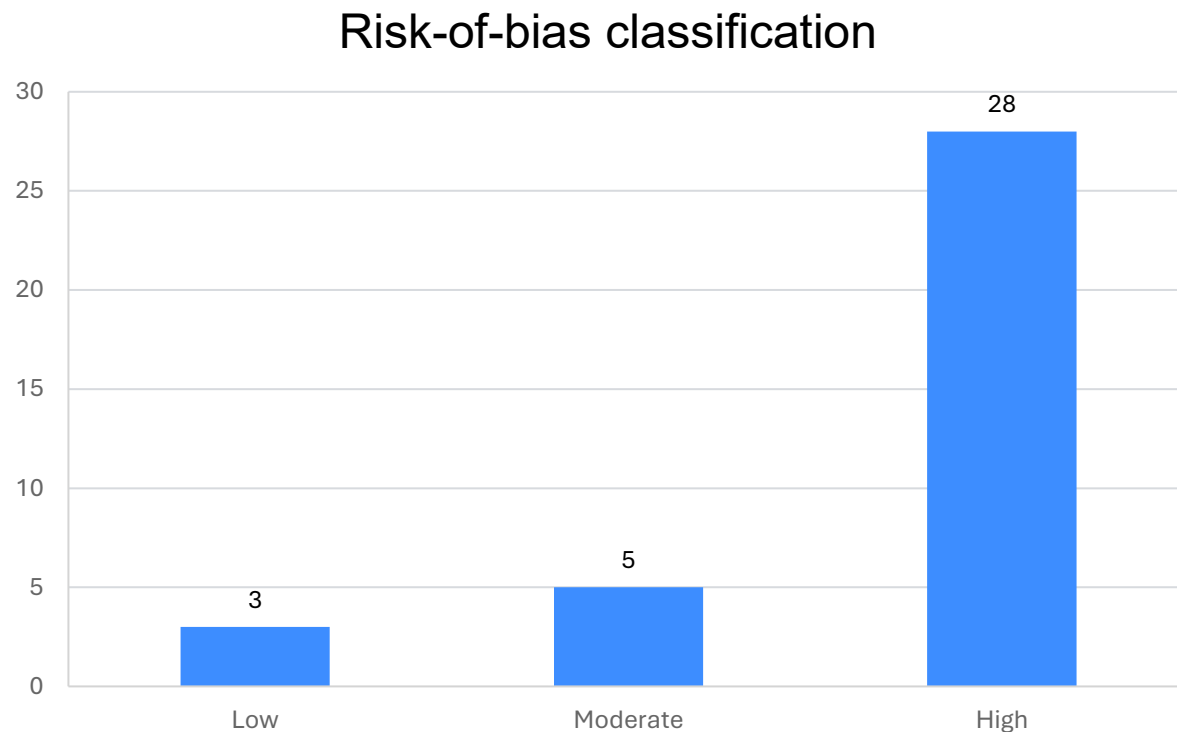
Common cannabinoid adverse effects

Dizziness 31%
Fatigue 15%
Dry mouth 14%
Drowsiness 14%
Nausea 13%
Headache 10%

Johal H, Devji T, Chang Y, et al. Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis. Clin Med Insights Arthritis Musculoskelet Disord. 2020;13

Trial quality sharply limits confidence in the benefit

Only 3 of 36 trials were judged at low risk of bias



What drove the downgrades

- Small, underpowered trials (mean ≈ 50 participants per study arm)
- Selective and inconsistent outcome reporting
- Imputation or additional calculations in 21 of 34 pain comparisons
- Publication bias at 2–8 weeks
- Little evidence in non-neuropathic chronic pain or older adults

Johal H, Devji T, Chang Y, et al. Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis. Clin Med Insights Arthritis Musculoskelet Disord. 2020;13

Do Cannabis and Cannabinoids Improve Outcomes in Chronic Pain, Multiple Sclerosis, Inflammatory Bowel Disease, and Cancer? An Umbrella Review of Meta-analyses and Observational Studies

Author, year	Cannabinoid specific exposure	Outcome
Chronic pain		
Mucke 2018	CBM	Psychological distress
Stockings 2018	CBM	Pain, chronic
Stockings 2018	CBM	Pain, chronic
Andreae 2015	Cannabis (inhaled)	Pain, chronic
Multiple sclerosis		
Da Rovare 2017	Cannabidiols	Spasticity
Da Rovare 2017	Cannabidiols	Spasticity
Da Rovare 2017	Cannabidiols	Spasticity
Da Rovare 2017	Cannabidiols	Spasticity
Torres-Moreno 2018	CBM	Spasticity
Torres-Moreno 2018	CBM	Spasticity
Inflammatory bowel disease		
Doeve 2020	Cannabidiols	Spasticity
Cancer		
Noori 2021	CBM	Daily break
Noori 2021	CBM	Daily break
Noori 2021	CBM	Daily break
Hauser 2019	CBM	Daily break
Hauser 2019	CBM	Daily break



For numbered affiliations see end of the article

Correspondence to: M Solmi msolmi@toh.ca (ORCID 0000-0003-4877-7233)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2023;382:e072348 <http://dx.doi.org/10.1136/bmj-2022-072348>

Accepted: 27 June 2023

Balancing risks and benefits of cannabis use: umbrella review of meta-analyses of randomised controlled trials and observational studies

ital

Marco Solmi,^{1,2,3,4,5,6,7} Marco De Toffol,⁸ Jong Yeob Kim,⁹ Min Je Choi,⁹ Brendon Stubbs,^{10,11} Trevor Thompson,¹² Joseph Firth,^{13,14} Alessandro Miola,¹⁵ Giovanni Croatto,¹⁶ Francesca Baggio,¹⁶ Silvia Michelon,¹⁷ Luca Ballan,¹⁷ Björn Gerdle,¹⁸ Francesco Monaco,^{19,20} Pierluigi Simonato,²¹ Paolo Scocco,²² Valdo Ricca,²³ Giovanni Castellini,²³ Michele Fornaro,²⁴ Andrea Murru,²⁵ Eduard Vieta,²⁵ Paolo Fusar-Poli,^{5,26} Corrado Barbui,²⁷ John P A Ioannidis,^{28,29,30} André F Carvalho,³¹ Joaquim Radua,³² Christoph U Correll,^{7,33,34} Samuele Cortese,^{6,35,36,37,38} Robin M Murray,³⁹ David Castle,^{40,41} Jae Il Shin,^{42,43} Elena Dragioti^{18,44}

ABSTRACT

OBJECTIVE

To systematically assess credibility and certainty of associations between cannabis, cannabinoids, and cannabis based medicines and human health, from observational studies and randomised controlled trials (RCTs).

DESIGN

Umbrella review.

DATA SOURCES

PubMed, PsychInfo, Embase, up to 9 February 2022.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Systematic reviews with meta-analyses of observational studies and RCTs that have reported on the efficacy and safety of cannabis, cannabinoids, or cannabis based medicines were included. Credibility was graded according to convincing, highly suggestive, suggestive, weak, or not significant (observational evidence), and by GRADE (Grading of Recommendations, Assessment, Development and Evaluations) (RCTs). Quality was assessed with AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2). Sensitivity analyses were conducted.

