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Does medical cannabis use increase or decrease the use of opioid analgesics and other prescription drugs?

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Abstract

In observational and retrospective studies, people who use cannabis are more likely than people who do not use cannabis to also use other drugs. People who take medical cannabis are also more likely to report medical and non-medical use of opioid analgesics, stimulants, and tranquilizers. Given that people who take medical cannabis and those who do not are likely to have different underlying morbidity, it is possible that medical cannabis use reduces prescription drug use yet prescription drug use remains relatively high. Studies comparing people who take medical cannabis with people who do not take it cannot draw conclusions about the effect of medical cannabis on drug use. To fully understand the effect of medical cannabis on the use of other drugs, prospective longitudinal studies randomizing individuals to cannabis versus other treatments are urgently needed.

Keywords

Medical Cannabis; Opioid Analgesics; Prescription Drug Misuse

As of February 2018, 29 states and the District of Columbia had passed laws legalizing cannabis for certain qualifying medical conditions, and nine states and the District of Columbia had broadly legalized cannabis for purchase by adults age 21 years and older. Since 1996, when California became the first state to pass a medical cannabis law, the United States has experienced a dramatic surge in opioid analgesic prescribing and its resulting harms such as misuse, use disorder, and overdose. Given that people take both cannabis and opioids to treat pain, is there a connection?

In observational and retrospective studies, people who use cannabis are more likely than people who do not use cannabis to use other drugs also (National Academies of Sciences Engineering and Medicine 2017). Specifically with respect to opioids, cannabis use is associated with opioid analgesic misuse and use disorder (Fiellin et al. 2013, Olfson et al.

2018). However, more information is needed about the relationships between *medical* cannabis use and the use of opioid analgesics and other drugs.

In this issue of the *Journal*, Caputi and Humphreys report a detailed analysis of medical and non-medical use of prescription drugs among people taking medical cannabis. In a cross-sectional study using the nationally-representative National Survey on Drug Use and Health, they examine use of opioid analgesics as well as use of stimulants, sedatives (e.g., hypnotics such as zolpidem), and tranquilizers (e.g., benzodiazepines and muscle relaxants). They find that, compared with people who do not take medical cannabis, people who report taking medical cannabis are more likely to also report any use of these prescription drugs (medical, non-medical, or both) as well as non-medical use of opioid analgesics, stimulants, and tranquilizers. Because chronic pain is the qualifying condition for most people who take medical cannabis, these findings raise concern about harmful outcomes among people with chronic pain.

Caputi and Humphreys' study is important and timely as cannabis legalization continues to expand in the United States. But do their findings indicate that medical cannabis use *causes* more prescription drug use?

In January 2017, the National Academies of Sciences, Engineering, and Medicine released a landmark report on the health effects of cannabis that found "substantial evidence" that cannabis is an effective treatment for chronic pain in adults (National Academies of Sciences Engineering and Medicine 2017). People taking medical cannabis consistently report substituting cannabis for other prescription and illicit drugs (Reiman 2009, Corroon et al. 2017, Lucas and Walsh 2017, Piper et al. 2017, Reiman et al. 2017, Vigil et al. 2017). In one survey, people taking medical cannabis reported decreasing opioid analgesic use by 64% (Boehnke et al. 2016). Substitution may explain the state-level findings that medical cannabis laws are associated with relatively lower rates of analgesic prescribing in both Medicare Part D and Medicaid over time (Bradford and Bradford 2016, Bradford and Bradford 2017). Although, as noted by Caputi and Humphreys, one cannot draw conclusions about patient-level relationships between medical cannabis and opioid analgesic use from physician- and state-level analyses.

But, if medical cannabis potentially reduces prescription drug use, what explains Caputi and Humphreys' findings? Even if medical cannabis leads to reductions in opioid and other prescription drug use, the level of prescription drug use in people who take medical cannabis may remain relatively high. In other words, when examined at a single point in time, the overall level of prescription drug use among people who take medical cannabis will still be higher than the level of prescription drug use among people who do not take medical cannabis, even though people taking medical cannabis may reduce their prescription drug use after starting medical cannabis.

