ACLP DEBATE

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CLP 2018 DISCLOSURES FOR J. MICHAEL BOSTWICK, MD, ILANA BRAUN, MD & JOJI SUZUKI, MD

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HARVARD MEDICAL SCHOOL

DANA-FARBER CANCER INSTITUTE

IS IT LEGITIMATE TO SUBSTITUTE MEDICAL MARIJUANA FOR OPIOIDS IN PAIN MANAGEMENT?

IS MEDICAL MARIJUANA A LEGITIMATE ALTERNATIVE TO OPIOIDS FOR CHRONIC PAIN TREATMENT?

TO BE BLUNT, YES!

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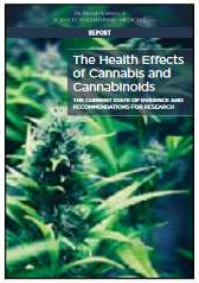
THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS

COMMITTEE'S CONCLUSIONS

January 2017



In the report *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*, an expert, ad hoc committee of the National Academies of Sciences, Engineering, and Medicine presents nearly 100 conclusions related to the health effects of cannabis and cannabinoid use.

The committee developed standard language to categorize the weight of the evidence regarding whether cannabis or cannabinoids used for *therapeutic* purposes are an effective or ineffective treatment for certain prioritized health conditions, or whether cannabis or cannabinoids used primarily for *recreational* purposes are statistically associated with certain prioritized health conditions. The box on the next page describes these categories and the general parameters for the types of evidence supporting each category.

The numbers in parentheses after each conclusion correspond to chapter conclusion numbers. Each blue header below links to the corresponding chapter in the report, providing much more detail regarding the committee's findings and conclusions. To read the full report, please visit **nationalacademies.org/CannabisHealthEffects.**

CONCLUSIONS FOR: THERAPEUTIC EFFECTS

There is conclusive or substantial evidence that cannabis or cannabinoids are effective for:
- For the treatment for chronic pain in adults (cannabis) (4-1)
- Antiemetics in the treatment of chemotherapy-induced nausea and vom
- For improving patient-reported multiple sclerosis spasticity symptoms (oral ca

There is moderate evidence that cannabis or cannabinoids are effective for:
- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obst
  syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-1

There is limited evidence that cannabis or cannabinoids are effective for:
- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
- Improving symptoms of posttraumatic stress disorder (nabilone; one single, small fair-quality trial) (4-20)

There is limited evidence of a statistical association between cannabinoids and:
- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are *ineffective* for:
- Improving symptoms associated with dementia (cannabinoids) (4-13)
- Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
- Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

There is conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of chronic pain in adults.

-The National Academies of Sciences, Engineering, and Medicine 2017 as quoted in the High Times magazine (jk)

THE BUDDING LITERATURE PUBLISHED SINCE THEN CONFIRM MEDICAL MARIJUANA'S EFFECTIVENESS FOR CHRONIC PAIN

- Nugent et al 2017 Annals of Internal Medicine
  - Systematic Review, included 27 chronic pain trials
  - "Low-strength evidence that cannabis alleviates neuropathic pain but insufficient evidence in other pain populations."
- Blake et al 2017 Annals of Palliative Medicine
  - Systematic Review, included 5 clinical studies examining THC of CBD on controlling cancer pain
  - "…evidence suggesting medical cannabis reduces chronic or neuropathic pain in advanced cancer patients. However, the results of many studies lacked statistical power."
- Aviram et al 2017 Pain Physician
  - Systematic Review, included 43 RCTs (2,437 patients), but 24 RCTs (1,334 patients) eligible for meta-analysis.
  - "Limited evidence showing more pain reduction in chronic pain (-0.61) especially by inhalation (-0.93) compared to placebo. Some studies shoe 30-50% or more improvement in pain scores, many studies showed no effect. The current systematic review suggests that cannabis-based medicines might be effective for chronic pain treatment, based on limited evidence, primarily for neuropathic pain."

