DEPARTMENT OF HEALTH

Opioid Use Disorder Issue Brief

OCTOBER 2022

Introduction

This briefing was prepared in response to a petition to consider adding opioid use disorder as a new condition to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, members of the Medical Cannabis Review Panel, and interested members of the public, scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment are provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) were included, especially if there are few clinical trials or observational studies. Interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses; however, surveys published in peer-reviewed journals were included for completeness. When found, published recommendations or opinions of national medical organizations were also included.

Searches for published clinical trials and observational studies of cannabis therapy were conducted using the National Library of Medicine's Medline using key word searches appropriate for the petition condition. Articles identified as clinical trials, observational studies, or review articles were collected and reviewed. References in the identified articles were examined to ensure all the articles associated with the petitioned condition were identified and included. Moreover, clinicaltrials.gov, a federal government-maintained website responsible for tracking current clinical trials funded, was used to identify any ongoing or completed clinical trials.

Definition

An "opioid" refers to natural or synthetic chemicals that bind to the opioid receptors found in the central nervous system (Hoffman et al., 2019). Opioids are manufactured as prescription medications, and can be prescribed to control pain, diminish cough, or relieve diarrhea (Shuckit et al., 2016). The Diagnostic Statistical Manual of Mental Disorders 5th edition (DSM-5) describes opioid use disorder as a problematic pattern of opioid use leading to problems or distress with at least two of the following occurring within a 12-month period (First, M., 2013, Coffa et al., 2019):

- Taking opioids for longer than intended or higher than intended quantities.
- Persistent desire or unsuccessful efforts to cut down or control opioid use.
- Spending high amounts of time obtaining, using, or recovering from opioid use.
- A craving, an urge, or a strong desire to use opioids.

- Inability to fulfill work, attend school, or complete home obligations.
- Continued opioid use regardless of social or interpersonal problems.
- Reduced activity due to opioid use.
- Use of opioids in a physically hazardous situation.
- Continued opioid use despite ongoing physical or psychological problems.
- Increased opioid tolerance.
- The experience of withdrawal symptoms when taken off opioids.

Opioid use disorder has many similarities to other use disorders; however, the condition differs in regard to two specific aspects. First, opioids can lead to physical dependence within a short time period, as little as 4-8 weeks. Second, the abrupt stopping of opioids among chronic users can result in generalized pain, chills, cramps, diarrhea, dilated pupils, restlessness, anxiety, nausea, vomiting, insomnia, and very intense craving, thus, reinforcing opioid dependence. Like other use disorders, environmental and genetic factors impact opioid use disorder (Sharam et al., 2016).

Epidemiology

In 2015, the United States was estimated to lead the world in opioid consumption and prescriptions for hydrocodone and oxycodone. While traditionally used for cancer-related pain, opioids are also commonly prescribed as a treatment for chronic and acute non-cancer pain (Hoffman et al., 2019).

Greater than 700,000 people died from a drug overdose between 1999 and 2017 in the United States. Further, drug overdose fatalities surpassed 70,000 in 2017 alone, with 68% of fatalities being attributed to opioids (Hoffman et al., 2019). The Centers for Disease Control and Prevention (CDC) estimates from 2002 to 2017, there was a 22-fold increase in the total number of deaths involving fentanyl and other synthetic opioids, with heroin deaths increasing seven-fold. Sixty percent of all opioid-involved overdose deaths are due to synthetic opioids, which was a 45% increase from 2016 to 2017 (Hoffman et al., 2019). Deaths from heroin related overdoses have remained relatively stable in 2017 at approximately 15,000 deaths (Hoffman et al,. 2019). Finally, in 2020, the CDC reported greater than 92,000 Americans died from drug overdoses, and 2.1 million Americans aged 12 years and older had opioid use disorder in 2016 (Coffa et al., 2019).

Costs from opioid use disorder and fatal opioid overdoses in 2017 were estimated to be $1.02 trillion (Florence et al., 2020).

Current Therapies

While treatments are available, it is estimated that only 1 in 4 people with an opioid use disorder receive specialty treatments (Sharma et al., 2016). Specialty treatment centers refers to treatment centers, facilities, departments, wards, or units designed for the treatment of substance use disorder. These centers can be standalone facilities, such as drug treatment

