Cannabis and Health

Module 6

Lecture 5: Cannabis and Opioid Use Disorder

The Opioid Epidemic and Cannabis

- Can cannabinoids be used to address opioid epidemic?
  - Pain management is central to opioid epidemic
  - Reviews indicate that cannabis products are effective at reducing experience of pain (see NAS review)
  - Studies of prescription data suggest people are substituting cannabis for prescription pain medication
  - Cross sectional studies suggest people report that cannabis is effective substitute for opioids
  - Experimental studies (animal and human) suggest opioid sparing effect
  - No gold standard studies but enough evidence to suggest that we need some!
- Or might cannabinoids make opioid use disorder worse?

States with active dispensaries: 3.742 million fewer daily doses

Table 1. Daily Doses Prescribed for All Opioids[a]

Variable[b]	Coefficient (95% CI)[c]	Percentage Change	*P* Value
Modeling any type of MCL as 1 variable			
MCL in effect	−2.211 (−4.574 to 0.152)	−8.5	.06
Modeling MCL by type with separate variables			
Medical cannabis dispensary open	−3.742 (−6.289 to −1.194)	−14.4	.005
Medical cannabis home cultivation allowed	−1.792 (−3.532 to −0.052)	−6.9	.04

Abbreviation: MCL, medical cannabis law.

[a] There were 306 observations for each model. Ordinary least-squares regression coefficients from models in which the dependent variables are total opioid prescriptions. Percentage changes from the average "no MCL" state level of prescribing are in parentheses. Data are aggregated to all prescriptions in opioid category by state and year.

[b] The MCL coefficient from a model in which MCL is measured as being any type. Variables included in all models but not shown in this table: whether state has adopted legal recreational cannabis, whether the state has an operational electronic prescription drug monitoring program; Herfindahl index of physician market competition, percentage of the population below the poverty line, percentage of population enrolled in Medicare, percentage of Medicare in Medicare Advantage plans, total state population, a time trend, and state fixed effects.

[c] MCL coefficients from a model in which dispensary-based or home cultivation only MCLs are measured separately.

May 2018

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

Ashley C. Bradford, BA[1]; W. David Bradford, PhD[1]; Amanda Abraham, PhD[1]; et al

» Author Affiliations

JAMA Intern Med. 2018;178(5):667-672. doi:10.1001/jamainternmed.2018.0266

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

Marcus A. Bachhuber, MD[1,2,3]; Brendan Saloner, PhD[3,4]; Chinazo O. Cunningham, MD, MS[5]; et al

