PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

CANNABINOIDS

Cannabinoids and Pain Management

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Faculty Disclosure

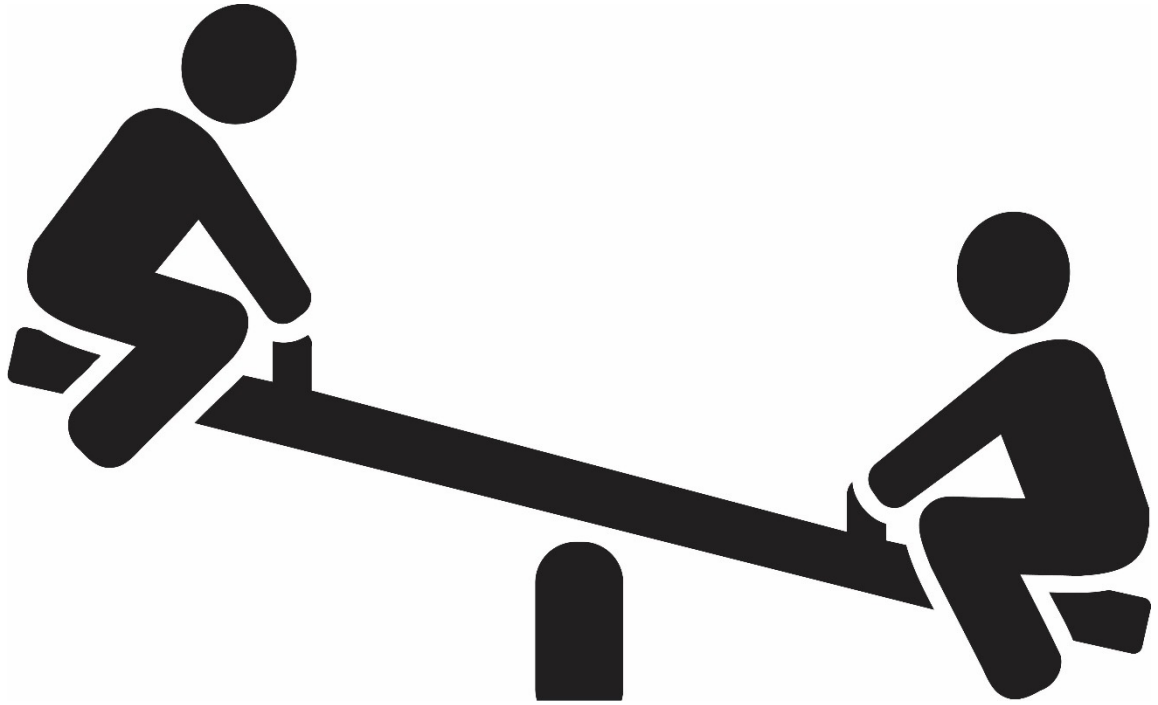
- **Consulting Fee**: HealthXL, Speranza
- **Other**: Expert Witness—Cardinal Health

This presentation was not a part of the presenter's official duties at the WVU and does not represent the opinion of WVU

Learning Objectives

- Recall that cannabis-based medications were better than placebo for pain, sleep, and psychological distress within the 2018 Cochrane Review, even though all studies lacked high quality evidence.
- Review CYP-450 drug-drug interactions involving cannabidiol (CBD), cannabinol (CBN), and delta-9-tetracannabinol (THC).
- Recall important clinical considerations of cannabis/cannabinoids utilization, with or without other substances of abuse, in respect to side effects (cardiovascular, pulmonary, etc), pregnancy, psychosis, withdrawal, and addiction.

Opioids vs Marijuana



Chlor Anodyne

"When indicated I have repeatedly employed Chlor-Anodyne with the most gratifying and brilliant results." (S. H. POTTER, M.D.)

"Chlor-Anodyne has justly acquired a high reputation as an anodyne. The formula as improved by Parke, Davis & Co. we have found most reliable." (*Southern Medical Record.*)

"Despite the fact that I have long used the Gilman chlorodyne, I find in the preparation devised by Parke, Davis & Co. and sold under the name of Chlor-Anodyne a more efficient and elegant combination. *I do not hesitate to say that nothing as yet made is quite so satisfactory.*" (E. P. HURD, M.D., Newburyport, Mass., in *Therapeutic Gazette.*)

"Chlor-Anodyne is not only elegant, but efficient in the highest degree. I have used it in several cases with perfect success. *I have learned never to go on a professional visit without my pocket vial of Chlor-Anodyne.*" (W. UNDERWOOD, M.D., in *New Preparations.*)

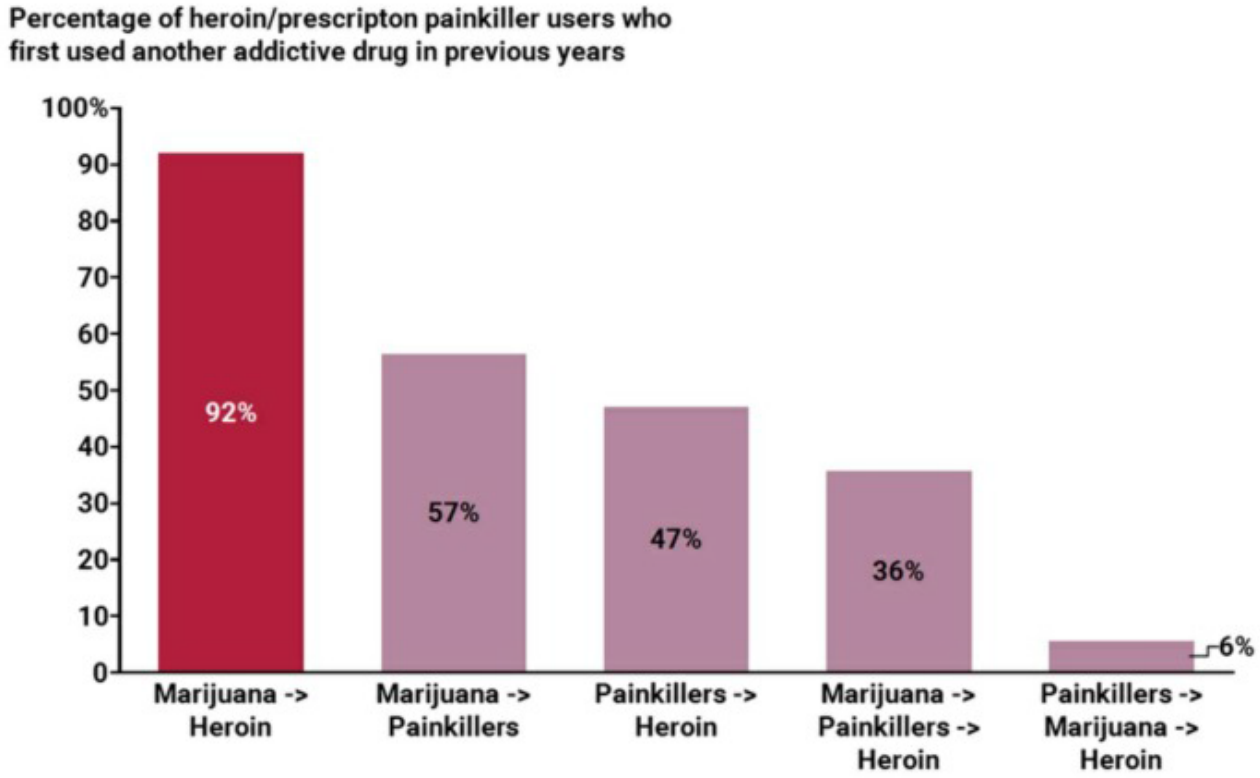
Chlor Anodyne

- **MORPHINE** hydrochloride, 2 7/8 grains
- Tincture Indian **CANNABIS**, 46 minims
- Diluted **HYDROCYANIC** acid, 9 minims
  - A.K.A. prussic acid (poison)
- **CHLOROFORM**, 46 minims
- Oil of peppermint, 1 ½ minims
- Tincture **CAPSICUM** 1 ½ minims

➢ A stimulant, sedative, and antispasmodic, all in one!

warmlandcentre.ca/2017/05/chlor-anodyne-from-parke-davis-co-1894/.

The Path to a Poppy



Can we please stop calling
these molecules
“Pain Killers”?

National Survey on Drug Use and Health (NSDUH, 2013 & 2014).

Cannabis and Opioids

JAMA Internal Medicine | Original Investigation | HEALTH CARE POLICY AND LAW

Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees

Hefei Wen, PhD; Jason M. Hockenberry, PhD

JAMA Network Open

Original Investigation | Substance Use and Addiction

Association of US Medical Marijuana Laws With Nonmedical Prescription Opioid Use and Prescription Opioid Use Disorder

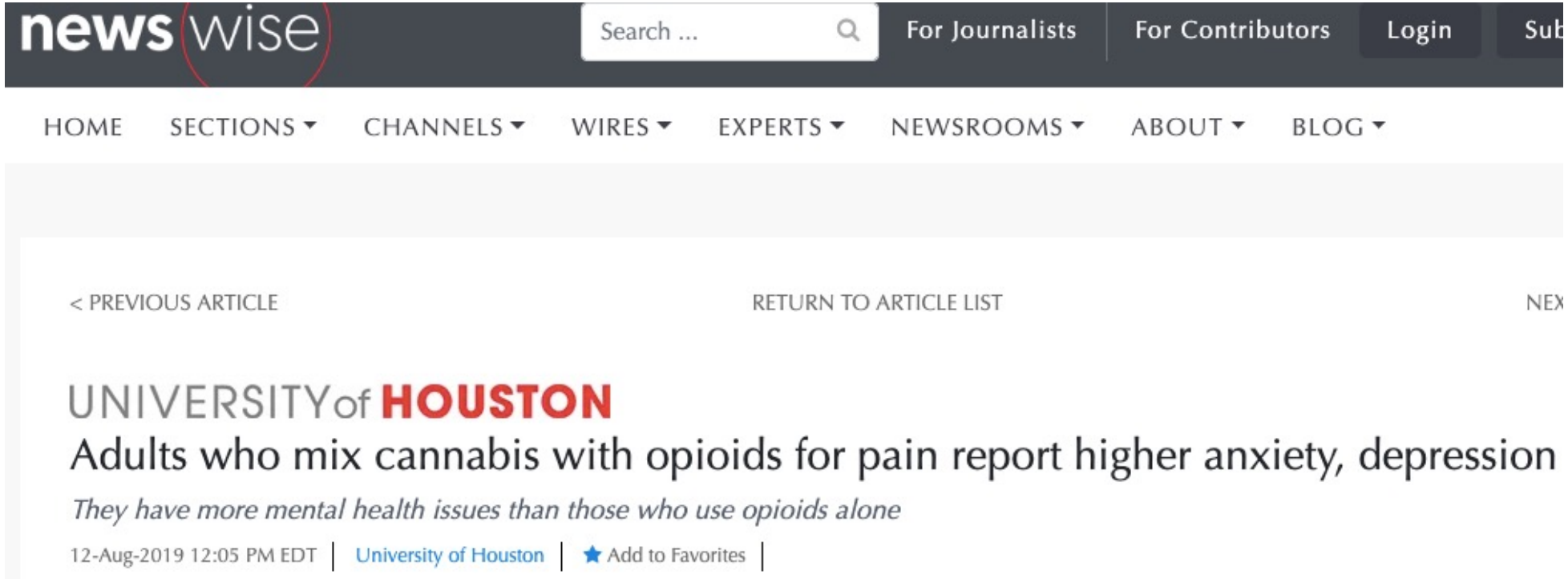
Luis E. Segura, MD, MPH; Christine M. Mauro, PhD; Natalie S. Levy, MPH; Nicole Khauli, MPH; Morgan M. Philbin, PhD; Pia M. Mauro, PhD; Silvia S. Martins, MD, PhD

JAMA Internal Medicine | Original Investigation | HEALTH CARE POLICY AND LAW

Association Between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population

Ashley C. Bradford, BA; W. David Bradford, PhD; Amanda Abraham, PhD; Grace Bagwell Adams, PhD

Cannabis + Opioids = Anxiety/Depression



www.newswise.com/articles/adults-who-mix-cannabis-with-opioids-for-pain-report-higher-anxiety-depression.