centers/clinics, or integrated with other health care facilities, clinics, or dispensaries (World Health Organization, 2022). The low success rate is attributed to the perception that patients can recover without need for specialty treatments (Sharma et al., 2016). An evidence-based OUD treatment therapy employed by primary care facilities and some specialty treatment centers medication-assisted treatment (MAT) (Mojtabai et al., 2019, Hadland et al., 2020). MAT involves the use of medication along with counseling and behavioral therapies to provide a whole-patient treatment approach to OUD treatment (Maglione et al., 2020). Notably, MAT is not a detoxification program, rather, it is an inclusive, long-term treatment plan utilized after withdrawal from opioids. MAT involves the use of one of three medications (buprenorphine, naltrexone, or methadone), in combination with psychosocial and/or behavioral therapy (Logan et al., 2021). The above-mentioned medication can also be used to relieve cravings, relieve withdrawal symptoms, and block the euphoric effects of opioids. Notably, the Substance Abuse and Mental Health Services Administration (SAMHSA) approved the renaming of MAT to "medication for opioid use disorder" (MOUD) (Logan et al., 2021).

While MAT is often considered the standard of care for opioid use disorder, access to MAT is limited. For example, 60% of specialty treatment facilities in the U.S. did not offer any FDA-approved MAT in 2017 (Huhn et al., 2020). Furthermore, specialty treatment facilities located in states that did not expand Medicaid were less likely to use MAT compared to states that expanded Medicaid (Huhn et al., 2020). Further research found that facilities that were not licensed or accredited where less likely to offer MAT than licensed or accredited facilities (Huhn et al., 2020). In an attempt to improve treatment success, U.S. federal requirements were developed requiring health care facilities that dispense methadone provide counseling, and federal legislation encourages health care provider who prescribe buprenorphine to refer patients for counseling. However, there are no validated counseling approaches designed specifically for patients with opioid use disorder, and evidence-based psychosocial interventions are seldom used (Hoffman et al., 2019). Finally, patient perception in both individual and group therapy can help patients remain engaged. For example, some patients were able to abstain from relapsing without counseling, however, counseling without MAT was associated with increased returned to use (Hoffman et al., 2019).

Medications

The most problematic aspect of opioid use disorder treatment is the prevention of drug relapse, which is common during withdrawal. Abstinence-based protocols are particularly ineffective, as an estimated 85% of individuals relapse within 1 year of the treatment initiation. Therefore, opioid replacement and medication-assisted therapies have been established as a more efficacious therapy. However, there are only three FDA-approved medications for the treatment of opioid use disorder (Wiese et al., 2018).

Three FDA-approved medications are commonly used:

1. Methadone prevents withdrawal symptoms and reduces cravings in people addicted to opioids. It does not cause a euphoric feeling once patients become tolerant to its effects. It

is available only in specially regulated clinics. While methadone boasts an encouraging safety profile, there is still a risk for misuse and mortality when the dose exceeds the patient's level of tolerance. Further, methadone, an opioid agonist, reduces opioid craving, withdrawal symptoms and blunts or blocks the effect of opioids. However, because methadone is an opioid agonist, the abrupt stopping or tapering of methadone can result in opioid withdrawal symptoms that can last three weeks (Wiese et al., 2018). There are substantial geographical disparities associated with the distribution of methadone due to the limited number of distribution centers that are highly regulated (Wiese et al., 2018). This, coupled with the stringent and stigmatizing compliance requirements, has been associated with a 40% relapse rate for patients within one year of methadone therapy (Wiese et al., 2018).

2. Buprenorphine blocks the effects of other opioids, reduces, or eliminates withdrawal symptoms and reduces cravings. Buprenorphine treatment (detoxification or maintenance) is provided by specially trained and qualified physicians, nurse practitioners, and physician assistants (having received a waiver from the Drug Enforcement Administration) in office-based settings. Buprenorphine can be administered with naloxone (an opioid antagonist) combined into its formulation. However, this combination can induce premature withdrawal soon after the most recent dose of other opioids (Wiese et al., 2018).
3. Naltrexone blocks the effects of other opioids preventing the feeling of euphoria. It is available from office-based providers in pill form or monthly injection. However, oral naltrexone has shown limited efficacy due to low treatment adherence (Coffa et al., 2019). The low treatment adherence with oral naltrexone is thought to be due to the poor efficacy of the oral medication in reducing opioid withdrawal symptoms and the high level of adherence needed to see any significant effect. Notably, injection naltrexone patients experience high drop-out during treatment induction because, while naltrexone injections are more effective than oral naltrexone, injection naltrexone requires repeated visits to a health care professional, thus, reducing adherence rates. Further, naltrexone use reduces opioid tolerance, increasing overdose risk among relapsing patients (Coffa et al., 2019).

The National Institute on Drug Abuse (NIDA) emphasize that these medications do not substitute one addiction for another. Unlike other opioids, the opioid medications (Methadone, Buprenorphine, and Naltrexone) used to treat opioid dependence do not get patients high. Rather, they help reduce opioid cravings and withdrawal symptoms. While the use of the above-mentioned medications is widespread and successful, especially methadone and buprenorphine, the shortcomings of each medication can make adherence to each of them difficult (Wiese et al., 2018).