» Author Affiliations | Article Information

JAMA Intern Med. 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005

Cannabis is already being used to reduce opiates

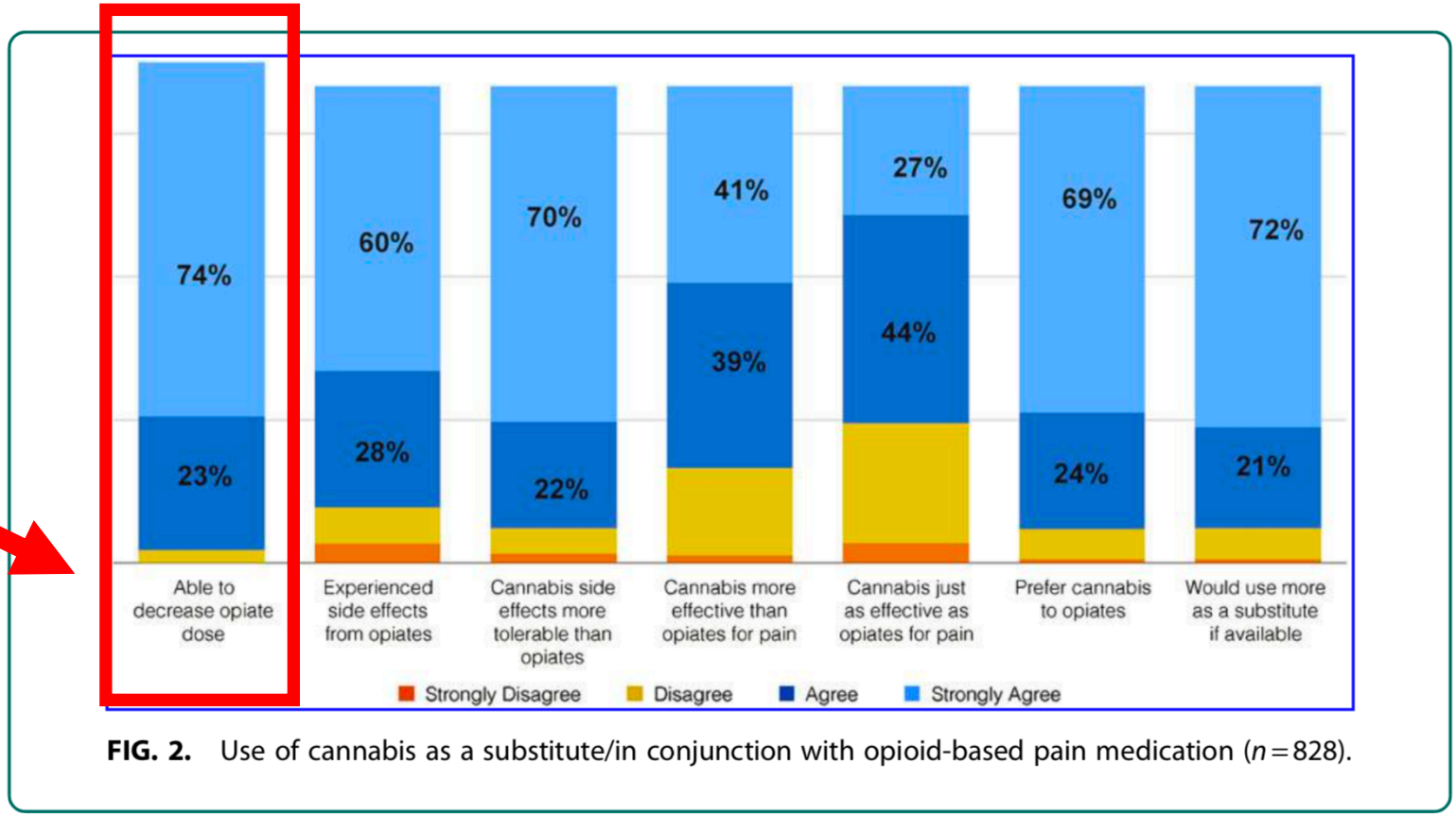


FIG. 2. Use of cannabis as a substitute/in conjunction with opioid-based pain medication ($n = 828$).

Cannabis as a Substitute for Opioid-Based Pain Medication: Patient Self-Report

Amanda Reiman,[1,*] Mark Welty,[2] and Perry Solomon[3]

RESEARCH ARTICLE

Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study

Jacob M. Vigil[1]*, Sarah S. Stith[2], Ian M. Adams[3], Anthony P. Reeve[3]

1 University of New Mexico, Department of Psychology, Albuquerque, New Mexico, United States of America, **2** University of New Mexico, Department of Economics, Albuquerque, New Mexico, United States of America, **3** Industrial Rehabilitation Clinics, Albuquerque, New Mexico, United States of America

* vigilj@unm.edu

Table 1. Effect of MCP enrollment on opioid prescription patterns (Means comparison).

Variable (N = 66)	Comparison (N = 29)	MCP (N = 37)	P Value
Ceased opioid prescriptions {0,1}	3.4% (1)	40.5% (15)	<0.001
Reduced prescribed daily opioid dosage {0,1}	44.8% (13)	83.8% (31)	0.001
Average daily opioid dosage in the 1st 3 months (mg)	16.2 ± 14.8	24.4 ± 23.3	0.103
Average daily opioid dosage in the last 3 months (mg)	12.3 ± 12.4	12.4 ± 20.1	0.974
Change in prescribed daily opioid dosage (mg)	-3.9 ± 13.2	-12.0 ± 23.4	0.101
Percentage point change in prescribed daily opioid dosage	10.4 ± 114.9	-47.0 ± 63.1	0.013
Male	54.1% (20)	69.0% (20)	0.219
Age	59.7 ± 13.8	53.6 ± 9.5	0.036

Table 3. Survey responses at one year Post-MCP enrollment.