Medical Cannabis in CHRONIC Pain Treatment

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

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Available online at www.jpain.org and www.sciencedirect.com

Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain

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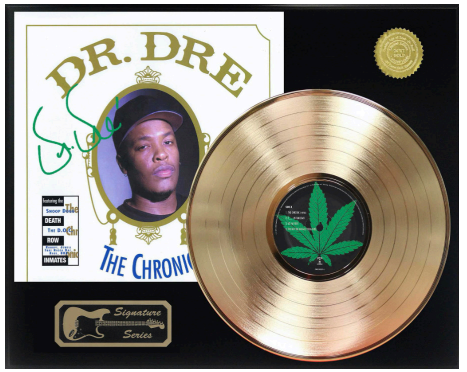
§Chronic Pain and Fatigue Research Center, Medical School, University of Michigan, Ann Arbor, Michigan.

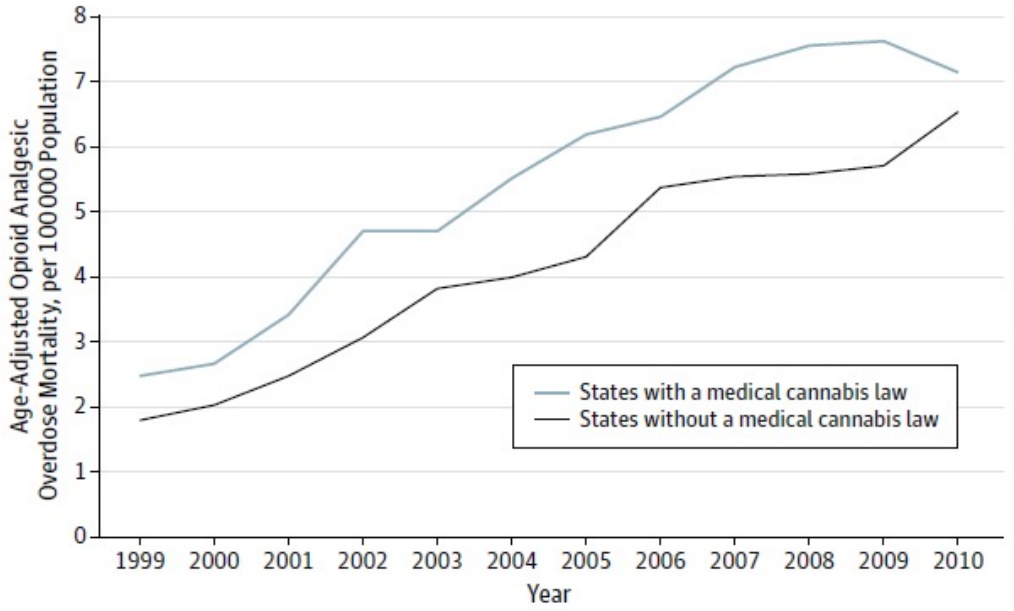
Abstract: Opioids are commonly used to treat patients with chronic pain (CP), though there is little evidence that they are effective for long term CP treatment. Previous studies reported strong associations between passage of medical cannabis laws and decrease in opioid overdose statewide. Our aim was to examine whether using medical cannabis for CP changed individual patterns of opioid use. Using an online questionnaire, we conducted a cross-sectional retrospective survey of 244 medical cannabis patients with CP who patronized a medical cannabis dispensary in Michigan between November 2013 and February 2015. Data collected included demographic information, changes in opioid use, quality of life, medication classes used, and medication side effects before and after initiation of cannabis usage. Among study participants, medical cannabis use was associated with a 64% decrease in opioid use (n = 118), decreased number and side effects of medications, and an improved quality of life (45%). This study suggests that many CP patients are essentially substituting medical cannabis for opioids and other medications for CP treatment, and finding the benefit and side effect profile of cannabis to be greater than these other classes of medications. More research is needed to validate this finding.



Medical Cannabis vs Opioid Overdose Deaths

Medical Marijuana	
California	1996
Alaska	1998
Oregon	1998
Washington	1998
Maine	1999
Colorado	2000
Hawaii	2000
Nevada	2000
Montana	2004
Vermont	2004
Rhode Island	2006
New Mexico	2007
Michigan	2008
Arizona	2010
New Jersey	2010
Washington, DC	2010
10 of 16 < US Avg Opioid Overdoses	

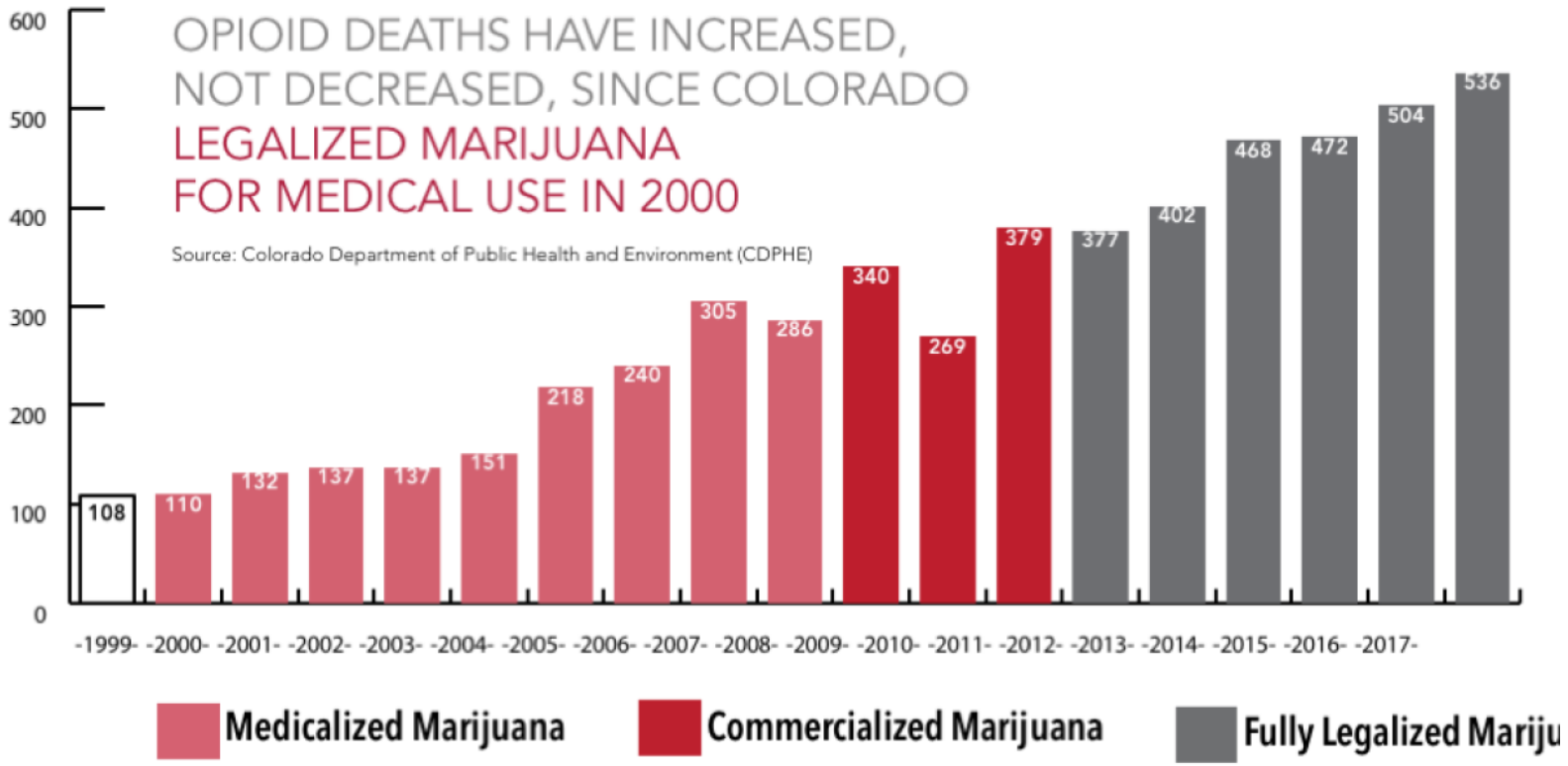
Figure 1. Mean Age-Adjusted Opioid Analgesic Overdose Death Rate



States passing a medical cannabis law experienced a 22.7% increase in opioid overdose deaths[2]

1. Bachhuber. *JAMA Intern Med*. 2014;174(10):1668-1673.
2. Shover. *PNAS*. 2019;10:1073.

Medical/Recreational Cannabis vs Opioid Overdose Deaths



Observation does not always correlate to causation

Colorado Department of Public Health and Environment. Monitoring Health Concerns Related to Marijuana in Colorado. 2016.

2020 Cannabinoid Utilizations Review

Circulation

Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association

Robert L. Page II, Larry A. Allen, Robert A. Kloner, Colin R. Carriker, Catherine Martel, Alanna A. Morris, Mariann R. Piano, Jamal S. Rana, Jorge F. Saucedo, ... See all authors

Originally published 5 Aug 2020 | https://doi.org/10.1161/CIR.0000000000000883 | Circulation. 2020;142:e131–e152