Overdose Prevention

Naloxone (Narcan, Evzio) is a potentially life-saving medication used to quickly reverse an opioid overdose. It can reverse and block the effects of other opioids and return normal breathing to someone whose breathing has slowed or stopped because of an opioid overdose. It is available as a prefilled auto-injection device, as a nasal spray, and as an injectable. In April 2018, U.S. Surgeon General Jerome M. Adams, M.D., M.P.H., released a public health advisory to urge more Americans to carry naloxone.

Pre-clinical research

A review published by Wiese et al. attempted to consolidate pre-clinical evidence of cannabis/cannabinoid use for the treatment of opioid use disorder (Wiese et al., 2018). Notably, research has found that cannabinoid receptors and opioid receptors are known to interact in multiple ways. First, because both receptors are distributed equally throughout a person's body. Second, the cannabinoid and opioid receptors experience what is called cross-sensitization, a process in which stimulation of the receptors is generalized to related stimulus. As a result of the cross-stimulation the effects of cannabinoid and opioid receptors can be amplified by both cannabis and opioids. Therefore, the overlap between both receptors and the cross-stimulation indicates a clear morphological association between the opioid and cannabinoid system in reward and withdrawal (Wiese et al., 2018)

Multiple published pre-clinical studies have shown that cannabis and cannabinoids can be used to decrease opioid withdrawal symptoms. While this evidence is promising, it is not without its limitations. First, as a pre-clinical study, this evidence was shown in animal models that obviously have biological differences. Second, conflicting evidence has been published showing that cannabinoid receptor 1 (CB1) agonism can increase rewarding properties of opioids, potentially increasing opioid withdrawal severity (Wiese et al., 2018). To further complicate the relationship between cannabis and opioids, some studies have shown that the administration of phytocannabinoid cannabidiol (CBD) can alleviate naloxone-precipitated withdrawal in morphine tolerant rates (Wiese et al., 2018).

While research surrounding CB1 agonism is conflicting, pre-clinical evidence has identified CBD as a potential therapeutic treatment for harm reduction. CBD does not have reinforcing effects in rodents, highlighting a low potential for misuse (Wiese et al., 2018). Moreover, CBD has been shown to reduce the reward aspects of multiple drugs including cocaine, amphetamine, and nicotine. Further, in rats, CBD reduces the effects of morphine- and heroin-seeking and anticipation without causing adverse events and decreased cued responses associated with receiving both drugs. Thus, this research would suggest that CBD has the potential to reduce seeking of other drugs, such as opioids, as well as decrease anticipatory effects of receiving opioids (Wiese et al., 2018). Thus, there is promising evidence for the use of CBD in opioid relapse therapy.

Clinical Trials

Clinical trials evaluating the efficacy of cannabis, either alone or as an adjunct therapy for acute opioid withdrawal, is limited. Dronabinol, an FDA-approved analog for THC, has been evaluated for opioid withdrawal relief in a clinical trial of patients receiving the opioid antagonist naltrexone. These studies found that low-dose adjunct dronabinol, in conjunction with extended-release Naltrexone, improved the tolerability of symptoms, including insomnia, reduced appetite, and reduced energy levels during opioid withdrawal. However, tachycardia was reported at higher dronabinol doses (Bisaga et al., 2015, Jicha et al., 2015, Lofwall et al., 2016). Other cannabinoids were shown to be safe and tolerable when administered in conjunction with an opioid or opioid replacement medication (Bisaga et al., 2015). However, clinical trials evaluating the efficacy of dronabinol or other cannabinoids as a replacement for traditional replacement therapies such as methadone or buprenorphine are limited.

In addition to clinical trials assessing dronabinol, a recent study by Hurd et al. (2019), noted that repeated administration of the CBD reduces cue-induced anxiety and craving (Hurd et al., 2019). It was also found to exert protracted effects one week later among opioid-dependent patients with short-term abstinence. Overall, while there is increased interest in examining the efficacy of cannabis on opioid use disorder, few new studies have been published. While the use of cannabis as an opioid use disorder therapy has shown potential, limited evidence is available.