MEDICAL MARIJUANA USERS REPORT OVERWHELMINGLY THAT IT HELPS WEED OUT PAIN AND RELIANCE ON OPIOIDS

- Corroon et al 2017 Journal of Pain Research
  - On-line survey of 2774 individuals in Washington state reporting cannabis use in the prior 90 days
  - 46% reported using MJ as a substitute for prescription medications (most commonly opioids)
- Boehnke et al 2016 Journal of Pain
  - Survey of 374 individuals receiving medical marijuana in Michigan.
  - 64% reduction in opioids use after initiation of cannabis… and associated with better quality of life in those with chronic pain, and fewer side effects, and fewer medications used.
- Sexton et al 2016 Cannabis and Cannabinoid Research
  - Survey of 1429 cannabis users in WA.
  - Pain most common reason for using cannabis (61.2%). On average reported 86% reduction in symptoms.
- Reiman et al 2017 Cannabis and Cannabinoid Research
  - Survey of 2897 medical cannabis users
  - 97% reported they are able to reduce their opioid consumption when they also use cannabis. 81% reported taking cannabis alone is ore effective at treating pain than combining cannabis with opioids.

STATES WITH MEDICAL MARIJUANA LAWS SAW OPIOID PRESCRIBING AND OPIOID-RELATED HOSPITALIZATIONS GO UP IN SMOKE

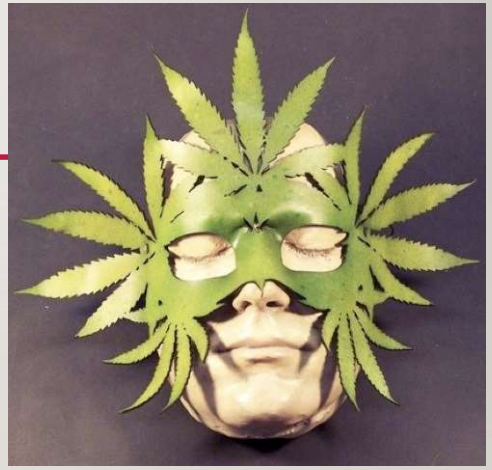
- Bachhuber et al 2014 JAMA
  - Examined opioid mortality in all US states including those that enacted medical marijuana laws.
  - States with medical marijuana laws had 24.8% lower mean annual opioid OD mortality rate (95% CI -37.5% to -9.5%, p=0.003).
  - "Medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates."
- Shi 2017 Drug and Alcohol Dependence
  - Examined hospitalizations related opioids in all US states.
  - Medical marijuana legalization was associated with 23% reduction in hospitalizations related to opioid use disorder, and 13% reduction in opioid pain reliever overdoses.
- Bradford et al 2018 JAMA
  - Examined opioid prescribing in all US states in Medicare Part D population
  - States with active dispensaries saw 3.7 million fewer daily opioid doses.
- Hen et al 2018 JAMA
  - Examined opioid prescribing in all US states in the Medicaid population
  - Implementation of medical marijuana laws associated with 5.88% lower opioid prescribing, and recreational laws associated with 6.38% lower opioid prescribing.

MARIJUANA IS NOT A BENIGN DRUG, BUT THE EVIDENCE JOINTLY SUGGESTS THAT THE BENEFITS OUTWEIGH THE RISKS:

- ….much safer than opioids
- ….effective for chronic pain (albeit evidence is still weak)
- ….can be used to reduce the reliance on opioids for chronic pain
- ….shown to reduce opioid overdoses and opioid-related hospitalizations in states that have cannabis laws
- …therefore a legitimate alternative to opioids for chronic pain treatment

IS IT LEGITIMATE TO ~~SUBSTITUTE~~ USE MEDICAL MARIJUANA ~~FOR~~ TO FIGHT THE OPIOID ~~IN PAIN MANAGEMENT~~ EPIDEMIC?

