Medical Cannabis and Opioid-related Deaths:
What is the Evidence?

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As the death toll of the US opioid epidemic increases, so does the search for ways to curb opioid use initiation, reduce misuse, prevent overdoses, and effectively treat those already experiencing opioid use disorder (OUD). Among the many approaches debated is the possible role of cannabis and policies that expand access to and use of cannabis, on decreasing opioid use, overdose, and associated mortality.

This brief reviews available studies on this topic, their caveats and limitations, and summarizes the implications of their findings. The review looks first at studies on medical marijuana policies and opioid-associated mortality at the population level, and secondly at research on cannabis substitution for opioid-based medications at an individual level.
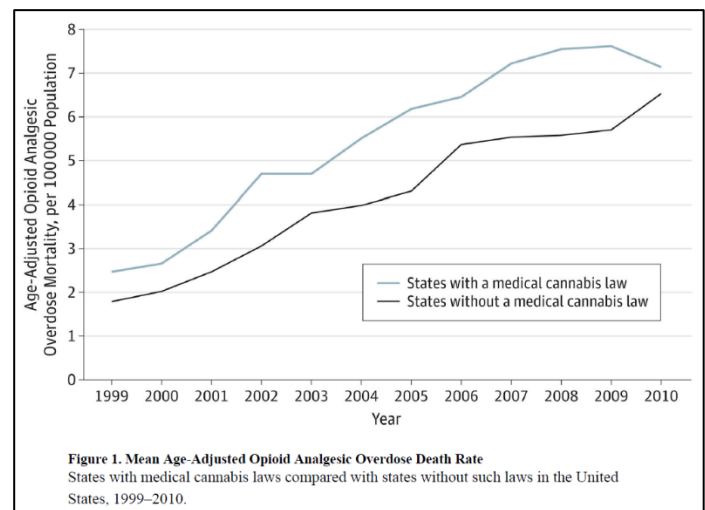
Medical cannabis laws and opioid overdose

The most comprehensive study to date on medical cannabis (MC) laws and opioid overdose was by Bachhuber et al (2014), published in the prestigious journal *JAMA Internal Medicine*. The authors compared opioid analgesic annual overdose mortality from 1999 to 2010 in US states with and without legal access to medical cannabis.

They found that from 1999 to 2010, overdose mortality due to opioid analgesic medication reached a plateau in states with MC laws while it continued to increase in states with no such laws (Figure 1).

This seminal article has been used by the pro-legalization community to promote cannabis as the solution to the opioid crisis and to suggest that cannabis can be used to wean people off opioids (indirectly preventing mortality). From a scientific-academic perspective, the findings of this article do not support such claims.

The chart below summarizes the study's findings and lists reasons why the claims described are not supported by the study data.

Figure 1. Mean Age-Adjusted Opioid Analgesic Overdose Death Rate
States with medical cannabis laws compared with states without such laws in the United States, 1999–2010.

Main Findings by Bachhuber et al (2014)
• Throughout the study period, US States with MC laws had higher opioid analgesic overdose mortality rates.
• Between 2009 and 2010 overdose mortality due opioid analgesic medication reached a plateau in states with MC laws while it continued to increase in states with no such laws.
• MC states had a 24.8% lower pharmaceutic opioid overdose mortality compared to no-MC states.
• Decline in opioid overdose mortality was accentuated the longer the marijuana policy was in effect.

| Does this study support the claim that "Cannabis legalization can solve the opioid crisis"? |
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No, it does not.

- The study is focused on mortality caused by **opioid analgesics**. The authors warn that "a connection between medical cannabis laws and opioid overdose mortality among individuals who misuse or abuse opioids is less clear."

- The study focus exclusively on MC laws; data are through 2010, before the existence of any state law legalizing non-medical use of cannabis.

- Policy studies are "real world" analysis, making it hard to control for other factors that might explain the association between MC laws and decreased mortality. While the authors control for the existence of Prescription Drug Monitoring Programs, they recognize that many other "time- and state-varying confounders were not included in the model." That is, there may be an association across time, but not a direct cause and effect relationship.

Does this study support the claim that "Cannabis can be used to wean people off opioids"?

No, it does not.

- This study uses an **ecological design**, meaning the data describes a group (everyone in a state) as a whole; ecological studies are often used to understand policies' impact on health.

- Findings at a group level often do not hold true at an individual level. This kind of erroneous assumption is termed ecological fallacy (Figure 2 from Check & Schutt (2012).

