DEPARTMENT OF HEALTH

Opioid Use Disorder

OCTOBER 2018

Introduction

Briefings such as this one are prepared in response to petitions to add new conditions 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, to members of the Medical Cannabis Review Panel, and to 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 is 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) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies of cannabis therapy are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Though the MN medical cannabis program does not allow smoked or vaporized dried cannabis, studies using these forms of cannabis administration were allowed for insight they could provide. Finally, the federal government-maintained web site of clinical trials, clinicatrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

The word "opioid" refers to chemicals derived from the poppy plant or synthetic agents based on those chemicals. Some opioids are manufactured as prescription medications, prescribed to control pain, diminish cough, or relieve diarrhea. Others are made specifically to sell illegally. In addition to the medical effects for which they are prescribed, opioids also produce feelings of euphoria, tranquility, and sedation that may lead a patient to continue to take these drugs despite the development of serious related problems. The problems include the need to increases doses in order to achieve these desired effects. At higher doses the drugs can reduce respiratory drive, leading to death (Schuckit 2016). Attempts to reduce or discontinue use after

repeated administrations leads to a highly uncomfortable withdrawal syndrome. The unpleasant physical and psychological symptoms of withdrawal produce negative reinforcement, leading to ongoing, escalating use both to produce desired effects and avoid withdrawal symptoms (Bart 2012).

The Diagnostic and Statistical Manual of Mental Disorders – fifth edition (American Psychiatric Association: DSM-5, 2013) defines opioid use disorder (OUD) as a problematic pattern of opioid use that results in significant impairment or distress on a clinical level. In order to confirm a diagnosis of OUD, at least two of the following should be observed within a 12-month period. Severity of OUD is categorized based on number of criteria met: mild (2-3), moderate (4-5), severe (6 or more).

- Opioids are often taken in larger amounts or over a longer period than was intended.
- There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
- A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
- Craving, or a strong desire or urge to use opioids.
- Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
- Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
- Important social, occupational or recreational activities are given up or reduced because of opioid use.
- Recurrent opioid use in situations in which it is physically hazardous.
- Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
- Tolerance, as defined by either of the following: 1) need for markedly increased amounts of opioids to achieve intoxication or desired effect, or 2) markedly diminished effect with continued use of the same amount of an opioid [not considered to be met for individuals taking opioids solely under appropriate medical supervision].
- Withdrawal, as manifested by either of the following: 1) the characteristic opioid withdrawal syndrome, or 2) the same (or a closely related) substance taken to relieve or avoid withdrawal symptoms [not considered to be met for individuals taking opioids solely under appropriate medical supervision].

The clinical course of OUD involves periods of exacerbation and remission, but the underlying vulnerability never disappears. This pattern is similar to that of other chronic relapsing conditions (e.g., diabetes and hypertension) in which perfect control of symptoms is difficult and patient adherence to treatment is often incomplete. Although persons with opioid problems are likely to have extended periods of abstinence from opioids and often do well, the risk of early death, primarily from an accidental overdose, trauma, suicide, or an infectious disease (especially HIV and hepatitis C) is increased by a factor of 20 (Schuckit 2016).

Prevalence

Over 2.5 million Americans suffer from opioid use disorder, which contributed to over 28,000 overdose deaths in 2014 (NIDA). Opioid-related deaths and hospitalizations for opioid abuse treatment in the US have increased dramatically over the past two decades and in 2013 the US Department of Health and Human Services declared opioid overdose death an epidemic (Volkow 2014).

Current Therapies

Detoxification is often an initial step in treating OUD. It involves discontinuation of the abused opioid drug while treating resulting withdrawal symptoms. A variety of drugs can be used to treat the withdrawal symptoms, which include diarrhea and dilated pupils, pain, restlessness, and anxiety. Two opioid medications are frequently used under medical supervision to reduce the withdrawal symptoms: methadone and buprenorphine. A very small proportion of persons are able to go through withdrawal without use of medications. Detoxification is usually not sufficient to avoid relapse and produce long-term recovery, but it helps the patient think more clearly and participate more effectively in their rehabilitation program (Schuckit 2016). Maintenance programs are needed after detoxification. This is due at least in part to changes in the brain caused by chronic opioid use (Bart 2012).

The most effective maintenance programs appear to be those that combine use of one of the FDA approved medications for treating OUD (methadone, buprenorphine, and naltrexone) in conjunction with psychosocial interventions. These are often referred to as medication-assisted therapies. Data indicate poor outcome in patients provided only psychosocial interventions (Bart 2012). Naltrexone blocks the effects of opioids and, in some highly motivated patients, can help maintain abstinence. Methadone and buprenorphine are more frequently used. Both activate the mu opioid receptor (buprenorphine activates it only partially). Though they activate the mu opioid receptor, the effects are much less strong that with most other opioid drugs. This makes them safer, though they are not without risks of their own. Overdose is possible and, in the case of methadone, a heart rhythm problem can occur. However, data suggest methadone maintenance programs decrease mortality by approximately 50% among persons with opioid-use disorders, decrease acquisition of HIV infection and hepatitis, decrease crime and illicit-substance use, improve social functioning, and increase the rate of retention in rehabilitation programs. Data also support the effectiveness of buprenorphine along these lines. Direct comparisons between methadone and buprenorphine show that both approaches improve outcomes, but most studies suggest that methadone maintenance might be associated with higher rates of patient retention (Schuckit 2016).