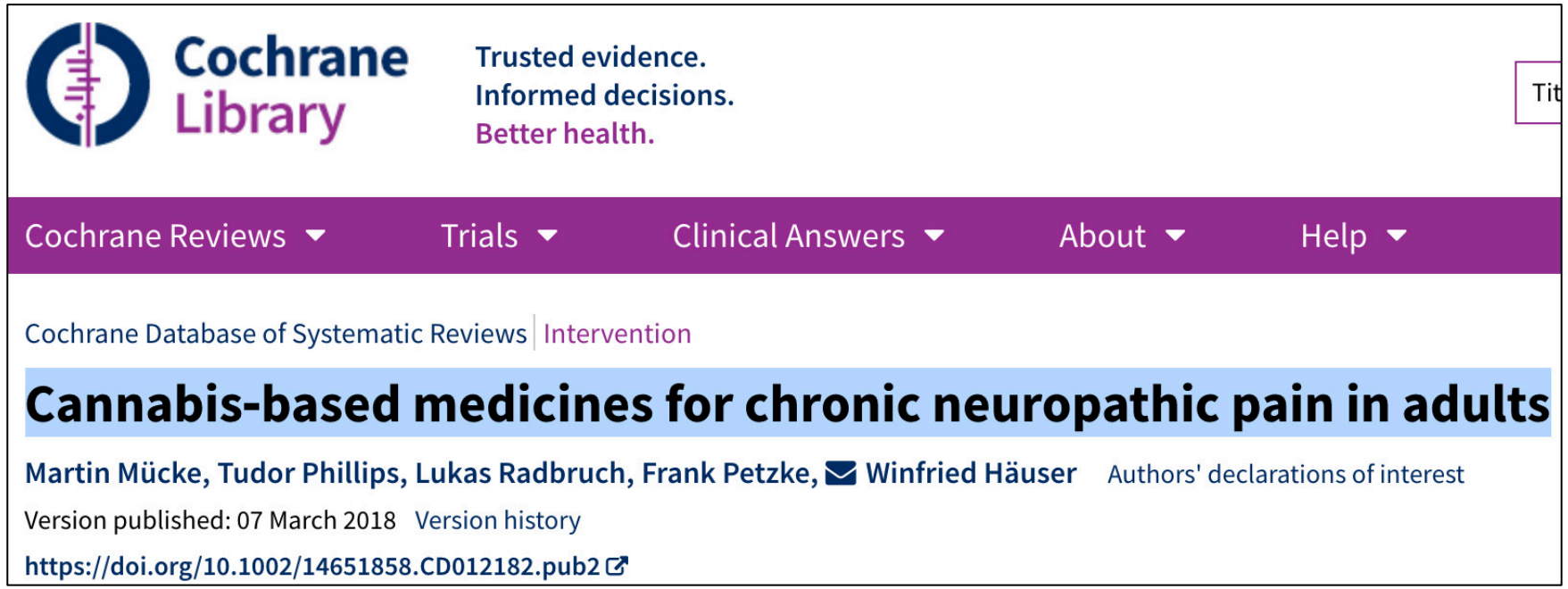
Abstract

Cannabis, or marijuana, has potential therapeutic and medicinal properties related to multiple compounds, particularly Δ-9-tetrahydrocannabinol and cannabidiol. Over the past 25 years, attitudes toward cannabis have evolved rapidly, with expanding legalization of medical and recreational use at the state level in the United States and recreational use nationally in Canada and Uruguay. As a result, the consumption of cannabis products is increasing considerably, particularly among youth. Our understanding of the safety and efficacy of cannabis has been limited by decades of worldwide illegality and continues to be limited in the United States by the ongoing classification of cannabis as a Schedule 1 controlled substance. These shifts in cannabis use require clinicians to understand conflicting laws, health implications, and therapeutic possibilities. Cannabis may have therapeutic benefits, but few are cardiovascular in nature. Conversely, many of the concerning health implications of cannabis include cardiovascular diseases, although they may be mediated by mechanisms of delivery. This statement critically reviews the use of medicinal and recreational cannabis from a clinical but also a policy and public health perspective by evaluating its safety and efficacy profile, particularly in relationship to cardiovascular health.

Page. *Circulation*. 2020;142(10):e131-e152.

KNOWN (Conclusive/Substantial Evidence)	
Pain	Neuropathic pain
	Fibromyalgia
	Cancer pain
Cachexia	HIV-associated anorexia/cachexia
	Cancer-associated anorexia/cachexia
Nausea and Vomiting	Chemotherapy-induced N/V *Caution: cannabis hyperemesis syndrome
Multiple Sclerosis	Central pain
	Spasticity
Epilepsy	Severe child-onset, drug-resistant epilepsy
	Treatment-resistant Dravet syndrome
	Treatment-resistant Lennox-Gastaut syndrome
	Refractory epilepsy

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)



Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

- 16 studies with 1,750 participants in total
  - 3 short term (2 to 4 weeks), 8 (4 to 12 weeks), and 5 intermediate (12 to 26 weeks)
  - Single center (9) and multicenter (7)
  - UK (5), Canada (3), multiple European countries (3), multiple continents (1), Romania (1), Germany (1), Denmark (1), and USA (1)
- Studies compared placebo to an oromucosal spray with a plant THC and CBD combo (10 studies), inhaled herbal cannabis (2 studies), synthetic THC nabilone (2 studies), and plant-derived THC dronabinol (2 studies)
- All studies compared cannabis-based medicines with placebo except 1 study that compared synthetic THC with dihydrocodeine (DHC)

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

Studies included adults aged ≥18yo with ≥1 chronic neuropathic pain condition including:

- Cancer-related neuropathy
- Central neuropathic pain
- Complex regional pain syndrome (CRPS) type II
- HIV neuropathy
- Painful diabetic neuropathy
- Peripheral polyneuropathy
- Phantom limb pain
- Postherpetic neuralgia
- Postoperative or traumatic peripheral nerve lesions
- Spinal cord injury
- Nerve plexus injury
- Trigeminal neuralgia

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

Primary outcomes

1. Participant-reported pain relief of 50% or greater
2. Patient Global Impression of Change much or very much improved
3. Withdrawals due to adverse events
4. Serious adverse events

Secondary outcomes

1. Participant-reported pain relief of 30% or greater
2. Mean pain intensity
3. Health-related quality of life
4. Sleep problems
5. Fatigue
6. Psychological distress
7. Withdrawals due to lack of efficacy
8. Any ADE
9. Specific ADEs
    - Nervous system and psychiatric disorders

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

1. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain*. 2004;112:299-306.

2. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34(3):672-80.

3. Frank B, Serpell MG, Hughes J, et al. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ*. 2008;336:199-201.

4. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebocontrolled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol*. 2013;260:984-997.

5. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. *J Pain Symp Manag*. 2014;47:166-173.

6. NCT 00710424. A study of Sativex® for pain relief due to diabetic neuropathy. clinicaltrials.gov/ct2/results? term=NCT00710424+&Search=Search (first Posted 4 July 2008).

7. NCT01606176. A Study to Evaluate the Effects of Cannabis Based Medicine in Patients With Pain of Neurological Origin. clinicaltrials.gov/ct2/results? cond=&term=NCT01606176&cntry1=&state1=&recrs= (first posted 25 May 2012).

8. NCT 01606202. A study of cannabis based medicine extracts and placebo in patients with pain due to spinal cord injury. clinicaltrials.gov/ct2/results?term= NCT 01606202&Search=Search (first posted 25 May 2012).

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Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

9. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain*. 2007;133:210-220.

10. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 2005;65:812-819.

11. Schimrigk S, Marziniak M, Neubauer C, et al. Dronabinol is a safe long-term treatment option for neuropathic pain patients. *Eur Neurol*. 2017;78:320-329.

12. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. *Diabetes Care*. 2010;33:128-130.

13. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J Pain*. 2014;18:999-1012.

14. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ.* 2004;329:253.

15. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain*. 2012;153:2073-2082.

16. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *Can Med Assoc J*. 2010;184:E694-E701.

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Berman JS, et. al. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomized controlled trial. Pain 2004;112:299-306.

- Objective: To investigate the effectiveness of cannabis-based medicines for treatment of chronic pain associated with brachial plexus root avulsion
- Methods
  - 48 participants with at least 1 avulsed root and baseline pain score of 4 or more on an 11-point ordinate scale
  - Randomized, double-blind, placebo-controlled, 3 period crossover study
  - Patients entered a baseline period of 2 weeks, followed by three, 2-week treatment periods during each of which they received 1 of 3 oromucosal spray preparations
    - Placebo, THC:CBD 1:1 extract, or GW-2000-02 (primarily THC)
- Primary outcome: mean pain severity score during the last 7 days of treatment
- Secondary outcome: pain related quality of life assessments
- Results
  - Primary outcome measure failed to fall by 2 points (hypothesis)
  - The study medications were generally well tolerated
- Studies of longer duration in neuropathic pain are needed

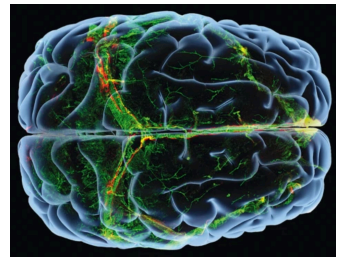
PAIN®
The Journal of the International Association for the Study of Pain

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
Berman. *Pain*. 2004;112:299-306.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Ellis RJ,, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009;34(3):672-80.

- Objective: Assess the impact of smoked cannabis on neuropathic pain in HIV
- Methods
  - Phase II, double-blind, placebo-controlled, crossover trial
  - 28 participants refractory pain to ≥2 previous analgesic classes (allowed to continue in study)
  - Regulatory considerations dictated that subjects smoke under direct observation in a hospital setting
  - Placebo vs 1 to 8% THC (smoked 4x/day x 5 days, in 2 treatment weeks around a 2-week washout)
- Primary outcome: Change in pain intensity as measured by the Descriptor Differential Scale (DDS)
- Secondary outcome: Assessments of mood and daily functioning
- Results
  - Pain relief was greater with cannabis than placebo
    - Median DDS difference: 3.3 points (p = 0.016)
  - Proportions of at least 30% pain relief with cannabis vs placebo were 0.46 (p 0.65) and 0.18 (p 0.32)
- Smoked cannabis was generally well tolerated and effective when added to concomitant analgesic therapy in patients with medically refractory pain due to HIV DSPN



Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
Ellis. *Neuropsychopharmacology*. 2009;34(3):672-680.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Frank B, et. al. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomized, crossover, double blind study. BMJ 2008;336:199-201.

- Objective: To compare the analgesic efficacy and side effects of the synthetic cannabinoid nabilone with those of the weak opioid dihydrocodeine for chronic neuropathic pain
- Design
  - 14 week randomized, 2x blind, crossover comparing dihydrocodeine 240 mg and nabilone 2 mg
  - 3 UK outpatient hospitals
  - 96 patients (aged 23 to 84 years)
- Primary outcome
  - VAS (Visual Analog Scale) difference between nabilone and dihydrocodeine
- Secondary outcomes: ADEs and changes in mood, quality of life, sleep, and psychometric function
- Results
  - VAS was 6.0 mm longer for nabilone than for dihydrocodeine
  - Side effects were more frequent with nabilone
- Dihydrocodeine provided better pain relief than nabilone and had slightly fewer ADEs

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
Frank. *BMJ*. 2008;336:199-201.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Langford RM, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. Journal of Neurology 2013;260:984-97.

- Phase 3 placebo-controlled study of nabiximols oromucosal spray efficacy to alleviate CNP in patients with MS
- 339 patients were randomized to phase A (167 nabiximols and 172 placebo)
- Of those who completed phase A, 58 entered the randomized-withdrawal phase B
- Primary endpoint: 30% pain reduction at 14 weeks (not met)
  - Interim 10-week: nabiximols 30% pain reduction ($p = 0.046$)
- Phase B: pain ($p = 0.028$) and sleep quality ($p = 0.015$) compared to placebo
- Findings suggest further studies

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
Langford. *J Neurol*. 2013;260:984-997.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Lynch ME, et. al. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. Journal of Pain and Symptom Management 2014;47:166-73.

Objectives

- Pilot trial of Nabiximols in the treatment of chemotherapy-induced neuropathic pain

Methods

- Randomized placebo-controlled crossover pilot study
- 16 patients
- Primary outcome: 0 to 10 Pain Scale Reduction

JPSM | JOURNAL OF PAIN AND SYMPTOM MANAGEMENT

Results

- No statistically significant difference

Conclusion

- Worthwhile to study nabiximols in a full randomized, placebo-controlled trial

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
Lynch. *J Pain Sympt Manag*. 2014;47:166-173.

2018 Cochrane Cannabis/Pain Review of 16 Studies

NCT 00710424. A study of Sativex® for pain relief due to diabetic neuropathy. clinicaltrials.gov/ct2/results? term=NCT00710424+&Search=Search (first Posted 4 July 2008).

- 15-week, multi-center, double blind, randomized, placebo controlled, parallel group study to evaluate the efficacy of Sativex in subjects with pain due to diabetic neuropathy
- Patient assessment at the end of weeks 2, 6, 10, 14, or earlier if they withdrew, along with a follow-up visit 28 days after completion or withdrawal
- 297 participants
- Study completed 2006
- Study sponsored by nabiximols manufacturer
- Results not published (yet included in 2018 Cochrane Review)

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
NCT 00710424. A study of Sativex® for pain relief due to diabetic neuropathy. clinicaltrials.gov/ct2/results? term=NCT00710424+&Search=Search.