RESULTS

101 meta-analyses were included (observational=50,

RCTs=51) (AMSTAR 2 high 33, moderate 31, low 32, or critically low 5). From RCTs supported by high to moderate certainty, cannabis based medicines increased adverse events related to the central nervous system (equivalent odds ratio 2.84 (95% confidence interval 2.16 to 3.73)), psychological effects (3.07 (1.79 to 5.26)), and vision (3.00 (1.79 to 5.03)) in people with mixed conditions (GRADE=high), improved nausea/vomit, pain, spasticity, but increased psychiatric, gastrointestinal adverse event, and somnolence among others (GRADE=moderate). Cannabidiol improved 50% reduction of seizures (0.59 (0.38 to 0.92)) and seizure events (0.59 (0.36 to 0.96)) (GRADE=high), but increased pneumonia, gastrointestinal adverse events, and somnolence (GRADE=moderate). For chronic pain, cannabis based medicines or cannabinoids reduced pain by 30% (0.59 (0.37 to 0.93), GRADE=high), across different conditions (n=7), but increased psychological distress. For epilepsy, cannabidiol increased risk of diarrhoea (2.25 (1.22 to 3.81)), had no effect on sleep disruption (GRADE=high), reduced seizures across different populations and measures (n=7), improved global impression (n=2), quality of life, and increased risk of somnolence (GRADE=moderate). In the general population, cannabis worsened positive psychotic symptoms (5.21 (3.36 to 8.01)) and

Source: Solmi et al BMJ 2023;382:e072348. Fig 2 | Moderate and high certainty evidence from randomised controlled trials on outcomes: chronic pain, multiple sclerosis, inflammatory bowel disease, and cancer. Only associations for which the evidence was moderate or high certainty are shown. CBM=cannabis based medicines.

Landmark RCT - cannabis for chronic low back pain, 2025

-Randomized, double-blind, placebo-controlled trial (N=820 adults) including:

Run-in (one week)

Titration (3 weeks)

Treatment (12 weeks)

-Dose unit:

THC 2.5 mg

CBG 0.1 mg

CBD 0.02 mg

-Participants:

Low back pain >3 months

+/- neuropathy

Nonopioid analgesics optimized

Article

<https://doi.org/10.1038/s41591-025-03977-0>

Full-spectrum extract from *Cannabis sativa* DKJ127 for chronic low back pain: a phase 3 randomized placebo-controlled trial

Received: 2 May 2025

Accepted: 25 August 2025

Published online: 29 September 2025

 Check for updates

Matthias Karst¹, Winfried Meissner², Sabine Sator³, Jens Keßler⁴, Volker Schoder⁵ & Winfried Häuser^{6,7}

Chronic low back pain (CLBP) affects over half a billion people worldwide. Current pharmacologic treatments offer limited efficacy and carry substantial risks, warranting the development of safe and effective alternatives. This multicenter, randomized, placebo-controlled phase 3 trial evaluated the efficacy and safety of VER-01 in CLBP. It enrolled 820 adults with CLBP (VER-01, $n = 394$; placebo, $n = 426$) and included a double-blind 12-week treatment phase (phase A), a 6-month open-label extension (phase B), followed by either a 6-month continuation (phase C) or randomized withdrawal (phase D). The primary endpoint of phase A was a change in mean numeric rating scale (NRS) pain intensity, with a change in total neuropathic pain symptom inventory (NPSI) score as a key secondary endpoint in participants with a neuropathic pain component (PainDETECT > 18). The primary endpoint for phase D was time to treatment failure. The study met its primary endpoint in phase A, with a mean pain reduction of -1.9 NRS points in the VER-01 group (mean difference (MD) versus placebo = -0.6 , 95% confidence interval (CI) = -0.9 to -0.3 ; $P < 0.001$). Pain further decreased to -2.9 NRS points in phase B, with effects sustained through phase C. The study also met its key secondary endpoint of phase A, with a mean NPSI decrease of -14.4 (standard error, 3.3) points from baseline in the VER-01 arm (MD versus placebo = -7.3 , 95% CI = -13.2 to -1.3 ; $P = 0.017$). Although phase D did not meet its primary endpoint (hazard ratio = 0.75, 95% CI = 0.44–1.27; $P = 0.288$), pain increased significantly more with placebo upon withdrawal (MD = 0.5, 95% CI = 0.0–1.0; $P = 0.034$). In phase A, the incidence of adverse events—mostly mild to moderate and transient—was higher with VER-01 than with placebo (83.3% versus 67.3%; $P < 0.001$). VER-01 was well-tolerated, with no signs of dependence or withdrawal. VER-01 shows potential as a new, safe and effective treatment for CLBP. ClinicalTrials.gov registration: NCT04940741.

The trial addresses the field's most persistent evidence gaps

A well-characterized product in one defined pain condition

Why prior cannabinoid evidence was difficult to interpret

Small samples

Short treatment periods

Inconsistent dosing

Heterogeneous pain conditions and outcomes

Variable cannabinoid compositions

What VER-CLBP-001 adds

820 randomized adults

66 sites in Germany and Austria

12-week double-blind placebo comparison

Standardized full-spectrum extract

Long-term extension plus randomized withdrawal

The main advance is specificity and internal validity

VER-01 was standardized, THC-rich and individually titrated

Investigational product

Full-spectrum Cannabis sativa DKJ127 extract

5% THC, with smaller amounts of CBG and CBD

Chromatographic and spectrometric characterization

Batch-to-batch fingerprint consistency

One dose unit contained 2.5 mg THC

Dose strategy

Individualized titration over 3 weeks

Maximum: 13 dose units/day

Maximum THC exposure: 32.5 mg/day

Oral administration

RCT Results

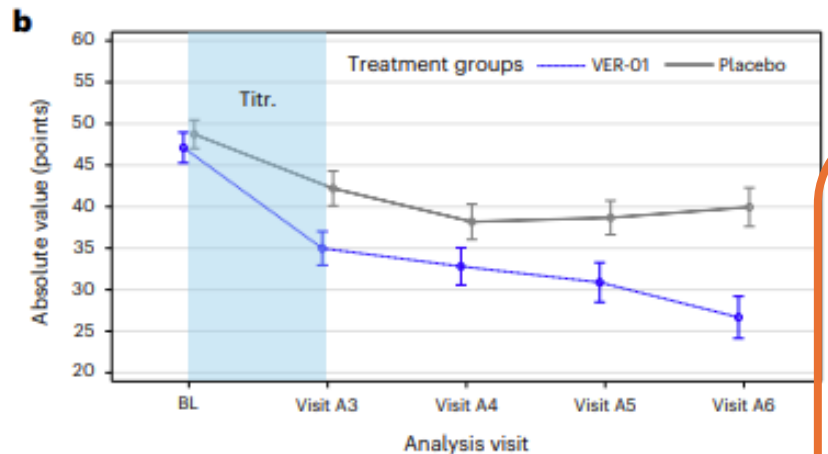
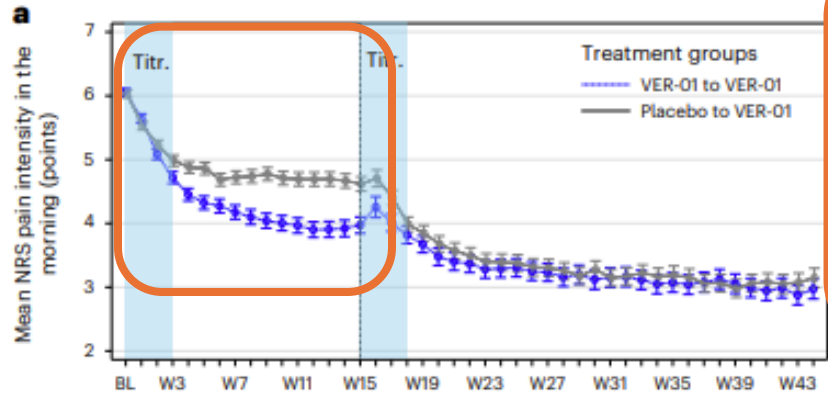