A hypothetical illustration with two people helps demonstrate this point. Person A is selected from the population of those who take medical cannabis. He has severe chronic pain from a car accident and was initially taking a high dose opioid analgesic, an antiepileptic, two non-opioid analgesics, and a nightly benzodiazepine. When his pain and insomnia

flared, he obtained other analgesics and benzodiazepines from a neighbor. He tried numerous medications and non-pharmacological therapies, yet his symptoms were poorly controlled and he sought out medical cannabis certification. While he continued most of his medications, after starting medical cannabis he was able to reduce his opioid analgesic dose modestly and he stopped obtaining benzodiazepines from a neighbor. In contrast, Person B is selected from the general population of those who do not take medical cannabis. Person B is therefore relatively healthy and, on average, does not have chronic pain.

Comparing these two people, it is clear that Person A's prescription drug use (both medical and non-medical) is higher than Person B's. Cross-sectional surveys of people like these would find medical cannabis use to be strongly associated with higher medical and non-medical use of prescription drugs. But does medical cannabis use *cause* more prescription drug use? In this illustration, no. Person A's prescription drug use actually decreased after starting medical cannabis. The main driver of the apparent association between medical cannabis and prescription drug use is that Person A's prescription drug use was higher than Person B's at baseline due to severe chronic pain.

Compared with people who do not take medical cannabis, the population of those who take medical cannabis is enriched with people like Person A—people who sought out medical cannabis because of severe chronic pain and associated comorbidities. While not all individuals who take medical cannabis have severe chronic pain, on average their disease burden is likely to be higher than a sample of the general population that does not use medical cannabis. Even if we compare people who take medical cannabis with a sample of people selected from the general population that accesses health care and takes any prescription drug (as in Caputi and Humphreys' subgroup analysis), prescription drug use may still be higher among people who take medical cannabis because they are still more likely to have severe chronic pain.

Analogous examples can be found in other conditions. Consider, for example, a survey of people with diabetes mellitus comparing people who take insulin with those who do not. We might find that, compared with people who do not take insulin, those taking insulin are more likely to take other hypoglycemic medications. But insulin does not cause use of other hypoglycemic medications; rather, people who take insulin have more severe disease.

While hypothetical individuals and an argument by analogy have inherent limitations, we provide the above examples to illustrate one way to integrate seemingly conflicting findings. It is clear from Caputi and Humphreys' results that people who take medical cannabis have higher medical and non-medical prescription drug use on average than people who do not take medical cannabis. But it is possible that medical cannabis use decreases prescription drug use over time, due to people substituting cannabis for other medications. A survey providing a snapshot of prescription drug use at one point in time does not offer insight into this longitudinal relationship. Further, comparisons of patients with different underlying morbidity cannot reveal the *effect* of medical cannabis on prescription drug use. As Caputi and Humphreys state, only prospective studies that follow individuals over time can help us to understand the causal impact of medical cannabis use on people with chronic pain.

The influence of medical cannabis may also be complex. Even if the average effect of medical cannabis is to decrease (or increase) prescription drug use, there may be subgroups of patients where use is increased (or decreased). Or, there may be specific formulations, routes of administration, or delivery devices for medical cannabis that are associated with distinct impacts on patients. There are a vast number of questions that need answering; unfortunately, the current regulatory and funding environments severely limit the speed and scale of research.

Given that people who use medical cannabis do have higher risk of non-medical use of prescription drugs, how can we reduce this risk? Caputi and Humphreys argue for screening. While the higher risk of non-medical use of prescription drugs makes it intuitively appealing to selectively screen people who take medical cannabis, screening recommendations require additional consideration of factors other than prevalence, such as the availability of effective interventions (Wilson and Jungner 1968). Although an updated review is in progress, previously the United States Preventive Services Task Force reported insufficient evidence to recommend screening for drug use among adults in primary care settings (Polen et al. 2008). While overdose education and naloxone distribution may reduce risk in people taking opioids, recent trials of screening paired with brief behavioral interventions for drug use have not found efficacy (Saitz 2014). Until broadly effective interventions are developed, the benefit of routine screening of people who take medical cannabis is unclear.

In the past two decades, access to medical cannabis has expanded markedly. The impact of medical cannabis on the use of opioid analgesics and other prescription drugs is of clear importance to patients, health care providers, policymakers, and the public. While surveys of people taking medical cannabis have strongly suggested that they substitute cannabis for other prescription drugs, these surveys are based on self-report and may not be generalizable. To fully understand the effect of medical cannabis on the use of other drugs, prospective longitudinal studies randomizing individuals to cannabis versus other treatments are urgently needed.

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