Variable	N	Mean ± SD	Min	Max	Null Hypothesis	P Value
Pain reduction from Cannabis usage (Yes = 1/No = 0)	34	0.97 ± 0.17	0	1	Pain reduction = 0	<0.001
Pain prior to Cannabis Program (0 to 10)	34	8.6 ± 1.4	4	10	Pain prior = 0	<0.001
Pain after Cannabis Program (0 to 10)	34	5.3 ± 1.7	2	10	Pain post = 0	<0.001
Change in pain (pain post—pain prior)	34	-3.4 ± 2.1	-7	3	Change< = 0	<0.001
Side effects from Cannabis usage (Yes = 1/No = 0)	34	0	0	0	Side effects = 1	.

Notes: Yes/No responses were coded as yes = 1, no = 0. Pain scale ranges from 0 (pain free) to 10 (worst pain).One-sided t-tests were performed for ranked variables, and chi-squared tests were used for yes/no responses.

https://doi.org/10.1371/journal.pone.0187795.t003

Neuropsychopharmacology

ARTICLE

Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability

Ziva D. Cooper[1], Gillinder Bedi[2], Divya Ramesh[3], Rebecca Balter[1], Sandra D. Comer[1] and Margaret Haney[1]

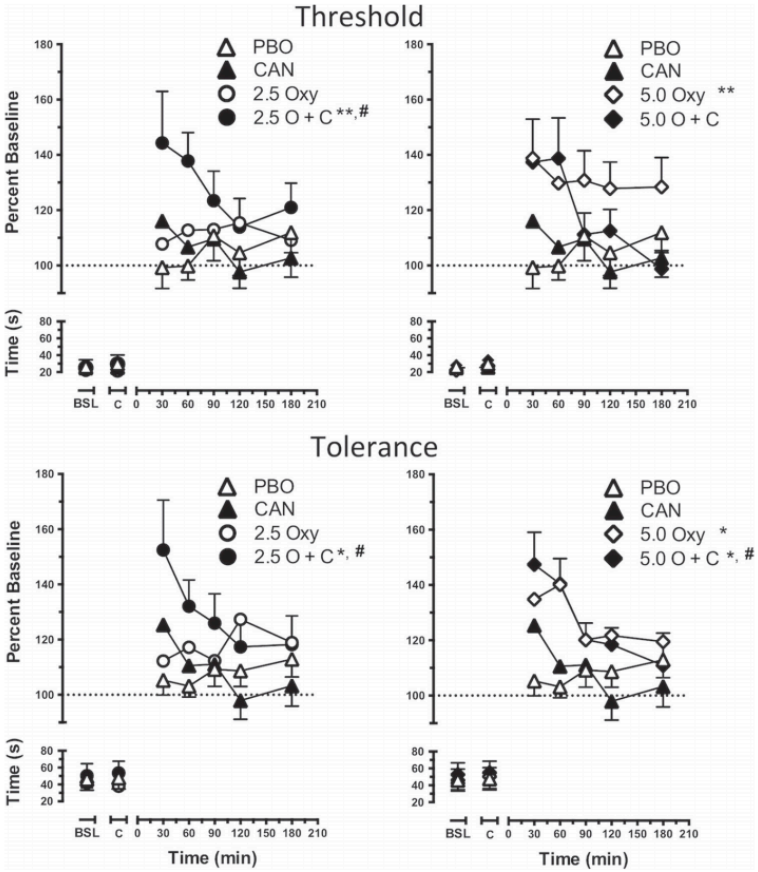


Fig. 1 Cold Pressor Task pain threshold (top panels) and tolerance (bottom panels) as calculated by percent baseline latency (seconds) to report pain and withdraw the hand from cold water. Data are presented as mean values +/- SEM according to cannabis strength, oxycodone dose (2.5 mg, left panels; 5.0 mg, right panels), and time. Placebo oxycodone + inactive cannabis condition = PBO; placebo oxycodone + active cannabis condition = CAN; 2.5 mg oxycodone + inactive cannabis condition = 2.5 Oxy; 2.5 mg oxycodone + active cannabis condition = 2.5 O + C; 5.0 mg oxycodone + inactive cannabis condition = 5.0 Oxy; 5.0 mg oxycodone + active cannabis condition = 5.0 O + C. Baseline response is shown as BSL on the x-axis; response after oxycodone is indicated by C on the x-axis. Significant differences from placebo are indicated by $^{*}p \leq 0.05$ and $^{**}p \leq 0.01$; significant differences from active cannabis alone are indicated with $^{\#}p \leq 0.05$

The Opiate Epidemic and Cannabis

- Can cannabinoids be used to address opioid epidemic?
- Or might cannabinoids make opioid use disorder worse?

The Two Studies Often Cited by Detractors

- National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Olfson et al., 2018)
  - Cannabis use at Wave I associated with non-prescription OUD at Wave 2
  - Number of methodological concerns
  - It makes sense that people who use drugs recreationally to get high at time 1 might be more at risk for OUD
  - But irrelevant to question about whether chronic pain patients can use cannabis medicinally as a substitute for opioids

Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States

Mark Olfson, M.D., M.P.H.[1], **Melanie M. Wall, Ph.D.**[1], **Shang-Min Liu, MS**[1], and **Carlos Blanco, M.D., Ph.D.**[2]

[1]Department of Psychiatry, New York State Psychiatric Institute / Columbia University, New York, NY 10032

[2]Division of Epidemiology, Services, and Prevention Research, National Institute on Drug Abuse, Bethesda, MD 20892