Table 1 | Demographics and other trial baseline characteristics for participants starting phase A

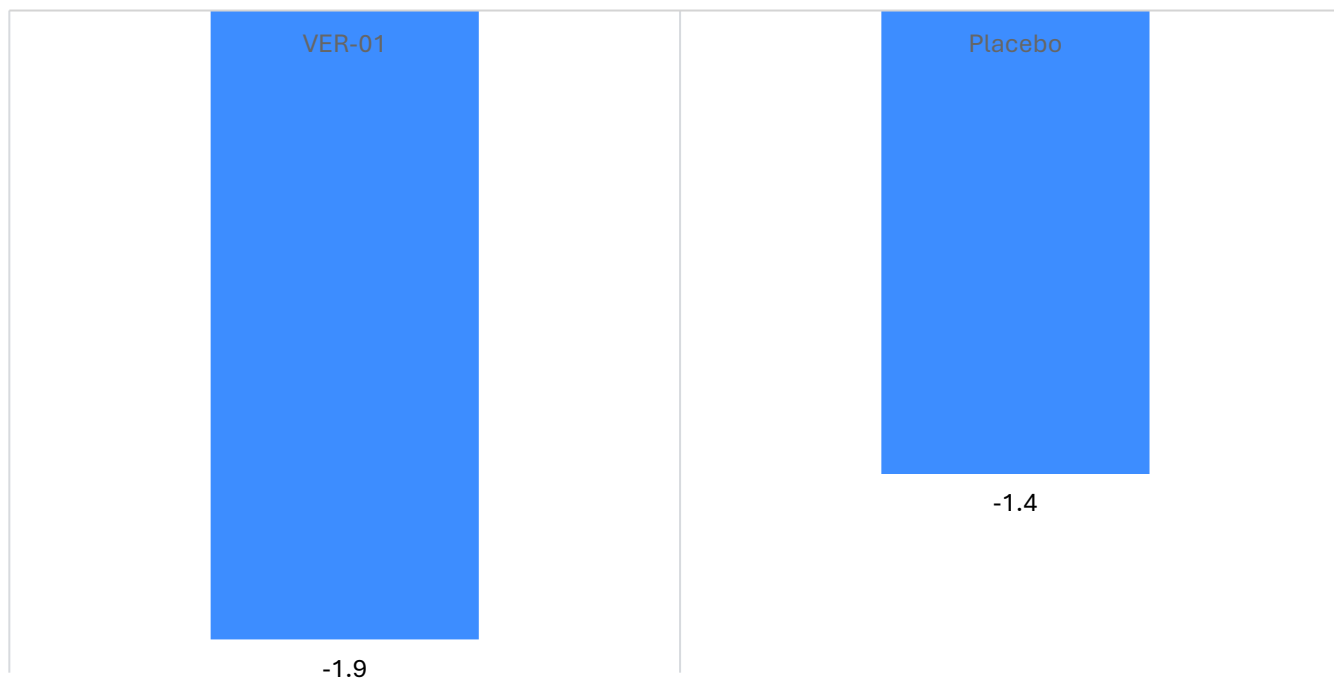
Characteristics	VER-01 (n=390)	Placebo (n=425)
Age (year), mean (s.d.)	52.3 (14.2)	52.2 (13.4)
Female sex, n (%)	224 (57.4)	237 (55.8)
Race, n (%)		
White	373 (95.6)	419 (98.6)
Other	17 (4.4)	6 (1.4)
BMI at baseline (kgm ⁻²), mean (s.d.)	28.88 (6.34)	29.01 (5.84)
Hypertension, n (%)	148 (37.9)	140 (32.9)
Type 2 diabetes, n (%)	43 (11.0)	36 (8.5)
Obesity, n (%)	115 (29.5)	146 (34.4)
Concomitant nondrug therapies, n (%)	117 (30.0)	115 (27.1)
Concomitant nondrug therapies for CLBP, n (%)	96 (24.6)	92 (21.6)
Prior nondrug therapy for CLBP, n (%)	38 (9.7)	37 (8.7)
PainDETECT baseline score, mean (s.d.)	12.4 (6.9)	13.0 (6.7)
PainDETECT baseline score >18, n (%)	88 (22.6)	91 (21.4)
Severe pain (NRS ≥ 7) at baseline, n (%)	100 (25.6)	93 (21.9)
Received ≥2 prior optimized therapies, n (%)	372 (95.4)	403 (94.8)
NRS pain baseline score, mean (s.d.)	6.1 (1.2)	6.0 (1.2)
NRS sleep baseline score, mean (s.d.)	5.2 (1.8)	5.2 (1.8)
RMDQ total score, mean (s.d.)	10.1 (4.7)	9.6 (4.9)
MOS-SS		
Sleep problems index I, mean (s.d.)	42.82 (9.23)	43.05 (9.57)
Sleep problems index II, mean (s.d.)	42.26 (8.82)	42.29 (9.19)
SF-36		
Mental component summary, mean (s.d.)	51.8 (10.8)	52.5 (10.4)
Physical component summary, mean (s.d.)	36.1 (7.2)	37.2 (7.2)

Table 2 | Secondary endpoints of phase A

Parameters	VER-01 (n=390)	Placebo (n=425)	Difference between VER-01 and placebo	Odds ratio (95% CI)	P value
≥30% pain responder at week 15 (%)	54.1	39.5	14.6	1.7 (1.22–2.26)	<0.001 ^c
≥50% pain responder at week 15 (%)	32.2	22.8	9.4	1.6 (1.11–2.22)	0.010 ^c
Cumulative dose (ibuprofen tablets) of rescue medication (s.d.)	10.5 (14.2)	18.3 (53.8)	–7.8	–	<0.001 ^d
Cumulative dose (ibuprofen in g) of rescue medication (s.d.)	8.4 (11.4)	14.6 (43.1)	–6.2	–	<0.001 ^d
Mean CFB to week 15 in NRS sleep quality (s.d.)	–2.2 (2.2)	–1.5 (2.0)	–0.7	–	<0.001 ^e
MOS-SS—mean CFB to visit A6 in sleep problems index I (s.d.)	6.5 (9.1)	4.1 (8.8)	2.4	–	<0.001 ^e
MOS-SS—mean CFB to visit A6 in sleep problems index II (s.d.)	6.8 (8.9)	4.5 (8.3)	2.3	–	0.001 ^e
RMDQ total score—mean CFB to visit A6	–3.1 (4.0)	–2.0 (4.1)	–1.1	–	<0.001 ^e
≥30% RMDQ responder at visit A6 (%)	51.7	42.2	9.5	1.5 (1.06–2.01)	<0.001 ^f
PGIC—participants with improvement of symptoms ^a at visit A6 (%)	45.1	23.4	21.7	–	<0.001 ^e
SF-36—mean CFB to visit A6 for physical component summary (s.d.)	5.9 (6.8)	3.7 (7.0)	2.1	–	<0.001 ^e
SF-36—participants with improvement in quality of life ^b at visit A6 (%)	46.1	31.2	14.9	–	<0.001 ^e