Observational Studies

There are few clinical trials evaluating the efficacy of cannabis and cannabinoids as a treatment for opioid use disorder. A recent systematic review and meta-analysis by McBrien et al. (2019), examined the impact of cannabis use during methadone maintenance treatment for opioid use disorder. These studies evaluated multiple types of cannabinoids, including tetrahydrocannabinol (THC) and marijuana. The review found no consensus among studies that cannabis use is associated with reduced opioid use. Furthermore, they noted no consensus on the impact cannabis use had on longer treatment retention when used during methadone maintenance therapy in patients with opioid use disorder. McBrien et al. (2019) noted that the quality of evidence identified was low and had a high risk for bias. The results from the studies included in the review suggest that individual studies may potentially have no effect on opioid use in patients receiving methadone maintenance therapy. Therefore, the authors were unable to conclusively determine if cannabinoid use was an effective treatment for opioid use disorder (McBrien et al., 2019). Notably, this study contradicts preclinical literature, and brings into question the degree to which animal models can be readily translated to human effects as it relates to opioid use disorder treatments.

In an observational study of 2,315 patients treated for their opioid use disorder, Rosic et al. (2021) found no association with cannabis use as a treatment for opioid use disorder when compared to non-cannabis use patients (Rosic et al., 2021). The author attempted to further elucidate the relationship between cannabis use and opioid use disorder. Notably, Rosic et al. reported that daily cannabis use was associated with a lower likelihood of opioid use during treatment compared to occasional cannabis use. Additionally, the authors noted that cannabis use was inversely proportional to severity of opioid use disorder withdrawal symptoms. This work suggests that low cannabis use was associated with severe opioid use withdrawal symptoms, and high cannabis use was associated with mild opioid use withdrawal symptoms. Further, Rosic et al. (2021) noted that older age of first cannabis use was associated with lower odds of opioid use during treatment. Finally, Rosic et al. (2021) found that patients self-reported cannabis side effects were associated with a decreased likelihood for opioid use. However, the authors where unable to discern between reporting bias and cannabis side effects. Nevertheless, the findings suggest that patients are likely to substitute other medication for cannabis due to the perceived reduced side-effects.

A review by Wiese et al. reported on studies that noted both dronabinol and intermittent whole-plant cannabis appeared to increase the length of treatment adherence time. However, this effect was lost during chronic cannabis consumption (Wiese et al., 2018). Several epidemiologic studies evaluating the impact cannabis policies have had on opioid use disorder

found an association between cannabis use and reduced opioid use related hospitalizations (Shi., 2017, Bachhuder et al., 2014).

Surveys can provide valuable information regarding the use of medical cannabis as a therapy for opioid use disorder. Work by Reiman et al. (2017) noted that study participants reported cannabis use was effective at treating opioid use disorder. Further, multiple studies found a reduction in opioid use disorder in states with higher cannabis use rates (Powel et al., 2015, Lucas et al., 2019). However, two studies published by the State of Colorado found that increased use of CBD and THC was associated with increased opioid use (Oberbarnsheidt et al., 2020). A large-scale survey conducted in Canada found that as many as 63% of respondents reported using cannabis as a substitute for prescription drugs, with 30% of respondents stating they use cannabis to substitute pharmaceutical opioids (Lucas et al., 2017). Overall, these findings suggest that cannabis is being used as a substitute of multiple prescription medications; however, the true effects of this substitution has yet to be elucidated. Therefore, more large-scale studies are needed.

Work by Livingston et al. (2017) reported a reduction in opioid-related deaths following the legalization of cannabis in Colorado (Livingston et al., 2017). In a literature review, it was reported that medical cannabis laws could be associated with decreased prescription opioid medication-associated mortality, while also improving pain management, and significantly reducing health costs (Vyas et al., 2017). However, another review reported that study evidence was limited by selection bias, cross-sectional designs, and self-reported assessments of the opioid-sparing effects of cannabis (Campbell et al., 2018). Finally, a recently published review by Karimi-Haghighi et al. (2022), found that cannabinoids could effectively reduce the rewarding and reinforcing effects of addictive drugs, but that more clinical study evidence was needed before a definitive answer was determined (Karimi-Haghighi et al., 2022). Overall, the efficacy of cannabis as a treatment for opioid use remains inconclusive due to a sparsity of data and inconsistent results. Further, research from a clinical perspective and observational perspective is needed to elucidate the association between cannabis use and opioid use disorder.

National Medical Organization Recommendations

The National Institute on Drug Abuse funded a study that found the overdose death rate was 22.7% higher than expected in states that allowed medical marijuana as a treatment for opioid use disorder. Therefore, the National Institute on Drug Abuse does not support the use of medical marijuana as a treatment for opioid use disorder. Further, letters submitted to the Minnesota Department of Health by Allina Health, Hennepin Healthcare, Minnesota Psychiatric Society, and the Minnesota Chapter of the American Society of Addiction Medicine expressed opposition to adding opioid use disorder to the list of approved medical conditions.

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