- In the case in point, one cannot assume that the individuals who did not overdose from opiates in states with MC policies were in fact using medicinal cannabis. The data of the study only support the association of a policy (MC) with a health outcome (mortality) at a state level.

- Studies that generate information at the level of individuals are necessary to explore the potential of cannabis to wean people off opioids (see next section)
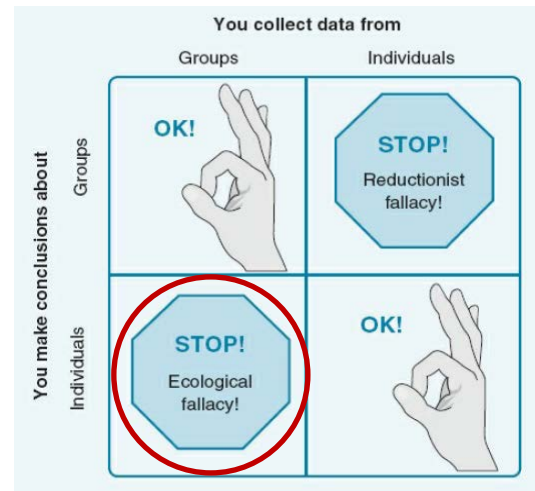
Does this study have little merit and make misleading statements?

No. This is a well-conducted study using an accepted approach to evaluate the impact of public policies on health outcomes.

- The authors are very careful on their considerations and did not suggest at any point that their findings were causal or could be valid at a individual level.

- The authors employed a longitudinal ecologic design, meaning they analyzed 11 years of data in 50 US states over time, with and without MC laws. They used different models to analyze the data, and excluded suicides (intentional overdose). They also tested if their results were still valid after including heroin mortality in the model and found no difference.

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Implications of the Bachhuber study:

The correlation between MC laws and lower opioid analgesic mortality can be considered a first step in better understanding MC policies. Additional studies have been published pointing in the same direction as Bachhuber. Two recent ecologic design studies found a correlation of MC laws and lower rates of prescriptions for opioid analgesic medications in two publicly-funded programs -- Medicare (Bradford & Bradford, 2016) and Medicaid (Wen & Hockenberry, 2018) -- when compared with states without MC legislation. Phillips and Gazmararian (2017) analyzed the role of Prescription Drug Monitoring Programs (PDMP) in conjunction with medical marijuana legislations from 2011 to 2014 and found that the combination of PDMP and MC laws combined were likely more effective in reducing opioid mortality than PDMP alone, suggesting a synergistic interaction between the two policies.

Studies using other research designs are needed to flesh out the role of other plausible factors before concluding that MC laws per se are a significant factor in reducing mortality of pharmaceutical opioids. States also vary widely in terms of evidence-based approaches to opioid overdose mortality, such as availability of medications for opioid use disorder, Good Samaritan Laws, and distribution of naloxone.

Maybe even more importantly, research is needed to explore possible correlations between MC laws and heroin and, more recently, illicit fentanyl use. The correlation detected in the studies available to date is exclusively between MC laws and opioid analgesic medication mortality.

Cannabis substitution for opioid-based medications at an individual level

As mentioned above, to generate information that can be applied to individuals, studies need to be done at the individual level and ideally follow people over time. The handful of studies described below focus on individuals reporting use of medical cannabis (MC patients).

Bruce et al (2017) conducted semi-structured interviews with a sample of 30 MC patients recruited through flyers distributed in MC dispensaries. Using qualitative analysis they identified three main patterns of MC use: alternative/replacement, complimentary/combination, or as a tapering-off mechanism to prescribed opioid medications. Specific reasons to use MC as alternative to opioids included feeling the effects more quickly, reducing potential harm, better management of symptoms, and fewer side effects. Corroon et al (2017) utilized an online questionnaire to survey a convenience sample of 1,248 self-selected cannabis users. About half of them (46%) reported using cannabis as a substitute for prescription drugs; the most frequent substitution was "narcotics/opioids" (35.8%). Reiman et al (2017) examined the use of cannabis as a substitute for opioid-based medication in an online survey of 2897 cannabis patients recruited through Hello MD, a California-based MC patient database. Thirty percent of the sample (n=841) reported using an opioid-based pain medication currently or in the past 6 months, 61% of them with cannabis.