Pain improved in both groups; the added benefit was 0.6 points

Mean change from baseline



Change in 0–10 NRS pain intensity after 12 weeks

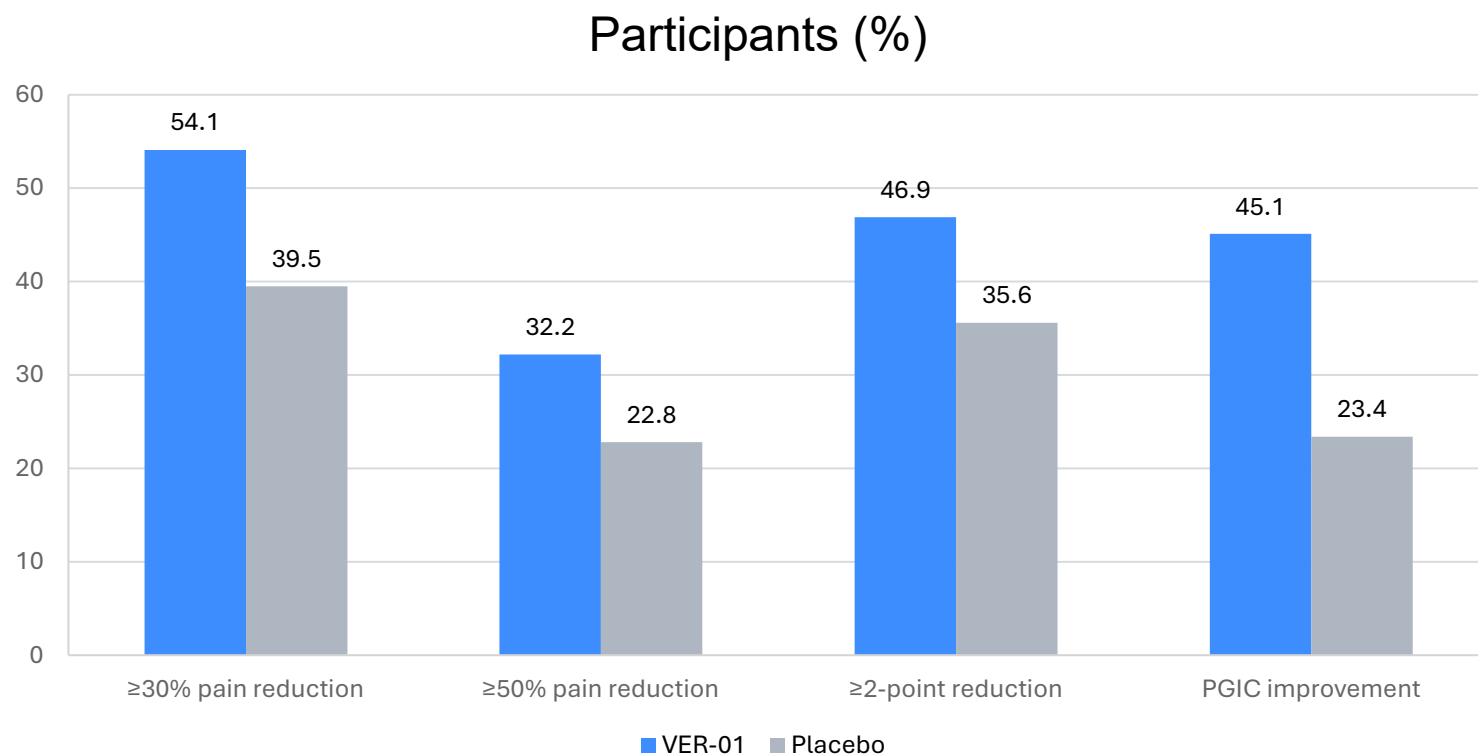
Primary comparison

Mean difference vs placebo
–0.6 NRS points

95% CI –0.9 to –0.3
P < 0.001

Difference favored VER-01 at
every study week.

Clinically meaningful responses



Clinical translation

≥30% response
NNT 6.8

PGIC improvement
NNT 4.6

Rescue ibuprofen
10.5 vs 18.3 tablets

Neuropathic low-back pain showed the strongest signal

-1.5

NRS points

VER-01 vs placebo in neuropathic
subgroup
95% CI -2.2 to -0.9

-7.3

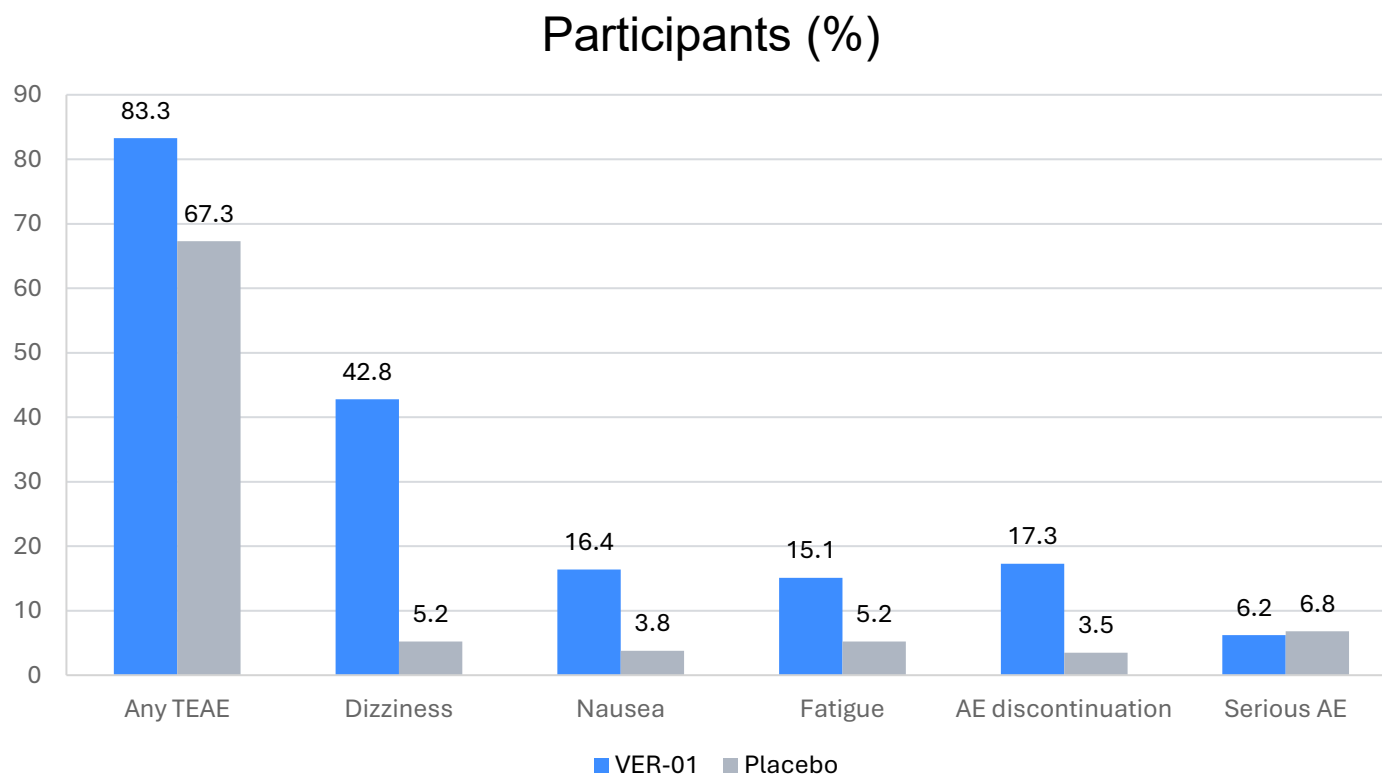
NPSI points

Neuropathic symptom inventory
95% CI -13.2 to -1.3

-0.7

Sleep NRS

Placebo-adjusted improvement
95% CI -1.0 to -0.3



VER-01 produced a reproducible, modest analgesic effect with meaningful responder, sleep and function signals.