2018 Cochrane Cannabis/Pain Review of 16 Studies

NCT01606176. A Study to Evaluate the Effects of Cannabis Based Medicine in Patients With Pain of Neurological Origin. clinicaltrials.gov/ct2/results?cond=&term=NCT01606176&cntry1=&state1=&recrs= (first posted 25 May 2012).

- Patients with multiple sclerosis and chronic refractory pain
- 21 day randomized, double blind, parallel group comparison of GW-1000-02 with placebo
- Primary outcome: change from baseline in daily Pain Box Scale-11 (BS-11)
- 70 participants
- Study completed 2002
- Study sponsored by nabiximols manufacturer
- Results not published (yet included in 2018 Cochrane Review)

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
NCT01606176. A Study to Evaluate the Effects of Cannabis Based Medicine in Patients With Pain of Neurological Origin. clinicaltrials.gov/ct2/results?cond=&term=NCT01606176&cntry1=&state1=&recrs=.

2018 Cochrane Cannabis/Pain Review of 16 Studies

NCT 01606202. A study of cannabis-based medicine extracts and placebo in patients with pain due to spinal cord injury. clinicaltrials.gov/ct2/results?term= NCT 01606202&Search=Search (first posted 25 May 2012).

- Multi-center, double-blind, randomized, placebo-controlled, parallel-group study evaluating efficacy and tolerability of GW-1000-02 vs placebo in central neuropathic pain associated with spinal cord injury
- Patient assessment occurred at the end of weeks 1 and 3, or upon withdrawal
- Patients were permitted to take paracetamol for breakthrough pain
- 116 participants
- Study completed 2005
- Study sponsored by Nabiximols manufacturer
- Results not published (yet included in 2018 Cochrane Review)

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
NCT 01606202. A study of cannabis based medicine extracts and placebo in patients with pain due to spinal cord injury. clinicaltrials.gov/ct2/results?term= NCT 01606202&Search=Search.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Nurmikko TJ, et. al. Sativex successfully treats neuropathic pain characterized by allodynia: a randomized, double-blind, placebo-controlled clinical trial. Pain 2007;133:210-20.

- 125 patients with neuropathic pain
- 5-week, randomized, double-blind, placebo-controlled, parallel trial
- Patients remained on their existing stable analgesia medications
- 63 Sativex and 62 placebo
- Primary outcome: mean reduction in pain intensity scores
- Results
  - Pain intensity score reduction was greater with nabiximols than placebo (-1.48 vs -0.52, $p = 0.004$)
  - Improvements in Neuropathic Pain Scale composite score ($p = 0.007$)
  - Sleep NRS ($p = 0.001$)
  - Dynamic allodynia ($p = 0.042$)
  - Punctate allodynia ($p = 0.021$)
  - Pain Disability Index ($p = 0.003$)
  - Patient's Global Impression of Change ($p < 0.001$)
  - Sedative and GI ADEs were more common with Sativex
  - 18% on Sativex and 3% on placebo withdrew

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
Nurmikko. *Pain*. 2007;133:210-220.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Rog DJ, et. al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65:812-9.

Methods

- Single-center, 5-week, randomized, double-blind, placebo-controlled, parallel-group trial
- 66 patients with MS and central pain states
- THC:CBD oromucosal spray, as adjunctive analgesic treatment
  - THC 2.7 mg and CBD 2.5 per spray (max 48 sprays in 24 hours)

Neurology®

Results

- Mean number of daily sprays taken of THC:CBD was 9.6 and of placebo was 19.1
- THC:DBD was superior to placebo in reducing the mean intensity of pain (THC:CBD -2.7, placebo -1.4, p=0.005)
- Sleep disturbance (THC:CBD -2.5, placebo -0.8, p=0.003)

Conclusions

- Cannabis-based medicine is effective in reducing pain and sleep disturbance in patients with multiple sclerosis related central neuropathic pain and is mostly well tolerated

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
Rog. *Neurology*. 2005;65:812-819.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Schimrigk S, et. al. Dronabinol is a safe long-term treatment option for neuropathic pain patients. European Neurology 2017;78:320-9.

- Objective: Assess benefit-risk ratio of dronabinol in patients with MS neuropathic pain
- 240 participants in a 16-week placebo-controlled phase-III study
- 100 participants continued therapy for full term
- Primary endpoint: Pain Intensity Scale Reduction
- Results
  - Pain intensity reduced by 1.92 and 1.81 points without significant difference between dronabinol and placebo ($p = 0.676$)
  - Although the proportion of patients with ARs was higher under dronabinol compared to placebo (50.0 vs 25.9%), it decreased during long-term use of dronabinol (26%)
  - No signs of drug abuse and only one possible case of dependency occurred
- The trial results demonstrate that dronabinol is a safe long-term treatment option

European Neurology

RESEARCH

Karger

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
Schimrigk. *Eur Neurol*. 2017;78:320-329.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Selvarajah D, et. al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding f Diabetes Care 2010;33:128-30.

- Objective: To assess the efficacy of Sativex as adjuvant treatment in painful diabetic peripheral neuropathy (DPN)
- Randomized controlled trial of 30 subjects with painful DPN received daily nabiximols or placebo
- Primary outcome: change in mean daily pain scores
- Secondary outcome: quality-of-life assessments
- Results
  - Significant improvement in pain scores in both groups, but mean change between groups was not significant
  - No significant differences in secondary outcome measures
- Conclusions: Sativex was no more efficacious than placebo in painful DPN

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Selvarajah D, et. al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care 2010;33:128-30.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Serpell M, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. European Journal of Pain 2014;18:999-1012.

Objective
- Nabiximols (THC/CBD) oromucosal spray efficacy

Methods
- 15-week randomized, double-blind, placebo-controlled parallel group study
- 246 participants (128 THC/CBD and 118 placebo)

Primary endpoints
- 30% responder rate in pain scale
- Mean change from baseline to end on pain scale

Results
- 30% responder rate: statistically significant treatment differences in favor of THC/CBD spray (intention-to-treat analysis)
- Sleep quality ($p = 0.0072$) and Subject Global Impression of Change SGIC ($p = 0.023$) treatment differences in favor of THC/CBD spray

Conclusions
- THC/CBD spray produced clinically important improvements in pain, sleep quality, and SGIC
- THC/CBD spray was well tolerated and no new safety concerns were identified.

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Serpell. *Eur J Pain*. 2014;18:999-1012.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Svendsen KB, et. al. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomized double blind placebo controlled crossover trial. BMJ 2004;329:253.

Objective: To evaluate the effect of the oral synthetic delta-9-tetrahydrocannabinol dronabinol on central neuropathic pain in patients with multiple sclerosis.

Design

- Randomized, double-blind, placebo-controlled, crossover trial
- Outpatient clinic (University Hospital of Aarhus in Denmark)
- 24 patients (aged 23 to 55 years)
- Oral dronabinol (max dose 10 mg daily) vs placebo for 3 weeks

Main outcome: median spontaneous pain intensity scale in the last week of treatment

Results

- Median spontaneous pain intensity significantly lower with dronabinol vs placebo (4 vs 5, P = 0.02)
- Median pain relief score was higher (3 vs 0, P = 0.035)
- Number needed to treat for 50% pain relief was 3.5
- Quality of life scale items, body pain, and mental health, indicated benefits from dronabinol vs placebo
- Number of patients with ADEs was higher with dronabinol

Conclusions

- Dronabinol has a modest but clinically relevant analgesic effect on central pain in patients with multiple sclerosis
- Adverse events were more frequent with dronabinol than with placebo

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
Svendsen. *BMJ*. 2004;329:253.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Toth C,, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain 2012;153:2073-82.

Objective

- Evaluate oral nabilone in the treatment of refractory diabetic peripheral neuropathic pain (DPN)

PAIN®
The Journal of the International Association for the Study of Pain

Methods

- Single-center, randomized, double-blind, placebo-controlled, flexible-dose study (enriched enrollment)
- DPN subjects with a pain score ≥4 (0 to 10 scale) continued regular pain medications and were administered single-blinded adjuvant nabilone for 4 weeks
- Subjects achieving ≥30% pain relief (26/37) were then randomized and treated with either flexible-dose nabilone 1-4 mg/day (n=13) or placebo (n=13) in a further 5-week double-blind treatment period, with 30% (11/37) of subjects deemed run-in-phase nabilone non-responders

Nabilone results

- Potential unmasking occurred in 62% of both groups
- Improvement in the change in mean endpoint neuropathic pain vs placebo (~1, P= 0.02)
- Greater global endpoint improvement with nabilone than with placebo (100% vs 31%; P< 0.05)
- Effective in relieving DPN symptoms, improving disturbed sleep, quality of life, and overall patient status
- Well tolerated and successful as adjuvant in patients with DPN

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182. Toth. *Pain*. 2012;153:2073-2082.

2018 Cochrane Cannabis/Pain Review of 16 Studies

Ware MA,, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. Canadian Medical Association Journal 2010;184:E694-701.

Methods

- Adults with post-traumatic or postsurgical neuropathic pain randomly received cannabis or placebo over 14-day periods in a crossover trial
- Cannabis at 4 potencies [0% (placebo), 2.5%, 6%, and 9.4% THC] over four 14-day periods in a crossover trial
- 21 participants inhaled (pipe) a single 25-mg dose 3 times daily x 5 days/cycle, followed by a 9-day washout period
- Measurements: daily average pain intensity mood, sleep, quality-of-life, as well as adverse events

THC results

- Daily pain intensity was lower for THC 9.4% vs THC 0% (5.4 vs 6.1)
- 2.5% THC and 6% THC yielded intermediate but nonsignificant degrees of pain relief
- 9.4% THC improved ability to fall asleep (easier, $p = 0.001$; faster, $p < 0.001$; more drowsy, $p = 0.003$) and improved quality of sleep (less wakefulness, $p = 0.01$) relative to 0% tetrahydrocannabinol
- No differences in mood or quality of life
- Most common ADEs: headache/dizziness, dry eyes, burning/numbing in areas of neuropathic pain, and cough

Conclusion

- 9.4% THC 25 mg inhalation 3x/day x 5 days reduced pain intensity, improved sleep, and was well tolerated
- Further long-term safety and efficacy studies are indicated

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.
Ware. *Can Med Assoc J*. 2010;184:E694-701.