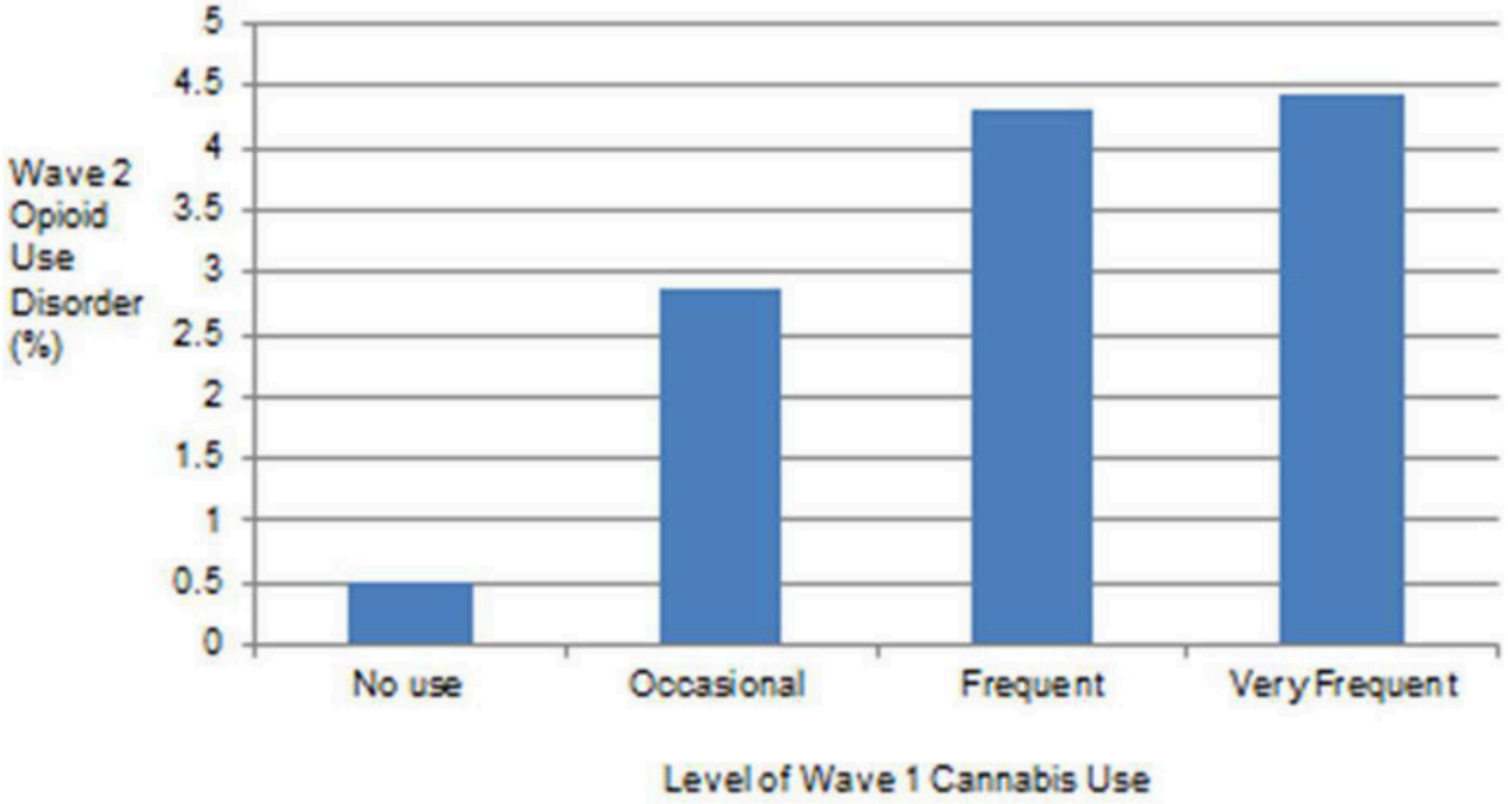
Abstract

Objective—To determine whether cannabis use is associated with a change in the risk of incident nonmedical prescription opioid use and opioid use disorder at 3 year follow-up.

Methods—We used logistic regression models to assess prospective associations between cannabis use at Wave 1 (2001–2002) and nonmedical opioid use and prescription opioid use disorder at Wave 2 (2004–2005) of the National Epidemiologic Survey on Alcohol and Related Conditions. Corresponding analyses were performed among adults with moderate or more severe pain and with nonmedical opioid use at Wave 1. Cannabis and prescription opioid use were measured with a structured interview (AUDADIS-IV). Other covariates included age, sex, race/ethnicity, anxiety or mood disorders, family history of drug, alcohol, and behavioral problems, and in opioid use disorder analyses, nonmedical opioid use.

Results—In logistic regression models, Wave 1 cannabis use was associated with increased incident non-medical prescription opioid use (OR=5.78, 95%CI=4.23–7.90) and opioid use disorder (OR=7.76, 95%CI=4.95–12.16) at Wave 2. These associations remained significant following adjustment for background characteristics (non-medical opioid use: AOR=2.26, 95%CI=1.86–3.69; opioid use disorder: AOR=2.18, 95%CI=1.14–4.14). Among adults with pain at Wave 1, cannabis use was also associated with increased incident non-medical opioid use (AOR=2.99, 95%CI=1.63–5.47) and approached significance with incident prescription opioid use disorder (AOR=2.14, 95%CI=0.95–4.83). Among adults with nonmedical opioid use at Wave 1, cannabis use was also associated with an increase in non-medical opioid use (AOR=3.13, 95%CI=1.19–8.23).

Conclusions—Cannabis use appears to increase rather than decrease the risk of developing nonmedical prescription opioid use and opioid use disorder.