The product-specific evidence is stronger than the class-wide inference.

Early dizziness and discontinuation matter clinically.

Efficacy comes with substantial early tolerability costs

Across three evidence levels, cannabinoids alter pain experience more consistently than nociception

Experimental mechanism, acute pharmacology and chronic clinical treatment

2018

De Vita + Wang meta-analyses

Cannabis associated with small threshold and tolerance effects and with reduced unpleasantness; no effect on pain intensity

2023

Cooper + Abrams acute lab studies

Smoked/oral THC improved cold-pressor and other measures in daily users

2025

VER-01 phase 3

Modest mean clinical pain benefit with stronger responder, sleep and function signals

Bottom line: meaningful benefit may occur without a large sensory analgesic effect—and results remain product-, dose- and population-specific.

Outline

- Widespread use of cannabis
- Unregulated, regulated, and medical cannabis
- Pharmaceutical and botanical cannabinoids
- Cannabis and pain
 - Does cannabis work for acute pain
 - Does cannabis work for chronic pain?
 - **Does cannabis affect opioid use and overdoses?**
- Cannabis use disorder (CUD) and other adverse events

Medical cannabis states have fewer opioid rx's and fewer opioid-related adverse events

Author	Year	Population	Difference between medical cannabis states and non-medical cannabis states
Bradford			
Wen			
Shi			
Liang	2018	Medicaid enrollees	-30% reduction in opioid prescriptions in medical cannabis states -29% reduction in Medicaid spending in medical cannabis states

Ecological data

NYS opioid dosing decreased among patients who started medical cannabis

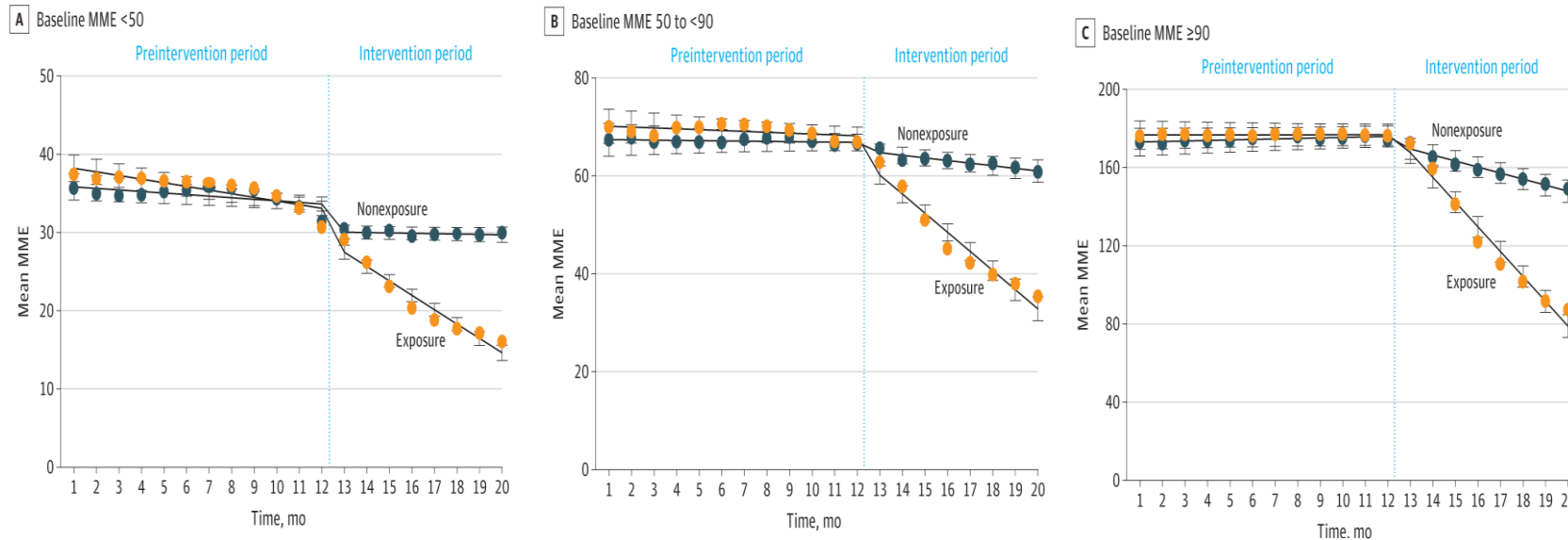
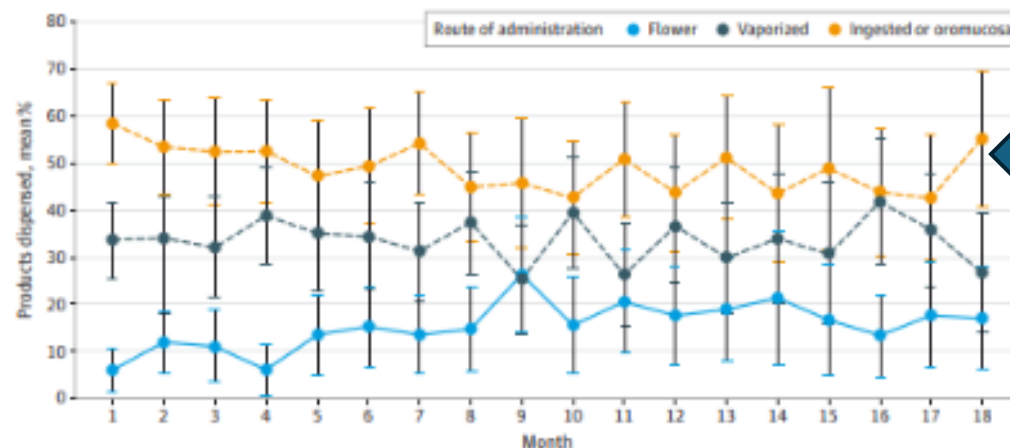


Figure 2. Mean Percentage of Each Route of Administration Dispensed Among Participants in the New York State Medical Cannabis Program From Month 1 to Month 18 of Follow-Up



Oromucosal

JAMA Internal Medicine | Original Investigation Medical Cannabis and Opioid Receipt Among Adults With Chronic Pain

Deepika E. Slawek, MD, MPH, MS; Chenshu Zhang, PhD; Stephen Dahmer, MD; Nancy Schler, PhD, MPH; Yuval Zolotov, PhD; Joanna L. Starrels, MD, MS; Yuting Deng, PhD; Giovanna Calderon DiFrancesca, BA; Frances R. Levin, MD; Jonathan Ross, MD, MS; Haruka Minami, PhD; Chinazo O. Cunningham, MD, MS; Julia H. Arnsen, MD, MPH

Supplemental content

IMPORTANCE Medical cannabis is increasingly considered a substitute for prescription opioid medications for chronic pain, driven by the urgent need for opioid alternatives to combat the ongoing epidemic.

OBJECTIVE To determine the association between participation in the New York State (NYS) medical cannabis program and prescription opioid receipt among adults with chronic pain.

DESIGN, SETTING, AND PARTICIPANTS This prospective, longitudinal cohort study used data from the NYS Prescription Monitoring Program (PMP) from September 2018 through July 2023. Adults prescribed opioids for chronic pain who were newly certified for medical cannabis use in NYS were recruited from a large academic medical center and nearby medical cannabis dispensaries in the Bronx, New York. Monthly dispensation of medical cannabis to study participants was monitored for 18 months. Data analyses were performed from February 3, 2025 to July 15, 2025.