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

Primary Outcomes

1. Participant-reported pain relief of 50% or greater
    - 8 studies (1,000 participants)
    - 21% (cannabis) and 17% (placebo) reports pain relief >50% (95% CI 0.00 to 0.09 and P-value 0.04)
    - NNTB: 20 (11 to 100)
    - Low quality evidence
    - No clinically relevant benefit of cannabis-based medicines

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

Primary Outcomes

2. Patient Global Impression of Change much or very much improved

- 6 studies (1,100 participants)
- 28% (cannabis) and 22% (placebo) reported much or very much improved (95% CI 0.01 to 0.17 and P-value 0.02)
- NNTB: 11 (6 to 100)
- Low quality evidence
- No clinically relevant benefit of cannabis-based medicines

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

Primary Outcomes

3. Withdrawals due to adverse events

- 13 studies (1,800 participants)
- 10% (cannabis) and 5% (placebo) withdrew to ADEs (95% CI 0.02 to 0.07 and P-value 0.0009
- NNTH was 25 (16 to 50)
- Moderate quality evidence
- No clinically relevant harm by cannabis-based medicines

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

Primary Outcomes

4. Serious adverse events

- 13 studies (1,900 participants)
- 7% (cannabis) and 5% (placebo) reported serious ADEs (95% CI -0.01 to 0.03 and P-value 0.29)
- Low quality evidenced

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

Primary Outcomes

- Cannabis-based medicines may increase the number of people achieving 50% or greater pain relief compared with placebo
- Low quality evidence for improvement in Patient Global Impression of Change (PGIC) with cannabis
- More participants withdrew from the studies due to adverse events with cannabis-based medicines than with placebo
- Not enough evidence to determine if cannabis-based medicines increase the frequency of serious adverse events compared with placebo

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

Primary

Secondary

Outcomes (Secondary)	Probable outcome with intervention 95% CI	Probable outcome with placebo	Relative effect Risk difference (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Participant-reported pain relief of 50% or greater	209 per 1000 (196 to 222)	173 per 1000	0.05 (0.00 to 0.09)	1001 (8 studies)	⊕⊕⊙⊙ **low** [1,2]	NNTB 20 (11 to 100)
Patient Global Impression of Change much or very much improved	261 per 1000 (246 to 276)	211 per 1000	0.09 (0.01 to 0.17)	1092 (6 studies)	⊕⊙⊙⊙ **very low** [1,3,4]	NNTB 11 (6 to 100)
Withdrawals due to adverse events	104 per 1000 (99 to 107)	47 per 1000	0.04 (0.02 to 0.07)	1848 (13 studies)	⊕⊕⊕⊙ **moderate** [1]	NNTH 25 (16 to 50)
Serious adverse events	66 per 1000 (63 to 69)	52 per 1000	0.01 (-0.01 to 0.03)	1876 (13 studies)	⊕⊕⊙⊙ **low** [1,2]	NNTH not calculated
Participant-reported pain relief of 30% or greater	377 per 1000 (358 to 396)	304 per 1000	0.09 (0.03 to 0.15)	1586 (10 studies)	⊕⊕⊕⊙ **moderate** [1]	NNTB 11 (7 to 33)
Specific adverse events: nervous system disorder	611 per 1000 (576 to 644)	287 per 1000	0.38 (0.18 to 0.58)	1304 (9 studies)	⊕⊕⊙⊙ **low** [1,3]	NNTH 3 (2 to 6)
Specific adverse events: psychiatric disorders	165 per 1000 (156 to 174)	49 per 1000	0.10 (0.06 to 0.15)	1314 (9 studies)	⊕⊕⊙⊙ **low** [1,3]	NNTH 10 (7 to 16)

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

Secondary Outcomes

- Cannabis-based medicines probably increase the number of people achieving pain relief of 30% or greater compared with placebo
- Cannabis-based medicines may increase nervous system adverse events compared with placebo
- Psychiatric disorders occurred in 17% of participants using cannabis-based medicines and in 5% using placebo
- No information about long-term risks

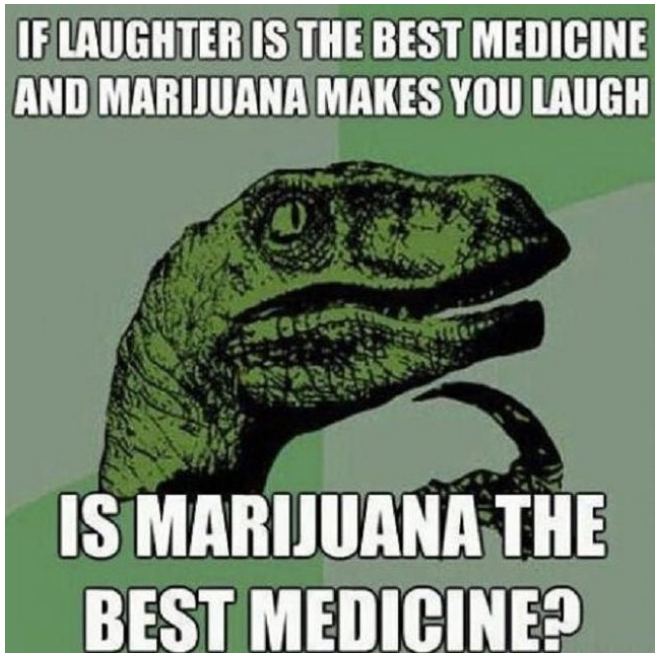
Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.

Cannabis-Based Medicines for Chronic Neuropathic Pain
2018 Cochrane Review (16 Studies)

Authors' Conclusions

- The potential benefits of cannabis-based medicine in chronic neuropathic pain might be outweighed by potential harms
- There is a lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain
- All cannabis-based medicines pooled together were better than placebo for:
  - Substantial and moderate pain relief
  - Global improvement
  - Pain intensity
  - Sleep problems
  - Psychological distress
- There was no difference between all cannabis-based medicines pooled together and placebo in:
  - Improving health-related quality of life
  - Stopping the medication because it was not effective
  - Frequency of serious side effects
- More people reported sleepiness, dizziness, and mental problems with all cannabis-based medicines than placebo
- More people dropped out due to side effects with cannabis-based medicines than with placebo
- Herbal cannabis not different from placebo in reducing pain and number of people who dropped out due to side effects

Mucke. *Cochrane Database Syst Rev*. 2018;3(3):CD012182.



Cannabinoid Safety Considerations

Practical THC and CBD Dosing

THC Practical Dosing	
Cannabis Experience	THC Daily Dose
Cannabis-naïve	2.5 mg to 5 mg
Daily to weekly utilizer	10 mg to 20 mg
Multiple times daily	25 mg +

CBD Practical Daily Dosing
300 to 1,500 mg daily

Without regulation, product contents are not absolute, thus there may be “overlap”

www.webmd.com/vitamins/ai/ingredientmono-1439/cannabidiol.
www.leafly.com/news/cannabis-101/cannabis-edibles-dosage-guide-chart.

Cannabinoid Adverse Effects

Adverse Effect	~Odds Ratio
Disorientation	5
Dizziness	5
Dry mouth	4
Euphoria	4
Drowsiness	4
Confusion	4
Balance issues	3
Hallucinations, nausea, vomiting, diarrhea, and fatigue	2

Colorado Department of Public Health and Environment. *Monitoring Health Concerns Related to Marijuana in Colorado: 2016*. Stout. *Drug Metab Rev*. 2014;46(1):86-95. Volkow. *N Eng J Med*. 2014;370:2219-2227.

Cannabinoid Interactions
Comprehensive

Cannabinoid	1A2	2C9	2C19	3A4	2D6
CBD	Inhibitor	Substrate Inhibitor	Substrate Inhibitor	Substrate Inhibitor*	Inhibitor*
CBN		Substrate Inhibitor		Substrate Inhibitor	Inhibitor
THC	Inducer	Substrate Inhibitor	Inhibitor	Substrate Inhibitor	Inhibitor

*Most potent inhibitor relative to all cannabinoids

Stout. *Drug Metab Rev*. 2014;46(1): 86-95.
Volkow. N Engl J Med. 2014;370:2219-2227.
Alsherbiny. *Medicines*. 2019;6(1):3.
Colorado Department of Public Health and Environment. *Monitoring Health Concerns Related to Marijuana in Colorado: 2016.*
Kocis. Med Cannabis Cannabinoids. July 7, 2020.

Cannabinoid Interactions
Simplified

Cannabinoid	1A2	2C9	2C19	3A4	2D6
CBD	X	X	X	X	X
CBN		X		X	X
THC	X	X		X	X

Kocis. *Med Cannabis Cannabinoids*. July 7, 2020.

Cannabinoid and NTI Medications Interactions

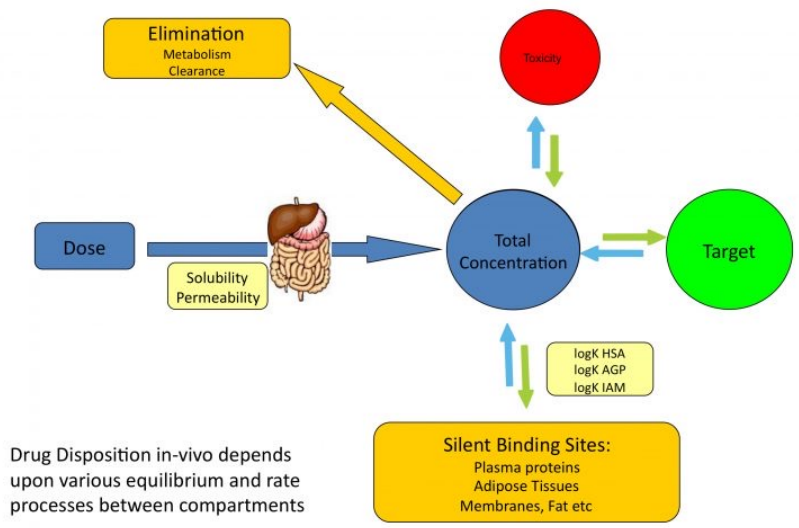
CYP-450

- Amiodarone (1A2, 2C19, 3A4)
- Amitriptyline (1A2, 2B6, 2C19, 3A4)
- Carbamazepine (1A2, 3A4)
- Clindamycin (3A4)
- Clonidine (1A2, 3A4)
- Cyclobenzaprine (1A2, 3A4)
- Cyclosporine (3A4)
- Desipramine (1A2, 2B6)
- Digoxin (3A4)
- Doxepin (1A2, 2C9, 2C19, 3A4)
- Fentanyl (3A4)
- Levothyroxine (3A4)
- Meperidine (2B6, 3A4)
- Nortriptyline (1A2, 2B6, 3A4)
- Phenytoin (2C9, 2C19)
- Valproic Acid (2C9)
- Warfarin (1A2, 2C9, 2C19, 3A4)

Kocis. *Med Cannabis Cannabinoids*. July 7, 2020.

Cannabinoid and NTI Medications Interactions
Protein Binding

- Cannabidiol (>94%)
- Dronabinol (97%)
- Nabilone (high)
- Nabiximols (>94%)



- Cyclosporine (90%)
- Levothyroxine (>99%)
- Phenytoin (90%)
- Quinidine (88%)
- Tacrolimus (>99%)
- Valproic acid (85%)
- Warfarin (99%)

www.europeanpharmaceuticalreview.com/article/4320/bio-mimetic-chromatography-to-predict-drug-distribution-in-vivo/.
Kocis. *Med Cannabis Cannabinoids*. July 7, 2020.

Cannabinoid Pain Management Interactions

Cannabinoid Pain Management Interactions			
CYP-450	**Common Substrates**	**Common Inhibitors**	**Common Inducers**
2C9	Amitriptyline, clopidogrel, diphenhydramine, fluoxetine, rosuvastatin, sildenafil, warfarin NSAIDs: Celecoxib, Diclofenac, flurbiprofen, Ibuprofen, indomethacin, meloxicam, naproxen, & piroxicam	Major: fluconazole Moderate: amiodarone Minor: Bactrim, fluoxetine, & metronidazole	Moderate: carbamazepine & rifampin Minor: phenobarbital & St. John's Wort
2C19	Carisoprodol, citalopram, clopidogrel, diazepam, & omeprazole	Major: amitriptyline & fluconazole Moderate: fluoxetine & omeprazole Minor: garlic, oral contraceptives, & nortriptyline	Moderate: rifampin
3A4	Fentanyl, oxycodone, buprenorphine, & benzos	Grapefruit juice, azoles, clarithromycin, diltiazem, erythromycin, & verapamil	Garlic & prednisone

Clinical Pharmacology Online Database, Drug interaction search for Epidiolex (CBD) and Dronabinol (THC) prescription medications.