Wave 2 Opioid Use Disorder (%)
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
No use
Occasional
Frequent
Very Frequent
Level of Wave 1 Cannabis Use

The Second Study Often Cited by Detractors

- Australian study of chronic pain patients between 2012 and 2014 (Campbell et al., 2018)
  - Cannabis use was not associated with reductions in pain or opioid use
  - Did NOT find that cannabis use increased opioid use
  - Medical cannabis not legalized in Australia until 2016 so this was black market cannabis – unclear about the dose, route of administration
  - Unlikely that there was any CBD in it
  - Unlikely that much of it was oral formulation

Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study

Gabrielle Campbell, Wayne D Hall, Amy Peacock, Nicholas Lintzeris, Raimondo Bruno, Briony Larance, Suzanne Nielsen, Milton Cohen, Gary Chan, Richard P Mattick, Fiona Blyth, Marian Shanahan, Timothy Dobbins, Michael Farrell, Louisa Degenhardt

Summary

Background Interest in the use of cannabis and cannabinoids to treat chronic non-cancer pain is increasing, because of their potential to reduce opioid dose requirements. We aimed to investigate cannabis use in people living with chronic non-cancer pain who had been prescribed opioids, including their reasons for use and perceived effectiveness of cannabis; associations between amount of cannabis use and pain, mental health, and opioid use; the effect of cannabis use on pain severity and interference over time; and potential opioid-sparing effects of cannabis.

Methods The Pain and Opioids IN Treatment study is a prospective, national, observational cohort of people with chronic non-cancer pain prescribed opioids. Participants were recruited through community pharmacies across Australia, completed baseline interviews, and were followed up with phone interviews or self-complete questionnaires yearly for 4 years. Recruitment took place from August 13, 2012, to April 8, 2014. Participants were asked about lifetime and past year chronic pain conditions, duration of chronic non-cancer pain, pain self-efficacy, whether pain was neuropathic, lifetime and past 12-month cannabis use, number of days cannabis was used in the past month, and current depression and generalised anxiety disorder. We also estimated daily oral morphine equivalent doses of opioids. We used logistic regression to investigate cross-sectional associations with frequency of cannabis use, and lagged mixed-effects models to examine temporal associations between cannabis use and outcomes.

Findings 1514 participants completed the baseline interview and were included in the study from Aug 20, 2012, to April 14, 2014. Cannabis use was common, and by 4-year follow-up, 295 (24%) participants had used cannabis for pain. Interest in using cannabis for pain increased from 364 (33%) participants (at baseline) to 723 (60%) participants (at 4 years). At 4-year follow-up, compared with people with no cannabis use, we found that participants who used cannabis had a greater pain severity score (risk ratio 1·14, 95% CI 1·01–1·29, for less frequent cannabis use; and 1·17, 1·03–1·32, for daily or near-daily cannabis use), greater pain interference score (1·21, 1·09–1·35; and 1·14, 1·03–1·26), lower pain self-efficacy scores (0·97, 0·96–1·00; and 0·98, 0·96–1·00), and greater generalised anxiety disorder severity scores (1·07, 1·03–1·12; and 1·10, 1·06–1·15). We found no evidence of a temporal relationship between cannabis use and pain severity or pain interference, and no evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation.

Interpretation Cannabis use was common in people with chronic non-cancer pain who had been prescribed opioids, but we found no evidence that cannabis use improved patient outcomes. People who used cannabis had greater pain and lower self-efficacy in managing pain, and there was no evidence that cannabis use reduced pain severity or interference or exerted an opioid-sparing effect. As cannabis use for medicinal purposes increases globally, it is important that large well designed clinical trials, which include people with complex comorbidities, are conducted to determine the efficacy of cannabis for chronic non-cancer pain.

Hypothetical Mechanisms?

- May work synergistically on pain at the level of the CB1 and OPRM1 receptor to enhance effect of opiate (i.e., opiate sparing)
- May work additively through separate mechanisms or may substitute for pain control
- May work by reducing withdrawal symptoms, anxiety, and craving
- May work by enhancing sleep or through other indirect mechanisms

Summary

- Data suggest cannabis products can be effective in treatment of pain
- Data suggest that people are already using cannabis to treat pain and to reduce opioids
- Prescription studies suggest these effects actually lead to reductions in opioid use
- Clearly, it is time for a clinical study on whether cannabis products can address opioid misuse