EXPOSURE Portion of days covered each month by pharmacist report of dispensed medical cannabis.

MAIN OUTCOMES AND MEASURES Prescription opioid receipt, defined as NYS PMP-reported prescription monthly opioid dispensation (mean daily dose in morphine milliequivalents [MME]), was assessed with marginal structural models adjusted for time-invariant and time-varying confounders, including self-reported unregulated cannabis use. Nonprescribed opioid use was also assessed during the study period.

RESULTS Among 204 participants, the mean (SD) age at baseline was 56.8 (12.8) years, and 113 (55.4%) were of female gender. At baseline, participants' mean (SD) pain severity score was 6.6 (1.8), out of 10, and mean (SD) pain interference score was 6.8 (1.9) out of 10. Baseline mean (SD) daily MME was 73.3 (133.0). During the 18-month follow-up period, participants' mean (SD) daily MME decreased to 57.4 (127.8). This reduction in mean daily MME was associated with the monthly portion of days covered with medical cannabis; compared with no medical cannabis dispensed, participants dispensed a 30-day supply of medical cannabis were exposed to 3.53 fewer MME per day ($\beta = -3.53$; 95% CI, -6.68 to -0.04; $P = .03$).

CONCLUSIONS AND RELEVANCE In this cohort study, participation in NYS's medical cannabis program was associated with reduced prescription opioid receipt during 18 months of prospective follow-up, accounting for unregulated cannabis use.

Nguyen et al JAMA Network Open 2023, Slawek et al JAMA IM 2026

The Bronx MEMO cohort adds real-world evidence on opioid-treated chronic pain

Prospective observational study embedded in New York's medical cannabis program

Who was studied

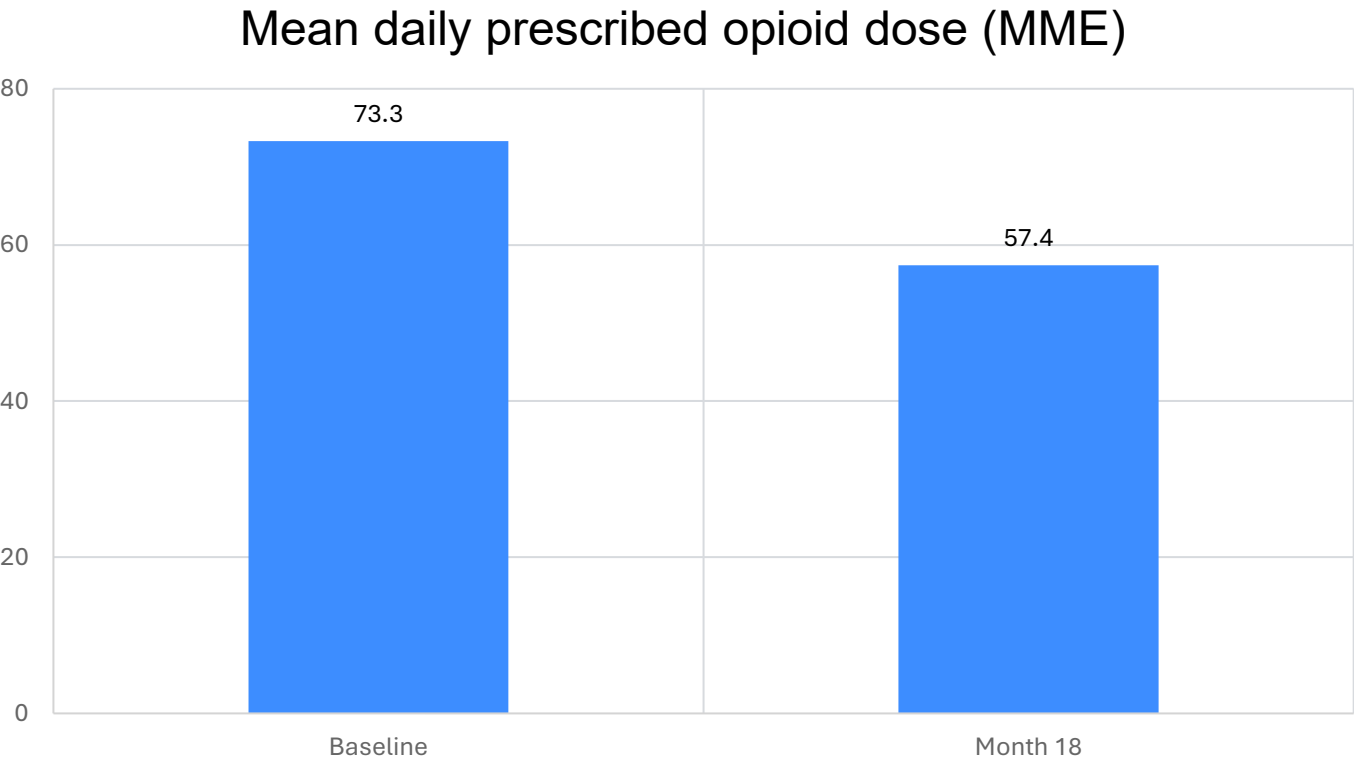
204 adults with chronic pain
Newly certified for medical cannabis
Recruited at Montefiore and nearby Bronx dispensaries
Mean age 56.8 years; 55% women
Baseline pain severity 6.6/10

What was tracked

18 months of prospective follow-up
Dispensary-reported medical cannabis coverage
NYS prescription-monitoring data
Monthly prescribed opioid dose in MME
Models adjusted for changing confounders, including unregulated cannabis use

This study evaluates opioid receipt in clinical practice—not cannabinoid analgesic efficacy versus placebo.

Opioid dispensing declined over 18 months, with a small cannabis-associated decrement



Mean prescribed opioid dose in the observational MEMO cohort

Adjusted association

A 30-day medical cannabis supply was associated with

–3.53 MME/day

95% CI –6.68 to –0.04

P = 0.03

Association does not prove substitution or causality.

The Bronx cohort extends the evidence chain—but answers a different question

MECHANISM

De Vita meta-analysis

Small effects on
threshold, tolerance
and unpleasantness

No pooled pain-
intensity effect

ACUTE RESPONSE

Cooper, Abrams lab studies

Reported (subjective) pain
changed more than cold-
pressor threshold or
tolerance (objective)

CLINICAL EFFICACY

VER-01 phase 3

Modest placebo-
adjusted chronic
low-back-pain
benefit

Product-specific RCT

REAL-WORLD USE

Slawek MEMO cohort

More cannabis
coverage associated
with slightly lower
opioid receipt

Not randomized

Convergence is suggestive, not interchangeable: each design supports a different claim and carries different causal limits.

Outline

- Widespread use of cannabis
- Unregulated, regulated, and medical cannabis
- Pharmaceutical and botanical cannabinoids
- Cannabis and pain
 - Does cannabis work for acute pain
 - Does cannabis work for chronic pain?
 - Does cannabis affect opioid use and overdoses?
- Cannabis use disorder (CUD) and other adverse events

Cannabis use disorder (CUD) and other adverse events

REVIEW ARTICLE

Dan L. Longo, M.D., Editor

Adverse Health Effects of Marijuana Use

Nora D. Volkow, M.D., Ruben D. Baler, Ph.D., Wilson M. Compton, M.D.,
and Susan R.B. Weiss, Ph.D.

