Cannabinoids for the Treatment of Opioid Use Disorder: Where is the Evidence?

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With the growing public interest in the potential therapeutic benefits of cannabis and cannabinoids in the treatment of opioid use disorder (OUD), some states have now either added or proposed to add OUD as an indication for their state’s medical marijuana program. However, these initiatives are based on weak evidence which at present do not support the listing of cannabis or cannabinoids as a treatment for OUD. Nevertheless, studying the potential therapeutic applications of carefully chosen components of cannabis or cannabinoids to treat specific aspects of OUD is not without scientific merit. Given the high rates of treatment discontinuation among those taking medications for OUD, interventions that further improve clinical outcomes are especially needed. The potential therapeutic applications of cannabis and cannabinoids in the treatment of OUD are worthy of further study, but it should be conducted with the same rigor that we expect of all pharmaceutical products. Until we have more research to show their efficacy, policy makers and clinicians should refrain from portraying cannabis and cannabinoids as evidence-based treatments for OUD.

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The evidence cited for the potential benefits of cannabis to treat OUD generally come from population-level research showing an inverse association between enactment of medical marijuana laws and opioid-related adverse outcomes.1-3 For example, Bachhuber and colleagues found that states that enacted medical marijuana laws from 1999 to 2010 experienced fewer fatal opioid overdoses compared to states that did not enact such laws.4 However, a subsequent study that examined the same data used by Bachhuber and colleagues further out to 2017 found that the association between medical marijuana laws and opioid overdoses actually reversed in direction.5 Indeed, there are other population-level studies that indicate cannabis use is associated with a higher risk of developing an OUD.5 As such, using population-level studies as justification to place cannabis in the same category as evidence-based treatments for OUD will give patients and their families the false impression that cannabis and related products are indeed effective treatments for OUD.

A recent meta-analysis of 23 studies of patients in methadone maintenance treatment compared outcomes (retention and nonprescribed opioid use) among those who did and did not use cannabis.6 The authors noted that although the overall quality of the evidence was low and quite possibly biased due to the observational nature of most studies, the results suggested that cannabis use did not affect patient outcomes overall. A sub-group analysis of studies conducted in the US showed an inverse relationship between cannabis use and treatment retention, whereas the association was in the opposite direction for studies in Israel. Unfortunately, it remains difficult to know how to interpret these findings. The included studies largely defined cannabis use through patient self-report or toxicology testing results. In evaluating the impact of cannabis on OUD outcomes, however, additional pharmacologic information would be needed. Given the complexity of the cannabis plant and its constituents, researchers would need to know not only the dosage used, but also the form of cannabis (flower vs extract), constituents (% tetrahydrocannabinol and cannabidiol [CBD]), route of administration (oral vs smoked), frequency of use (daily vs intermittent), and indication for use (recreational vs medical). In addition, studies would need to account for existing clinic policies that explicitly or implicitly prohibit or permit the use of cannabis for patients being treated with medications for OUD (MOUD).

There have been no prospective clinical trials of cannabis or cannabinoids for the treatment of OUD, nor trials that compare such compounds to existing MOUD such as buprenorphine. The potential for harm from both acute and chronic use of cannabinoids has been well-described, yet is often
ignored or minimized in the current climate of permitting greater access to cannabis.\textsuperscript{7,8} As clinicians and researchers, we need to follow the science; there are no data at present to support the listing by some states of cannabis or cannabinoids as a treatment for OUD, and we therefore strongly agree with those who have argued against recommending cannabis or cannabinoids as a substitute to existing MOUD options.\textsuperscript{9}

Nevertheless, studying the potential therapeutic applications of carefully chosen components of cannabis or cannabinoids to treat specific aspects of OUD are not without scientific merit. Although only a few controlled studies utilizing pharmaceutical cannabinoids in humans with OUD have been conducted, results of these trials have been informative. Two placebo-controlled randomized clinical trials of the synthetic tetrahydrocannabinol dronabinol have shown modest reduction in opioid withdrawal symptoms compared to placebo among individuals with OUD.\textsuperscript{10,11} In the study by Lofwall and colleagues, after abrupt cessation of an opioid, dronabinol 20 mg and 30 mg provided modest suppression of opioid withdrawal compared to placebo, although it was accompanied by adverse effects including tachycardia and subjective highs. Bisaga and colleagues compared dronabinol 30 mg to placebo in individuals with OUD undergoing a rapid buprenorphine detoxification; those receiving dronabinol experienced significantly less opioid withdrawal symptomatology than those given placebo. Furthermore, after study participants were successfully initiated on extended-release naltrexone, participants who intermittently smoked cannabis were significantly more likely to complete the 8-week trial than those reporting either regular cannabis use or no use.

Hurd and colleagues have conducted 2 placebo-controlled randomized trials examining the impact of CBD on cue-induced craving among individuals with OUD.\textsuperscript{12,13} CBD is a nonpsychoactive constituent of cannabis, which is now FDA-approved for the treatment of rare pediatric seizure disorders. In both of their studies, CBD (400 mg or 800 mg) or placebo were given for 3 consecutive days to individuals abstinent from all opioids, and not receiving any MOUD. When shown images that acted as reminders or cues of their addiction, those receiving CBD experienced significantly less craving compared to those taking placebo. No adverse effects were noted from either dosage used. Of note, their trial also demonstrated significant reductions in cue-induced anxiety among those taking CBD compared to placebo.

Despite its proven efficacy in improving treatment retention and opioid use outcomes and reducing overdoses, treatment with MOUDs is far from perfect: many individuals continue to use opioids, discontinue treatment, or both. Unfortunately, psychosocial treatments, which have robust empirical support for a range of substance use disorders, have not been as helpful as had been hoped as adjunctive treatments to MOUD.\textsuperscript{14}

The controlled studies of cannabinoids described above suggest the need for further rigorous research to better understand the role that cannabinoids might play in certain phases of OUD treatment. If CB\textsubscript{1} agonists like dronabinol can safely reduce opioid withdrawal symptoms, such compounds could be studied as adjunctive treatments during induction to and perhaps maintenance on extended-release naltrexone. With the growing interest in utilizing micro-dosing strategies to minimize the discomfort of buprenorphine inductions, CB\textsubscript{1} agonists could also be studied to facilitate difficult buprenorphine inductions.\textsuperscript{15} Additionally, CB\textsubscript{1} agonists could be studied as adjuncts to ease opioid withdrawal for patients attempting to taper off MOUD or patients with chronic pain who are tapering off of opioid analgesics. It is also possible that adjunctive CBD may aid in preventing relapse to opioid use by attenuating the response to environmental cues and stressors among individuals already taking MOUD. Given the high rates of treatment discontinuation of MOUD, pharmacologic treatments that help patients to initiate MOUD, remain in treatment for longer durations, and prevent relapse are especially needed.

In the context of the growing opioid crisis, research to improve treatment outcomes among those already taking MOUD is critically needed. The potential therapeutic applications of cannabis and cannabinoids in the treatment of OUD is worthy of further study, but it should be conducted with the same rigor that we expect of all pharmaceutical products. Until we have more research to show their efficacy, policy makers and clinicians should refrain from portraying cannabis and cannabinoids as evidence-based treatments for OUD.

REFERENCES