Cannabinoid Pain Management Interactions

Clinical Pharmacology Online Database.

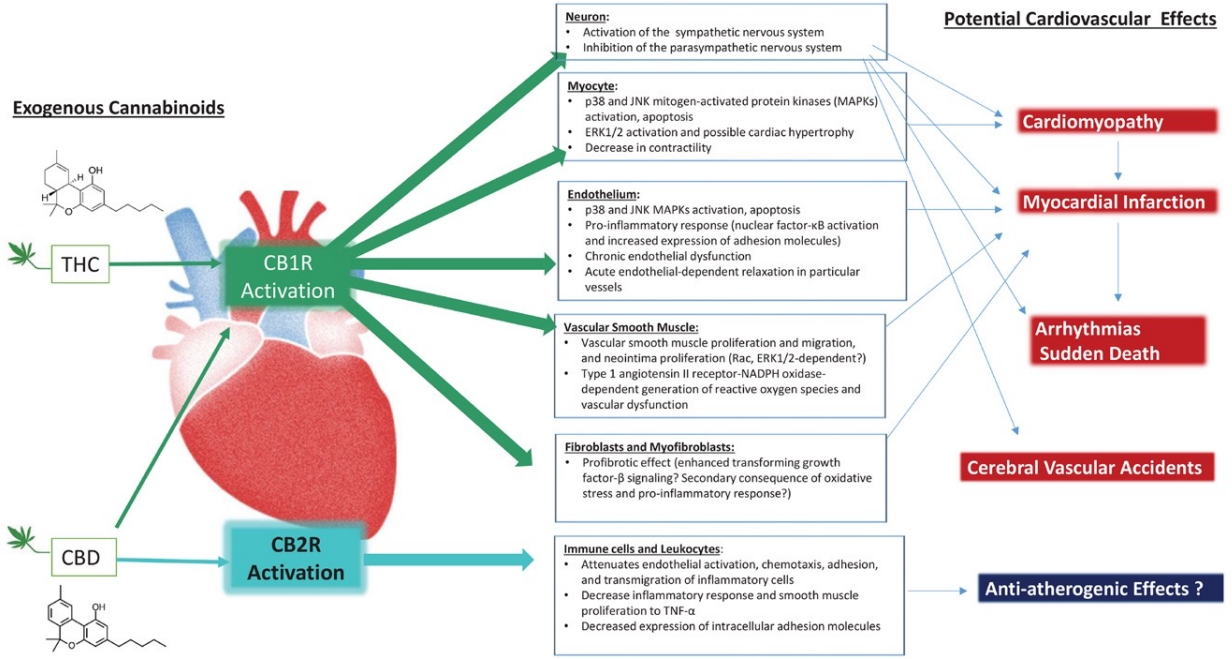
Cannabinoids, Hearts, and Meds

Cannabinoid	CYP-450	Medication	Medication Level
CBD CBN THC	3A4	Antiarrhythmics Amiodarone, Quinidine, Lidocaine	Increased
		Ca Channel Blockers Dihydropyridine + Non-DHP	
		Isosorbide Mono/Di Nitrate	
		Statins Atorvastatin, lovastatin, simvastatin	
	2C9	Warfarin	
		Statins Rosuvastatin, fluvastatin	
		NSAIDs Celecoxib, ibuprofen, naproxen	
	2D6	Beta-Blockers Carvedilol, metoprolol	
		Antiarrhythmics Flecainide, mexiletine, propafenone	
	1A2	Theophylline	

Defilippis. *J Am Coll Cardiol.* 2020;75(3):320-332.

Cannabis/Cannabinoid Effects
Cardio

- Increased heart rate
- Increased cardiac output
- Orthostatic hypotension



- Risk of myocardial infarction (MI) is rare
  - Patients with previous MI →
    5x risk w/n 1 hour of smoking cannabis

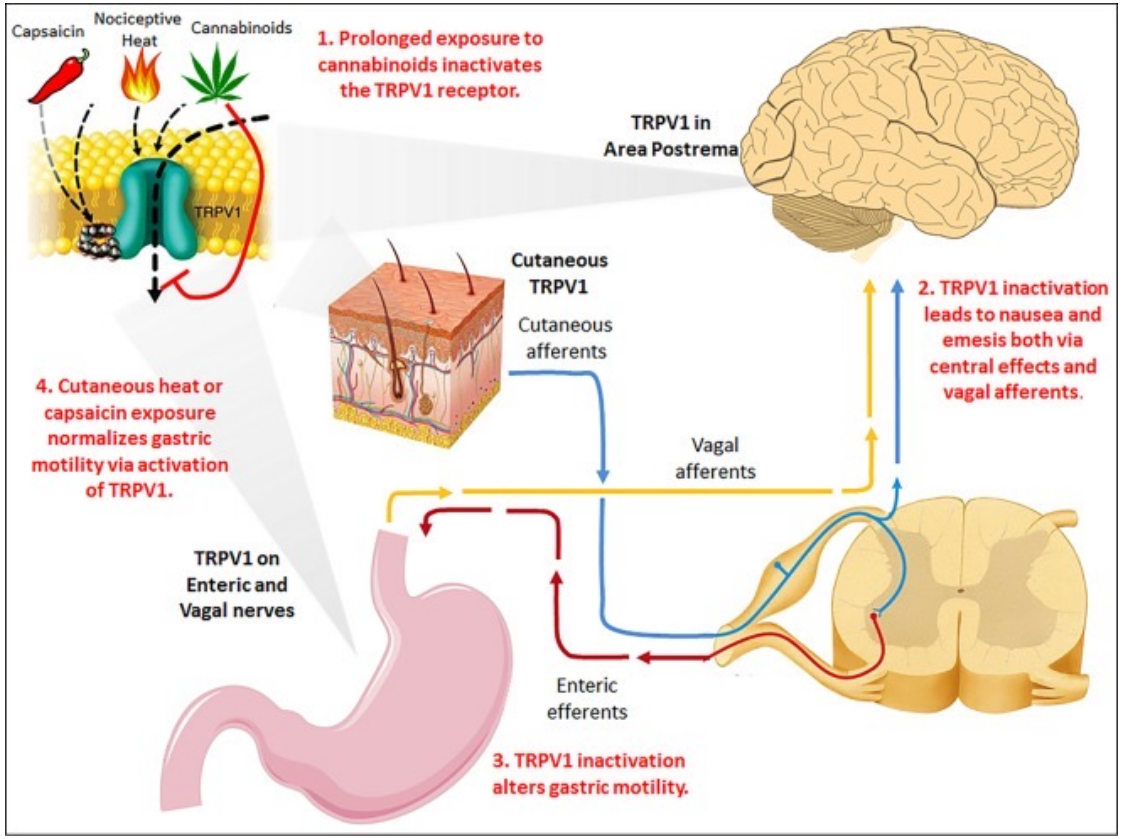
Mittleman. *Circulation*. 2001;103(23):2805.
Page. *Circulation*. 2020;142(10):e131-e152.
Thomas. *Am J Cardiol*. 2014;113:187-190.

Cannabis/Cannabinoid Effects
Pregnancy

- Women who utilized during pregnancy:
  - Moms more likely to be anemic
  - Babies more likely to have lower birth weight
  - Babies more likely to require NICU
  - Babies display altered responses to visual stimuli (high-pitched cry)
- Link between prenatal exposure and school years:
  - Impulse control
  - Visual memory
  - Attention
- THC is excreted in breast milk

Schempf. *J Urban Health Bull N Y Acad Med*. 2008;85(6):858-873.
Richardson. *Neurotoxicol Teratol*. 2002;24(3):309-320.
De Moraes Barros. *Early Hum Dev*. 2008;84(5):281-287.
Goldschmidt. *Neurotoxicol Teratol*. 2000;22(3):325-336.

Cannabinoid Hyperemesis Syndrome (CHS)
Treatment: Capsaicin or Hot Showers???



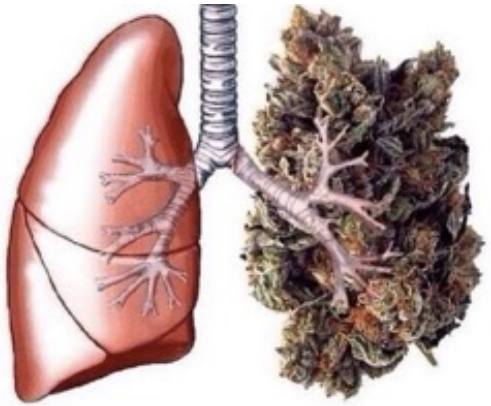
Symptoms:

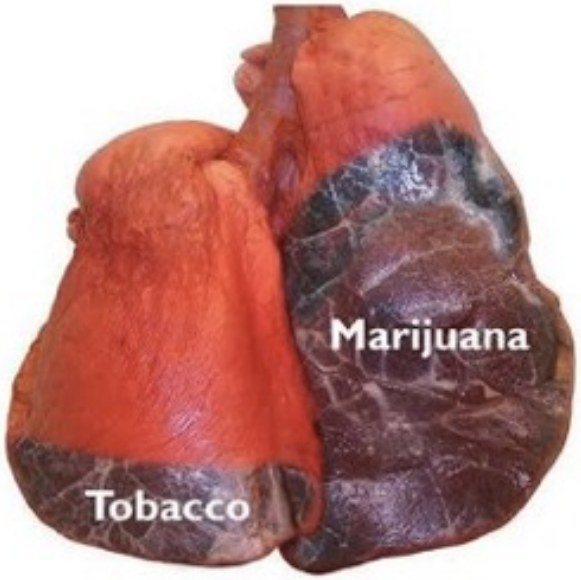
- Severe vomiting +/- diarrhea
- Stomach pain
- Difficulty eating
- Weight loss
- Tendency to take extremely hot baths/showers for relief

Moon. *ACG Case Rep J*. 2018;5:e3

Marijuana Lung

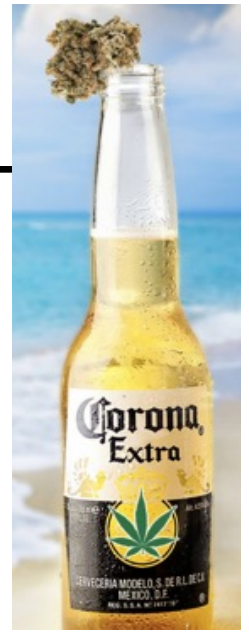
- Cannabis combustion comparisons: cannabis relative to tobacco
  - Carcinogens
  - 50% more benzopyrene
  - 75% more benzanthracene
  - > phenols, vinyl chlorides, nitrosamines, and oxidants
  - Tar
  - Deeper inhalations and held longer
    - Thus, 4x tar deposition





www.drugabuse.gov/publications/research-reports/marijuana/what-are-marijuanas-effects-lung-health.