Cannabis Use Disorder

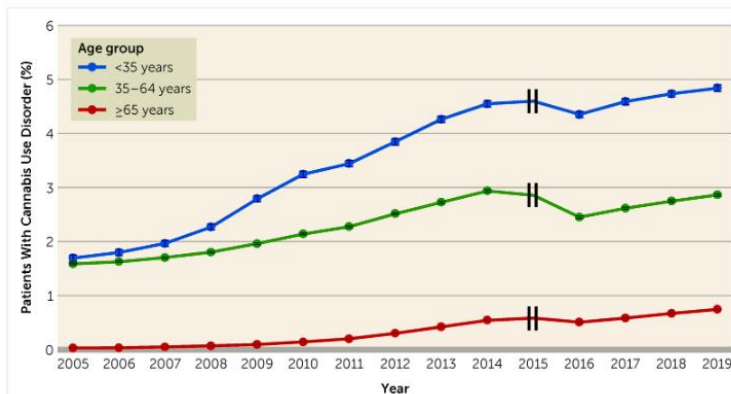


FIGURE 1. VHA patients diagnosed with cannabis use disorder, 2005–2019, by age group^a

^a For January 1, 2005, through September 30, 2015, ICD-9-CM diagnostic codes were used; for October 1, 2015, through December 31, 2019, ICD-10-CM codes were used; data for 2015 were omitted because of the transition from ICD-9-CM to ICD-10-CM on October 1, 2015. Error bars indicate 95% confidence intervals; confidence intervals are very small because of the large sample sizes. VHA=Veterans Health Administration.

Table 1. Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

Effects of short-term use

- Impaired short-term memory, making it difficult to learn and to retain information
- Impaired motor coordination, interfering with driving skills and increasing the risk of injuries
- Altered judgment, increasing the risk of sexual behaviors that facilitate the transmission of sexually transmitted diseases
- In high doses, paranoia and psychosis

Effects of long-term or heavy use

Addiction (in about 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users)*

- Altered brain development*
- Poor educational outcome, with increased likelihood of dropping out of school*
- Cognitive impairment, with lower IQ among those who were frequent users during adolescence*
- Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general population)*
- Symptoms of chronic bronchitis
- Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders

* The effect is strongly associated with initial marijuana use early in adolescence.

Heart Disease

RESEARCH ARTICLE | Originally Published 28 February 2024 |     

 Check for updates

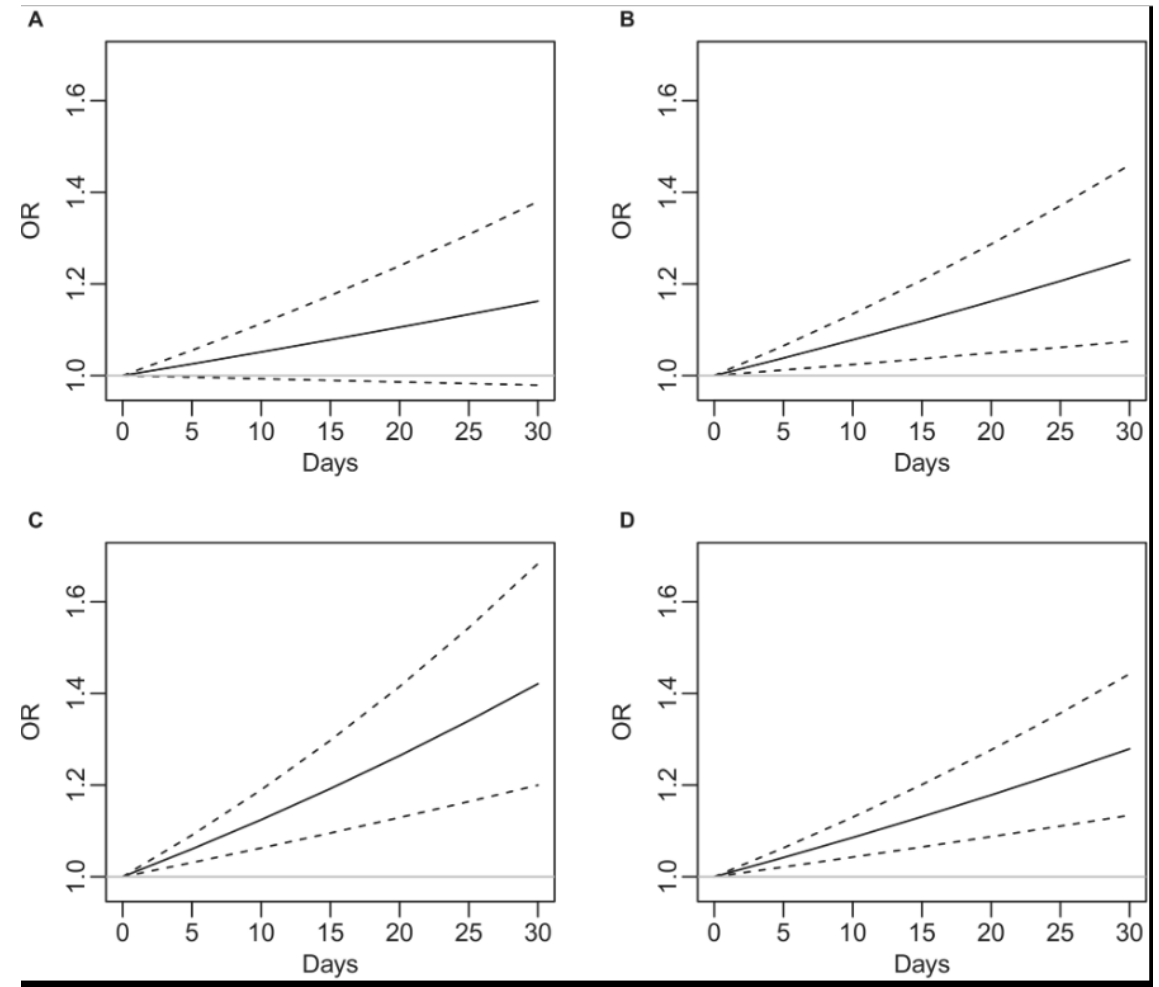
Association of Cannabis Use With Cardiovascular Outcomes Among US Adults

Abra M. Jeffers, PhD , Stanton Glantz, PhD , Amy L. Byers, PhD, MPH, and Salomeh Keyhani, MD, MPH  | [AUTHOR INFO &](#)

[AFFILIATIONS](#)

Journal of the American Heart Association • Volume 13, Number 5 • <https://doi.org/10.1161/JAHA.123.030178>

- -Population-based, cross-sectional study of 2016 to 2020 data
- -Past 30d cannabis use associated with MI, stroke, and composite outcomes of CHD, MI, and stroke in adults 18-74
- -Results not replicated in other population-based studies but caution is warranted