KNOCKING DOWN A REEFER MAN



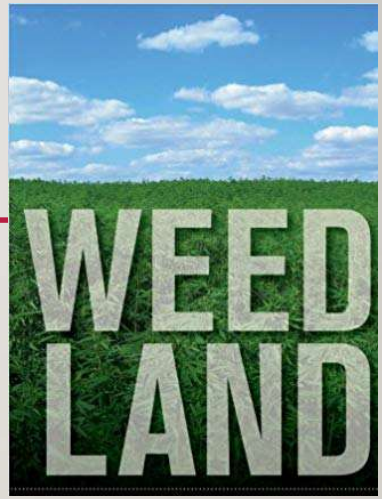
- No physician in the U.S. can legally prescribe medical marijuana (MM).
- First Amendment allow physicians to *recommend* MM.
- There is no agreement on what MM even is.
  - Is it homegrown weed – what Dupont called a 'crude chemical slush'?
  - Is it federally provided, Mississippi-grown research cannabis?
  - Is it state dispensary cannabis which can itself range from generic "by the bong" to manufactured "by the drop"?
  - Is it an FDA-approved pharmaceutical product – single-compound synthetics, single-compound purified plant material?
  - Is it whatever the user wants it to be?

GOOD FOR WHATEVER AILS YOU

- Whiting's 2015 meta-analysis cited 28 studies, finding "moderate evidence" for MM for "chronic pain" from cancer, neuropathies, fibromyalgia, MS, RA, etc. but NOT unspecified pain.
- MM users frequently have previous histories of recreational use and often continue to use cannabis recreationally, thus blurring medical and recreational boundaries.
- MM users claim benefit in the absence of RCTs for pain, depression, anxiety, nausea, psychosis, seizures, sleep disorders, you name it…
- Arguments for ORT (opioid replacement therapy) include:
  - MORTALITY — MML states have lower annual opioid-related death rates
  - ECONOMICS — Fewer insurance-covered opioid scripts for Medicare patients are written.
  - HARM REDUCTION — Unlike opioids, MM does not suppress brainstem respiratory centers.
  - SUBSTITUTION — Not just opioids but also benzo's, antidepressants, alcohol, other illicits

Lucas, Harm Reduction Journal 2017

FALLACIOUS REASONING

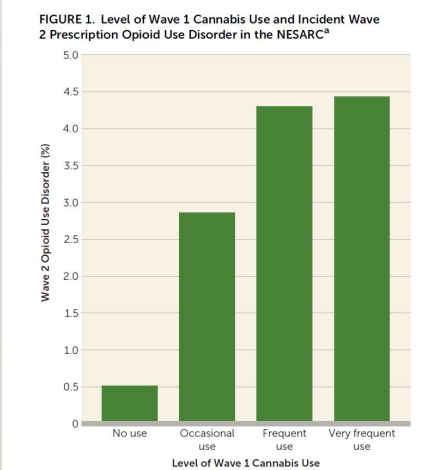


- The Ecological Fallacy
  - Assumption: Population-level data reflects individual use.
  - Fallacy #1 Population-level association explains individual-level causation.
  - Fallacy #2 Population-level data can tell us what individuals are doing.
- True
  - States with medical marijuana laws (MML) have lower opioid OD mortality rates, lower opioid-related hospitalizations, and reduced opioid prescribing.
  - Explanation could include greater awareness in MML states of dangers of opioid misuse, earlier detection of high-risk patients, more cautious opioid-prescription practices.
- False
  - Individuals in MML states are thus using less opioids, since they have access to medical marijuana.

"CANNABIS USE APPEARS TO INCREASE RATHER THAN DECREASE THE RISK OF DEVELOPING NONMEDICAL PRESCRIPTION OPIOID USE AND OPIOID USE DISORDER."