Marijuana and Alcohol

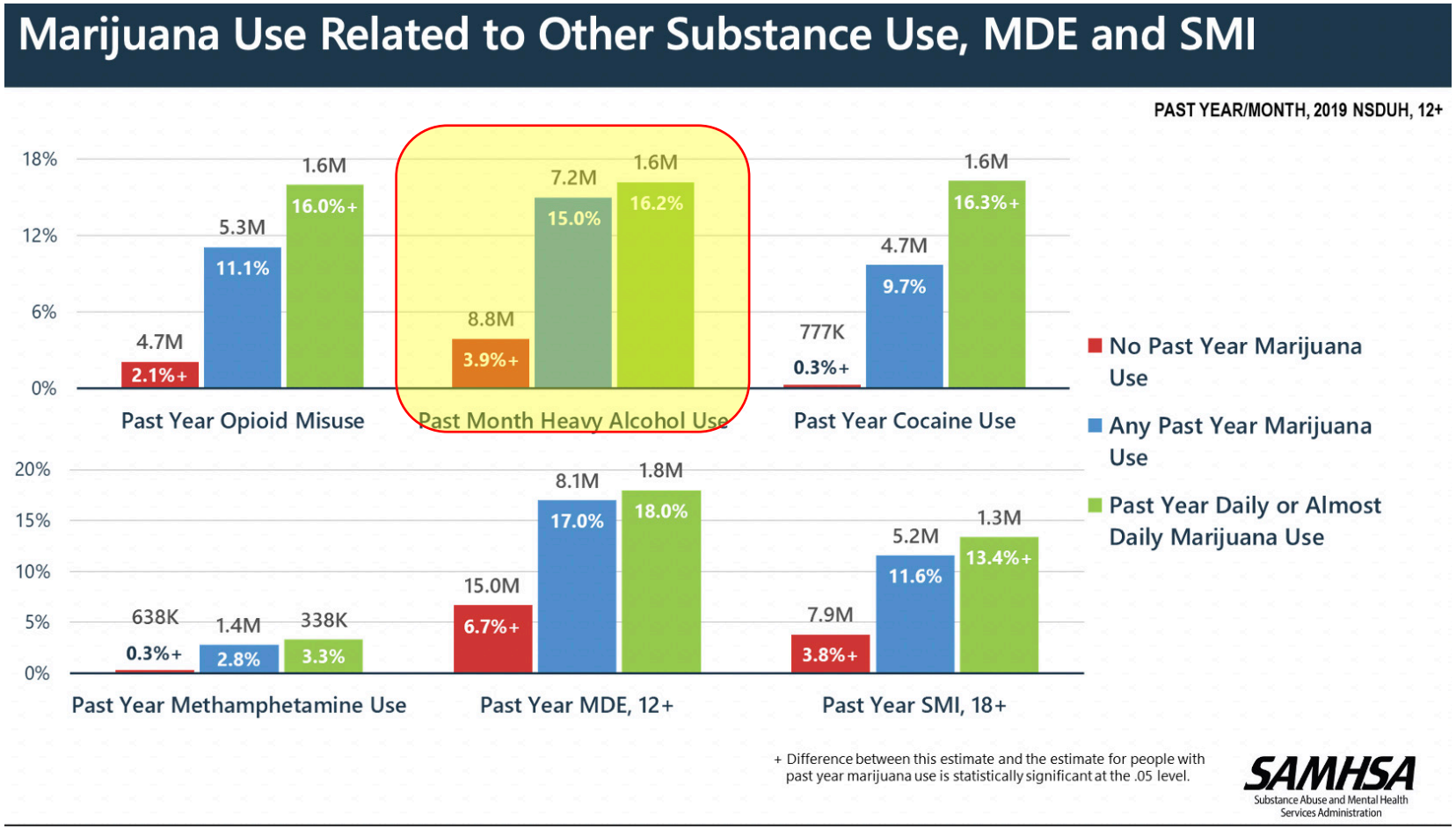


- Marijuana use coincides with alcohol use, not as one or the other
- If a car's headlights are broken, do you smash the tail lights for consistency?
  - Headlights: 100K alcohol-related annual deaths
  - Tail lights: legalize another sedative
- Colorado first 4 years of recreational marijuana legalization (2014-2018)
  - Spirits (higher ABV) increased ~8%
  - Beer (lower ABV) decreased ~4%
  - Wine remained steady

www.distilledspirits.org/wp-content/uploads/2019/01/Recreational-Marijuana-Impact-Study.pdf.

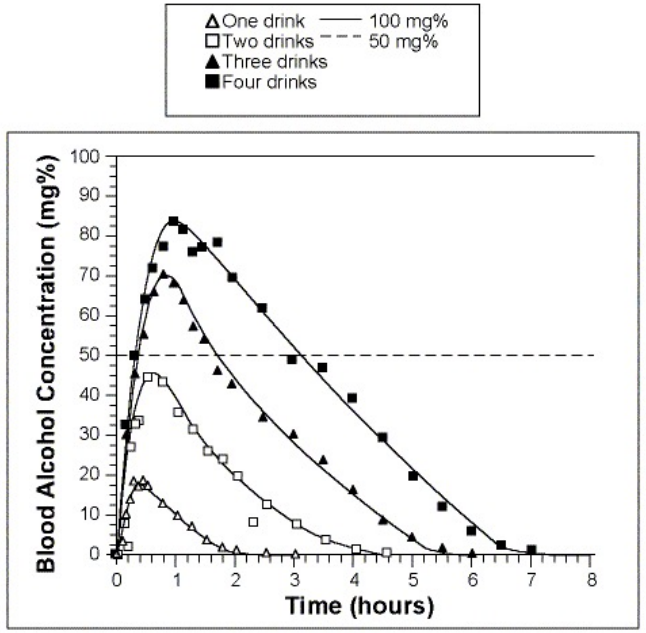
Red, White, and Booze

Cannabis

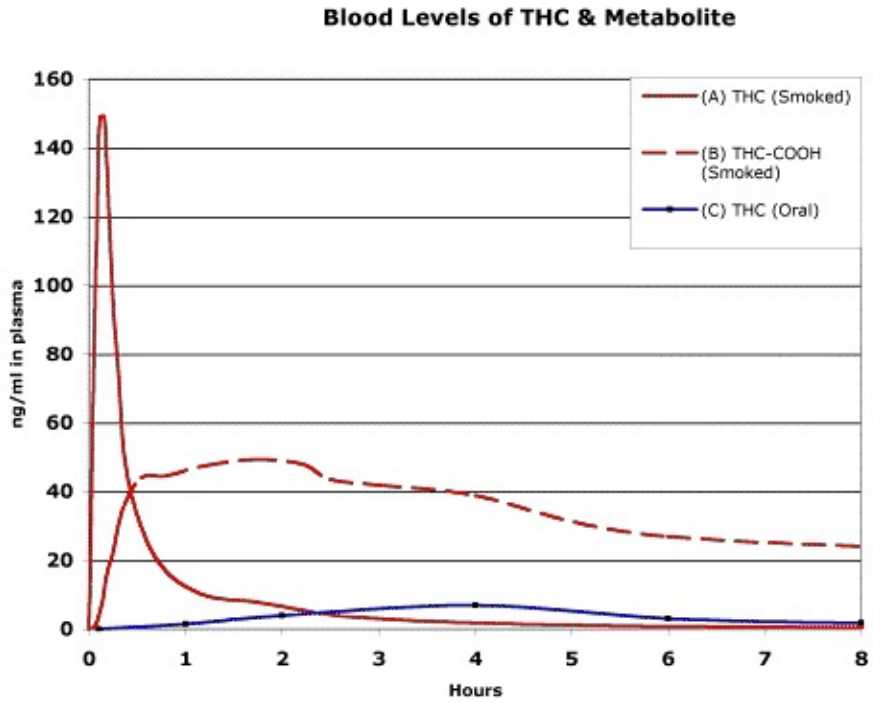


National Survey on Drug Use. SAMHSA 2019..

Alcohol vs Marijuana Metabolism



Blood alcohol concentration (BAC) after the rapid consumption of different amounts of alcohol by eight adult fasting male subjects.* (Adapted from Wilkinson et al., *Journal of Pharmacokinetics and Biopharmaceutics* 5(3):207-224, 1977.)



Musshoff. *Ther Drug Monit.* 2006;28(2).

THC Breathalyzers….

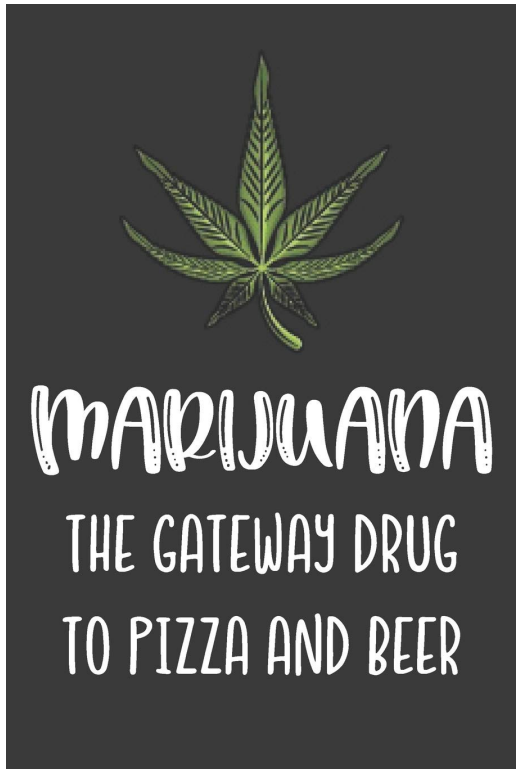
www.nejm.org/doi/pdf/10.1056/NEJMra1402309.

Traffic Fatalities

- Recreational cannabis laws
  - Colorado experienced an increase in traffic fatalities while Washington did not
    - Approximately 100 excess traffic fatality deaths in Colorado per year after legalization
  - Authors hypothesized Colorado's increased traffic fatalities may be due to its cannabis tourism industry, and lack of neighboring states with legalized recreational cannabis
- Medical cannabis laws
  - Approximately 100 excess deaths in states legalizing medical marijuana

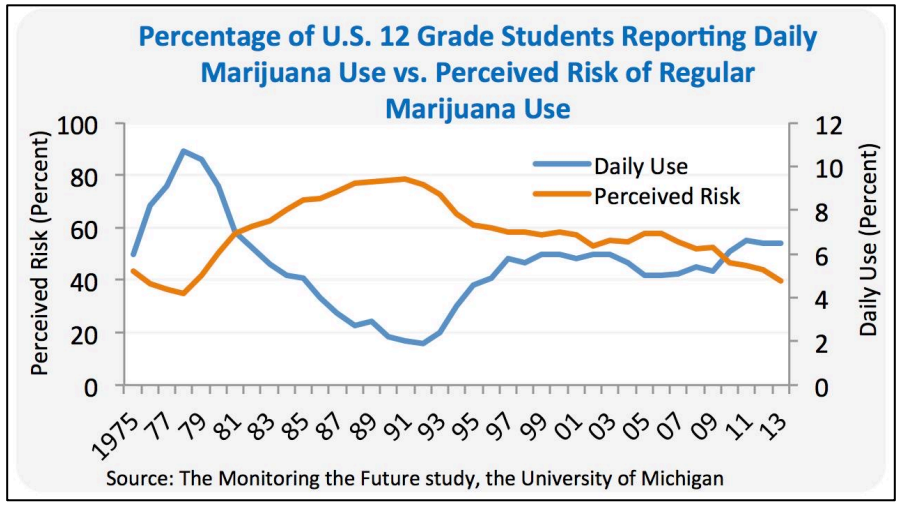
Rosekind. *JAMA Intern Med.* 2020;180(8):1068-1069.

Gateway Drug?



Gateway Drug?

- Cannabis use associated with increased non-medical prescription opioid use
- Cannabis use associated with increased opioid use disorder
- 9% of those who experiment will progress to cannabis use disorder
- 17% of adolescent first-time utilizers will progress to cannabis use disorder
- 25% to 50% of those daily utilizers will progress to cannabis use disorder



Volkow. *N Engl J Med*. June 5, 2014.
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Olfson. *Am J Psychiatry*. 2018;175(1):47-53.