Source: Jeffers et al Jour Am Heart Assn 2024

Mental Health

JAMA Psychiatry

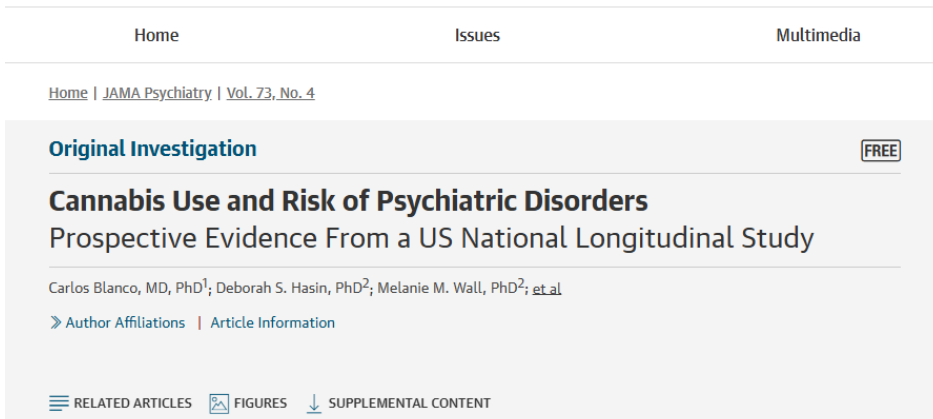
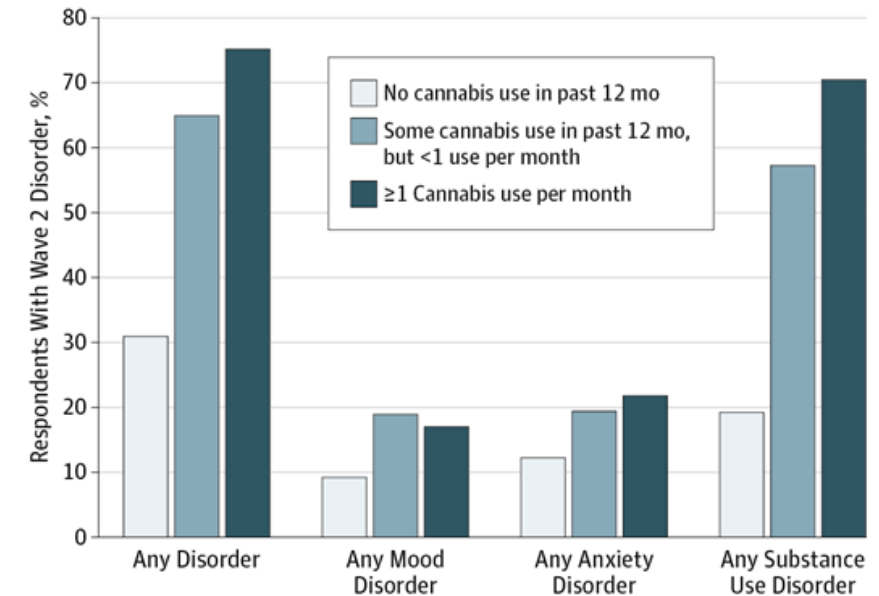


Figure. Prevalence of Psychiatric Disorders in Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions by Level of Cannabis Use in Wave 1



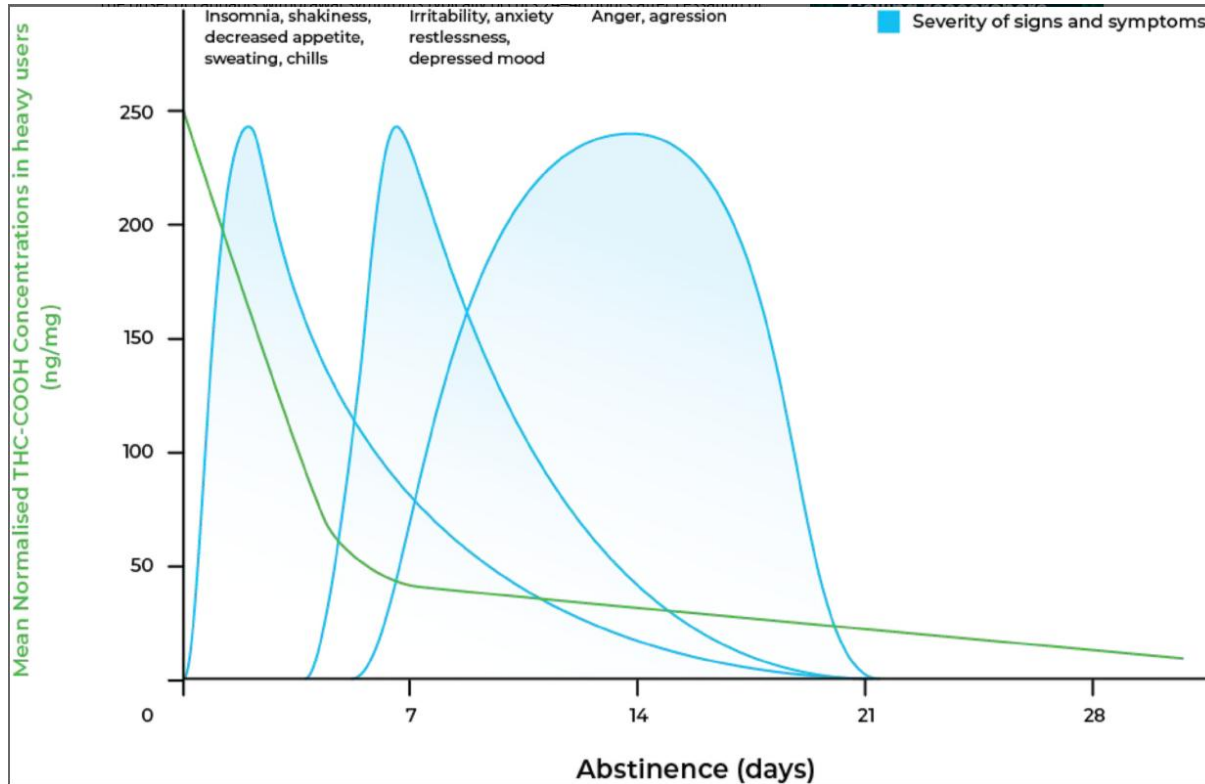
Source: Blanco et al JAMA Psych 2016

- -U.S. population-based, prospective observational cohort study
- -2001 to 2004 data
- -Cannabis use in Wave 1 associated with substance use disorders in Wave 2

Cannabis Withdrawal

- Occurs reliably following a specific time course with cessation of use
 - Transient
 - Ameliorated by re-administration of cannabis
 - Clinically significant
- Requires presence of ≥ 3 of 7 symptoms developing within 7 d of reduced cannabis use
 - Irritability
 - Anxiety
 - Sleep disturbance
 - Appetite disturbance
 - Restlessness
 - Depressed mood
 - Somatic symptoms (e.g. HA, N/V, abd pain, sweating)

Cannabis Withdrawal



- Typically occurs 24-48 hrs after cessation
- Early symptoms differ from late symptoms
- Prevalence of 47% among persons with regular cannabis use with notable differences:
 - General populations: 16%
 - Outpatients: 54%
 - Inpatients: 87%
- No medications currently approved to manage the cannabis withdrawal syndrome and no medications have been shown to be effective
- Short term symptomatic medications should be used to improve patient comfort by treating anxiety, nausea, and sleep disturbances

Sources: Connor et al, Addiction, 2021; Bahji et al JAMA Network Open 2020

Final thoughts

- Cannabinoids produce small average improvements in some chronic-pain conditions, with substantial variation by product, pain phenotype, and patient.
- Experimental acute-pain effects are inconsistent with generally greater improvements in pain unpleasantness and tolerance and smaller improvements in pain threshold and intensity, compared to placebo.
- Limited epidemiological data show fewer opioid prescriptions and opioid-related morbidity in states with medical cannabis, but these associations are ecological.
- Cannabis has short and long term adverse effects
 - Among those who are using, counsel abstinence or avoidance of daily/chronic use to patients <25, in pregnancy, and with unstable heart disease or mental health conditions
- Among those who are using, promote harm reduction by advising about source of cannabis, mode of use, dosage and titration