Methadone and buprenorphine block euphoric and sedating effects of superimposed opiates and normalize the stress response. Their role in the treatment of OUD is not simply replacement of an illicitly used opiate for a medically supervised opiate, but rather a medication that corrects many of the neurobiological processes contributing to relapse (Bart 2012). Consensus on how long a patient should continue receiving methadone or

buprenorphine therapy is lacking. Some clinicians try to taper patients off these medications after a year. Others emphasize the high rate of relapse and overdose deaths after leaving these programs and suggest that treatment should be open-ended and potentially lifelong (Schuckit 2016).

A variety of types of psychosocial therapies are used as part of medication-assisted therapy. These include cognitive-behavioral therapies, contingency management, motivational interviewing, and general supportive counseling. Systematic reviews have shown treatment that including psychosocial therapies is more effective than treatment with methadone, buprenorphine, or naltrexone alone (Dugosh 2016). In addition, patients are often encouraged to participate in support groups such as Narcotics Anonymous.

Research published in 2011 showed less than half of privately-funded substance use disorder treatment programs offered medication-assisted therapy and only a third of patients with opioid dependence at these programs actually received it (Knudsen 2011). A number of barriers contribute to the relatively low rates of access and participation in medication-assisted therapies. These include a limited number of trained, authorized prescribers, insurance limitations and requirements, and negative attitudes about addiction medications held by the public, providers, and patients. Some treatment-facility managers and staff favor an abstinence model. Studies have shown systematic prescribing of inadequate doses of methadone and buprenorphine, leading to relapse and reinforcement of a perception of ineffectiveness. Federal and state governments are taking efforts to increase access to medication-assisted therapies (Volkow 2014).

Success with medication-assisted therapy is often measured in terms of retention in treatment and reduction in illicit opioid use. Mean 1-year retention in methadone programs is around 60% and can vary based on dosing (Bart 2012). A 9-center trial of a six-month program where patients were assigned to either methadone or buprenorphine/naloxone showed retention to be higher with methadone (74% vs. 46%). Use of illicit opiates was lower with buprenorphine/naloxone during the first 9 weeks but similar thereafter at around one-third of patients (Hser 2014).There is room for improvement in treatment of patients with OUD – both in development of new therapies and in improved delivery of existing treatments. Federal and state governments and the private sector are working on both these fronts (NIDA).

Pre-Clinical Research

A recent review article summarizes pre-clinical evidence of a possible role for cannabis or cannabinoids in treating OUD (Wiese 2018). The endocannabinoid and opioidergic systems are known to interact in many different ways, from the distribution of their receptors to how activation of one system influences the function of the other. Both these systems are very complex, however, and detailed understanding of how these two systems interact is still emerging. Some rodent studies show stimulation of cannabinoid receptor 1 (CB1), as occurs with THC, decreases opioid withdrawal symptoms; others show CB1 activation increases the rewarding properties of opioids and may actually increase the severity of opioid withdrawal symptoms. In multiple studies administration of cannabidiol (CBD) has been shown to alleviate naloxone-precipitated withdrawal in morphine tolerant rats.

Clinical Trials

Information on cannabis or cannabinoids as part of OUD therapy is quite limited and is summarized in a recent review (Sloan 2017). Two small trials investigated the ability of dronabinol, synthetic THC, to alleviate opioid withdrawal side effects. They suggest that dronabinol has some effect, but the effect is likely weaker than opioid-based withdrawal therapies. The first trial randomized opioid-dependent participants to dronabinol or placebo while they were undergoing an 8-day inpatient detoxification and injectable naltrexone induction (Bisaga 2015). Dronabinol reduced the symptoms of opioid withdrawal compared to placebo, but this trial did not compare dronabinol to an active treatment. In the second trial regular opioid users were admitted to an inpatient unit for 5 weeks maintained on oxycodone, and then withdrawn from oxycodone to experimentally induce withdrawal on multiple test sessions (Lofwall 2016). Oxydone, but not dronabinol, attenuated physical symptoms of withdrawal, including changes in heart rate, blood pressure, and pupil diameter, whereas the 20 and 30 mg doses of dronabinol induced tachycardia. The 20 and 30 mg doses reduced scores on scales of withdrawal symptom severity compared to placebo, but were substantially less effective than oxycodone. There are no published studies investigating CBD treatment in patients with OUD, though pilot data reported in a recent review suggest that CBD may blunt cue-induced craving in OUD patients who have been abstinent for at least 7 days (Hurd 2015).

Observational Studies

Two investigator groups studied medical records of patients in naltrexone treatment programs, using positive urine screening tests to assess impact of cannabis use on measures of treatment success. Both studies divided patients into three groups based on cannabis screening tests: no use, occasional use, and heavy use (≥ 80% in Raby 2009; 100% in Church 2001). Compared to patients with no use or heavy use, patients with occasional cannabis use were found to have better adherence with taking naltrexone pills (Raby 2009; Church 2001), better abstention from opioids (Church 2001), and better retention in the treatment program (Raby 2009). Another paper reports on a retrospective medical record study of 91 patients on methadone maintenance therapy. More than half (56) of the patients had at least one positive urine screen for THC. Cannabis use during induction was associated with lower severity of withdrawal symptoms but had no association with persistent use of illicit opiates (Scavone 2013). As with all observational studies, caution is merited when interpreting the meaning of results; observed associations might not be causal.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of opioid use disorder were found.

The American Psychiatric Association in December, 2013 released a Position Statement on Marijuana as Medicine. The document includes the following: “There is no current scientific evidence that marijuana is in any way beneficial for any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of

psychiatric disorders…If scientific evidence supports the use of cannabis-derived substances to treat specific conditions, the medication should be subject to the approval process of the FDA." (APA web site).

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