Cannabis Use Disorder (DSM-5)

A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least 2 criteria…

CRITERION	SEVERITY
Use in larger amounts or for longer periods of time than intended	**0-1: No diagnosis** **2-3: Mild SUD** **4-5: Moderate SUD** **≥6: Severe SUD**
Unsuccessful efforts to cut down or quit	
Excessive time spent using the drug	
Intense desire/urge for drug (craving)	
Failure to fulfill major obligations	
Continued use despite social/interpersonal problems	
Activities/hobbies reduced given use	
Recurrent use in physically hazardous situations	
Recurrent use despite physical or psychological problem caused by or worsened by use	
Tolerance	
Withdrawal	

www.psychiatry.org/psychiatrists/practice/dsm.

Cannabis-Induced Psychotic Disorder (Acute)

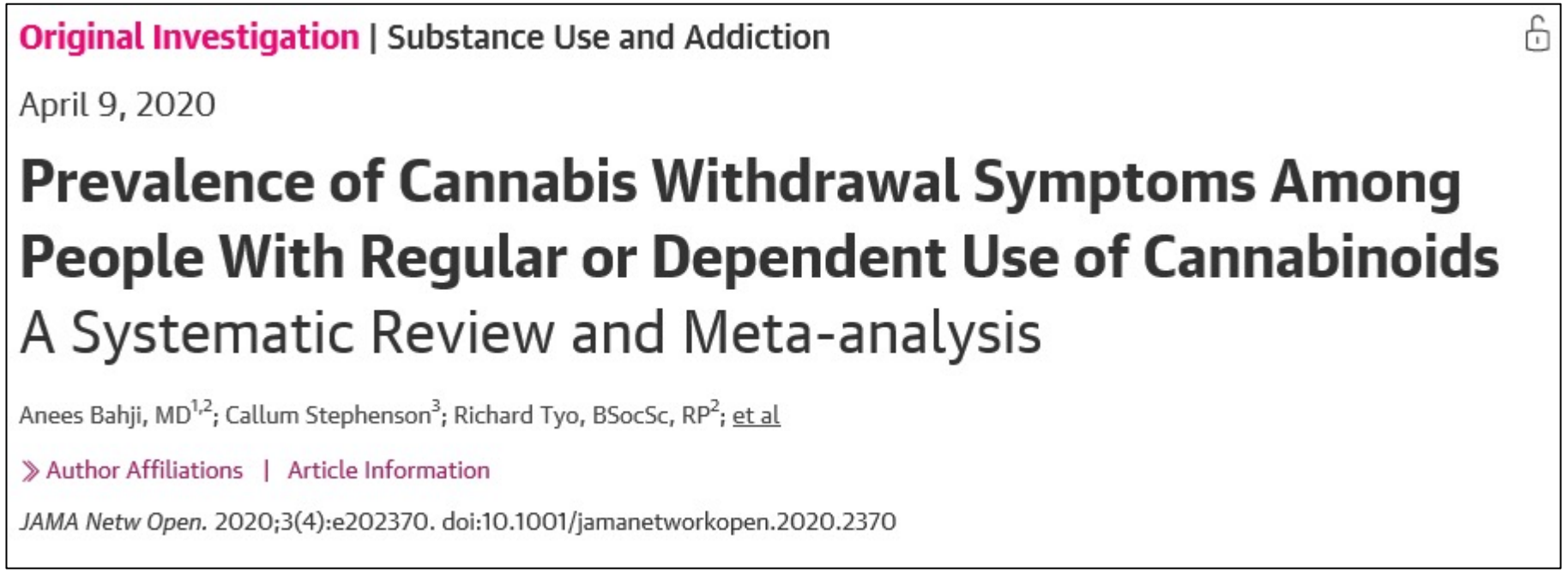
- Sudden onset of mood lability and paranoid symptoms, within 1 week of use but as early as 24 hours after use

- Commonly precipitated by a sudden increase in potency
  - THC percentage
  - THC consumption quantity

- THC: long half-life (30 day elimination) and lipophilicity

Grewal. *Psychiatric Times*. July 14, 2017. https://www.cannabisskunksense.co.uk/uploads/site-files/Psychiatric_Times_-_Cannabis-Induced_Psychosis_A_Review_-_2017-07-14.pdf

Cannabis Withdrawal



Original Investigation | Substance Use and Addiction

April 9, 2020

Prevalence of Cannabis Withdrawal Symptoms Among People With Regular or Dependent Use of Cannabinoids

A Systematic Review and Meta-analysis

Anees Bahji, MD[1,2]; Callum Stephenson[3]; Richard Tyo, BSocSc, RP[2]; et al

» Author Affiliations | Article Information

JAMA Netw Open. 2020;3(4):e202370. doi:10.1001/jamanetworkopen.2020.2370

- 23,518 participants
- 47% prevalence of cannabis withdrawal syndrome

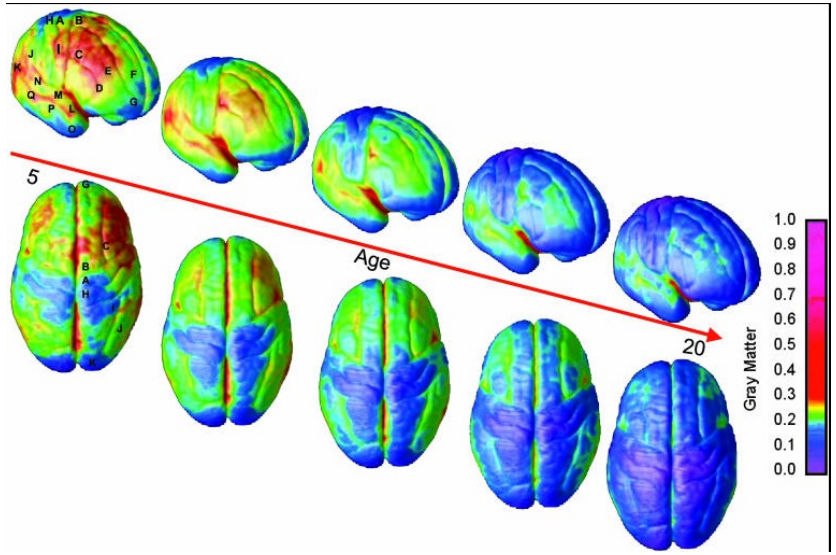
Human Brain Development Peak
25 Years of Age

FOR IMMEDIATE RELEASE
August 29, 2019

Contact: HHS Press Office
202-690-6343
media@hhs.gov

Surgeon General Releases Advisory on Marijuana's Damaging Effects on the Developing Brain

Encourages Youth and Pregnant Women Not to Use Marijuana



Gogtay. *PNAS*. 2014;101(21):8174-8179.
www.hhs.gov/about/news/2019/08/29/surgeon-general-releases-advisory-marijuana-damaging-effects.html.

Parenting???


DAD
GRASS
FIVE PRE ROLLED CBD JOINTS
100% ORGANIC HEMP FLOWER
NET WT. 3.5G
PREMIUM
PREMIUM
Organic

Marijuana/Cannabis Research

- National Center for Natural Products Research (NCNPR)
  - University of Mississippi (sole source of federal research marijuana plants in US)
- Center for Medicinal Cannabis Research
- National Institute on Drug Abuse (NIDA)
- National Institutes of Health (NIH)
- Canadian Institutes of Health Research
- Canadian Consortium for the Investigation of Cannabinoids (CCIC)
- Medicinal Cannabis Research Foundation (MCRF in United Kingdom)
- clinicaltrials.gov/cannabis

American Society of Addiction Medicine (ASAM)

Medical Purpose Recommendations (2020)

1. Reschedule from Schedule 1
2. “Medical” products require FDA review and approval
3. Healthcare professionals training
4. Patient-clinician relationship required
5. Potential benefits outweigh potential harms
6. Do not recommend cannabis use for OUD
7. Health department oversight, and treated conditions not specified by legislature nor public referendum
8. PDMP marijuana reporting
9. Potency labeling
10. Discourage combustion or vaporization
11. Encourage research and FDA-approved cannabinoids, and expand research grade cannabis

American Society of Addiction Medicine (ASAM). Public Policy Statement on Cannabis. 2020

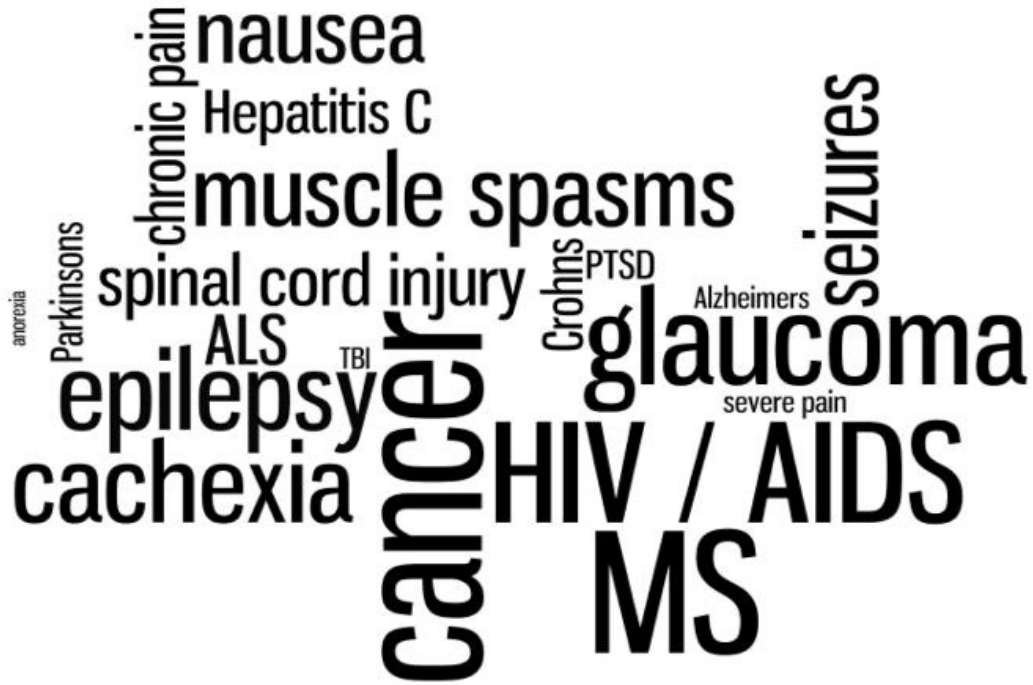
American Society of Addiction Medicine (ASAM)

Non-Medical Purpose Recommendations (2020)

1. Public health education efforts and avoid distribution to anyone under the age of 21
2. Decriminalize, civil fines and fees should be eliminated (instead utilize clinical referral)
3. Expungement for past minor cannabis-related convictions
4. CSA amendment
5. Use models other than commercialization, such as limiting production, marketing and sale
6. Strong public health-based regulatory framework
7. Health messages against use with mental illness and pregnancy, and warn of impaired driving risk
8. Limited potency
9. Substantial cannabis tax revenue percentage earmarked to fund prevention/mitigation of cannabis-related harm, substance use disorder prevention/treatment programs, and enforcement of laws
10. Healthcare professionals training
11. Avoid/discontinue use while pregnant or contemplating pregnancy
12. Pregnant women decide whether or not to provide consent for cannabis testing during labor and delivery
13. Future research

American Society of Addiction Medicine (ASAM). Public Policy Statement on Cannabis. 2020

Cannabinoid Possible Utilizations



Bestrashniy. *Psychol Addict Behav*. 2015;29(3):639-642.

PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

CANNABINOIDS

Cannabinoids and Pain Management

Mark Garofoli, PharmD, MBA, BCGP, CPE