> Many MC patients indicate that they have substituted all or some of their prescribed opiate-based medications with cannabis. This finding, while important, is specific to a group of opiate analgesic users: those comfortable using cannabis and who find benefit from its use.

The vast majority of these patients (97%) reported using less opioids when using cannabis, and experienced more tolerable side effects with cannabis than with opioid medications alone (92%). They also reported preferring cannabis to opioids for the treatment of their condition and would consider choosing only cannabis if it was more readily available (93%). Boehnke et al (2016) conducted another online survey with 244 MC patients recruited from MC dispensaries in Michigan. Patients reported that MC use was associated with decreased opiate medication use, reported improvement in quality of life, and a better side effect profile. In Canada, two online surveys (n= 473 and n=271) among MC adults (Lucas et al, 2016; Lucas & Walsh, 2017)

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found that substituting cannabis for prescription drugs was common and that the most frequent substitution was for opioid medications.

These studies of individual users of medical cannabis, while important, use cross-sectional designs, meaning they do not follow people over time, so do not allow for the determination of the order of events. An important caveat of these studies is that they do not use random samples, so do not allow for generalization beyond MC patients who are willing to share their experience with cannabis; in other words, these studies present a self-selection bias because they rely on self-selected samples.

Only one study so far (Vigil et al 2017) followed people longitudinally, making it possible to identify individuals' outcomes over time. This study followed 66 patients with a diagnosis of "severe chronic pain" validated by two independent physicians, including a board-certified specialist (APR); all patients were habitual users of prescribed opioid medications. The clinic where the study took place offered all 66 patients the opportunity to enroll in a medical cannabis program and followed them for 21 months after this opportunity. Those who accepted MCP enrollment (n=37) were compared with those who declined (n=29) in terms of their self-reported quality of life, functionality levels, and pain. Their PDMP data was used to determine opioid prescription utilization. By the end of the observation period, 40.5% of MC patients and 3.4% of non-MC patients ceased opioid prescriptions. Reduction in opioid dosages was also observed: MC enrollees presented a 47% reduction in daily dosages, while non-MC enrollees increased their daily doses by 10.4%. Results were significant after controlling for other variables, using regression analysis. MC program participants also indicated improvements in pain reduction, quality of life, social life, activity levels and concentration, and few side effects from using cannabis one year after enrolling in the MC program. This study – while small - suggests benefits to chronic pain sufferers who are willing to utilize cannabis as a medication, but presents the same limitations of the studies above – it cannot be generalized beyond MC patients.

Final considerations

A recent review by the National Academy of Sciences (2017) analyzed 42 good-quality randomized controlled trials and concluded that there is strong evidence that <u>cannabinoids are efficacious in reducing chronic pain</u>, even if this effect is relatively modest (Carlini, 2018). These findings lend legitimacy to the social movements asking for expansion of medical cannabis access through state-regulated mechanisms and for the claim of many chronic pain sufferers that

> A potential issue on giving premature emphasis to medicinal cannabis policies as a tool to reduce opioid deaths is to minimize the importance of effective policies already in place.

they find relief when using cannabis. Policies to expand access to MC for chronic pain patients are based on science, despite the limitations of the cannabis products available in the US. The illegality of cannabis under federal regulation is an impediment to research and to the development of standardized cannabinoid medications that would be available in pharmacies and covered by insurance, as is the case in more than 40 countries worldwide.

Cannabis' effectiveness in treating pain, however, does not necessarily imply that the solution for opioid-overdose mortality relies on cannabis policies. <u>While research suggests that MC policies might be helpful, there is not enough evidence to date to support that claim</u>. Solid scientific knowledge takes many years to develop – it depends on the ability to employ strong research designs, representative samples, and have long follow-ups. The need for more funding and fewer barriers to conduct studies on the benefits and risks of cannabis use cannot be overstated.

A potential risk of emphasizing medical cannabis policies as a way to reduce opioid deaths is that it minimizes the importance of effective policies already in place. As stated by Wayne Hall et al (2018): "Given the limitations of the evidence, it is premature to recommend the expansion of access to medical cannabis as a policy to

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reduce opioid overdose risks in the United States and Canada. The premature adoption of this could displace policies for which there is far better evidence of effectiveness in reducing opioid overdose deaths; namely, increasing access to methadone- and buprenorphine-assisted treatment for opioid dependence; reducing rates of imprisonment for opioid possession and low-level dealing; and distributing naloxone to users and family members to reverse opioid overdoses."

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