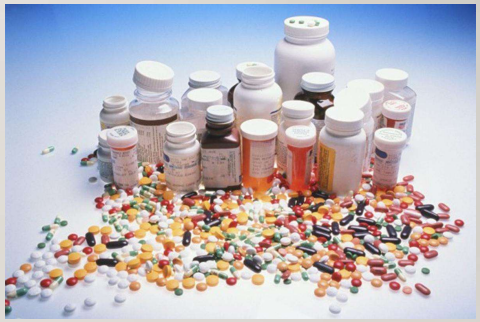
WOLFSON ET AL. AM J PSYCH 2018

- National Epidemiological Survey on Alcohol and Related Conditions of **INDIVIDUALS** ≥ 18 years old N = 34,653
- In non-opioid users
  - Wave 1 cannabis use is associated at wave 2 three years later with:
    - increased nonmedical prescription opioid use [OR = 5.78 (CI = 4.23-7.90)]
    - increased opioid use disorder [OR = 2.62 (CI = 1.96-2.62)]
- In pain patients
  - Wave 1 cannabis use is associated at wave 2 three years later with:
    - Increased nonmedical prescription opioid use: [adjusted OR = 2.99 (CI = 1;63-5.47)]
    - increased opioid use disorder [adjusted OR = 2.14 (CI = 0.95-4.83)]
- In opioid users
  - Wave1 cannabis use is associated at wave 2 three years later with:
    - increased nonmedical prescription opioid use [adjusted OR = 3.13 (CI = 1.19-8.23)]



"IF YOU'VE GOT 'EM, SMOKE 'EM!"

- National Survey on Drug Use and Health of **INDIVIDUALS** >12 years old N = 57,146
- MM users are significantly more likely to **use** prescription drugs.
  - any prescription drug [RR = 1.62 (CI 1.50-1.74)]
- MM users are significantly more likely to **abuse** prescription drugs.
  - any prescription drug [RR = 2.12 (CI = 1.67-2.62)]
    - pain relievers (including opioids) [RR = 1.95 (CI = 1.41-2.62)
    - stimulants [RR = 1.86 (CI = 1.09-3.02)]
    - tranquilizers [RR = 2.18 (CI = 1.45-3.16)]



- Conclusions: Providers should screen for prescription drug nonmedical use and have higher likelihood for suspicion of prescription drug abuse among their MM patients.

Caputi & Humphreys, J Addict Med 2018

ONE TOKE OVER THE LINE

- vulnerable populations
  - those with family h/o psychotic d/o, adolescents, the unborn
- potential problems
  - prenatal and unintentional childhood exposure (collateral damage)
  - decreased educational, occupational function from effects on adolescent brain
  - impaired driving and machinery use, increased MVAs and workplace accidents
  - cannabis use disorders, cannabis withdrawal, psychiatric comorbidity
- side effects
  - anti-nociception, sedation, hypotension, hypothermia, reduced intestinal motility, ataxia, etc.

SUBSTITUTE OR COMPANION?

- cannabinoid-opioid cross-talk
  - both belong to rhodopsin subfamily of g-coupled protein receptors
  - both localize to presynaptic terminals on GABA-ergic neurons
  - functional similarities between endogenous opioid and cannabinoid systems, with common final target of mesolimbic dopamine reward pathway
  - synergistic anti-nociceptive effects
    - opioids act on mu, THC on kappa and delta opiate receptors

    Robledo et al, Addiction Biology 2008
  - rates of cannabis use are high in opiate addicts, both prior history and current use
- It makes sense that both together could work better than either alone.

SINCE PHYSICIANS CANNOT PRESCRIBE, THIS DEBATE TOPIC IS ONLY THEORETICAL, BUT EVIDENCE SUGGESTS OPIATE ADDICTS WILL COMBINE MM AND OPIOIDS RATHER THAN SUBSTITUTE ONE FOR THE OTHER.

- …MM is safer than opioids – if breathing is the only measure – and if (and only if) opioids are dropped.
- …Users *say* MM works for pain NOS, but evidence remains weak and limited to specific pain conditions.
- …Population studies showing MM reduces opioid reliance mislead because of the Ecological Fallacy.
- …MM potentially replaces one addiction with another – or becomes a second addiction.
- …Remember the 5th Vital Sign debacle; if we had known then what we know now….

IS IT LEGITIMATE TO SUBSTITUTE MEDICAL MARIJUANA FOR OPIOIDS IN PAIN MANAGEMENT?