ISSN:2471-061X

Journal of
Addiction and Dependence

Peter A. Clark, S.J (2019) J Addict Depend 5(1): 1-18
DOI: 10.15436/2471-061X.19.2638
Volume 5 | Issue 1
OPEN ACCESS

Research Article

Is Medical Marijuana a Viable Option for Opioid Replacement Therapy?

Peter A. Clark, S.J.*, Gabriella Mamo*, Samuel Schadt, Sonul Gulati, Arun Minupuri, John Dubensky, Archen Krupadev, Rushabh Shah, Shengnan Zheng, Jesus Salas Noain, Cameron Fick, Olivia Nguyen, Patrick Laird, Rishi Gulati, Michael Fontana, Priscilla Rodriguez, Graham Clifford, Sean McDermott, Haley Patrick, Justin Stout, Jordan Davis

Institute of Clinical Bioethics, Saint Joseph's University, 5600 City Avenue, Philadelphia, Pennsylvania, USA

***Corresponding author:** Peter A. Clark S.J, Director, Institute of Clinical Bioethics, Saint Joseph's University, 5600 City Avenue, Philadelphia, Pennsylvania, USA 19131, Tel: 610-660-3425, E-mail: pclark@sju.edu
Gabriella Mamo, Philadelphia College of Osteopathic Medicine, 4170 City Avenue, Philadelphia, Pennsylvania, USA 19131; E-mail: gm270930@pcom.edu

Abstract

The opioid epidemic has become one of the most serious health crises in the United States. Current replacement therapies for opioid use disorder, such as methadone, buprenorphine, and naltrexone, are not sufficient enough to treat recovering opioid users due to disadvantages such as inadequate availability and potential side effects. As a result, new alternatives to these drugs must be addressed. This article addresses the permissibility of using medical marijuana as a potential replacement therapy for Opioid Use Disorder and opioid withdrawal from the pharmacological, medical, legal, and ethical perspectives. Pharmacologically, current replacement therapies are used to decrease the symptoms of withdrawal and lower the risk of overdose but have several limitations. Marijuana, in addition to current replacement therapies, could benefit as a treatment for opioid use disorder because of its safe, non-addictive qualities and effectiveness in inhibiting opioid-seeking behavior. Legally, the policies regarding the use of medical THC and CBD as replacement therapies are shifting in the right direction at the state level. The ethical principle of double effect is used to defend the permissibility of this replacement therapy. Lastly, we propose the institution of a potential medical marijuana clinic in Philadelphia, which offers this drug as a replacement therapy, serving as a paradigm for those suffering from drug addiction to seek alternative therapy and treatment.

Keywords: Addiction; Interpretative phenomenological analysis; IPA; Recovery; Whoonga/nyaope; Townships

Introduction

The opioid epidemic is an ongoing national crisis and public health issue. This crisis impacts individuals all over the nation, regardless of race or income status. From 1999 to 2017, over 700,000 people in the U.S. died of drug overdoses; almost 400,000 of those deaths involved opioids[1]. The number of deaths in 2017 due to opioid drug overdose (comprised of both prescription and illicit drugs) was 6 times higher compared to 1999. According to the Centers for Disease Control and Prevention (CDC), 130 opioid-related overdoses occur each day on average[2]. In October 2017, the U.S. Government declared this a public health emergency[3].

Commonly available prescription opioids include oxycodone, hydrocodone, codeine, fentanyl, and morphine. Other opioids are illegal, such as heroine[4]. Clinically, these drugs are commonly used to manage moderate to severe acute pain, such as pain experienced post-operatively or following trauma. They are also utilized to manage severe chronic pain experienced by terminally-ill patients or for easing the effects of pain related to cancer treatment[5]. Although these drugs are effective in managing pain, they are often over-prescribed, overused and misused. Examples of opioid misuse include

Received Date: December 11, 2019
Accepted Date: December 27, 2019
Published Date: December 30, 2019

Citation: Peter A. Clark, S.J. Is Medical Marijuana a Viable Option for Opioid Replacement Therapy?. (2019) J Addict Depend 5(1): 1-18.

taking the medication in order to achieve a high, taking another individual's prescription drug, or taking the drug in a manner/dose other than what was prescribed[4]. As a result, healthcare providers are challenged to find a balance between managing genuine pain and avoiding over-prescription[5].

Opioids have potent physiological and psychological effects, as they are able to evoke both euphoria and analgesia when taken acutely[6,7]. Recurrent use of the drugs can result in tolerance (needing to take higher subsequent doses of the drug in order to achieve the same effects) and physical dependence (experiencing withdrawal symptoms after discontinuation of the drug)[8]. With repeated or chronic use, opioids elicit adaptations and modifications in neuronal circuitry, forming a drug-dependent state[6]. The mechanism by which this occurs is the suppression of endogenous neurotransmitter production after chronic stimulation of opioid receptors in the brain. Abrupt cessation of the drug causes unopposed binding of counter-regulatory neurotransmitters to these receptors, contributing to undesirable withdrawal symptoms[7]. These symptoms may vary based on the type of drug used and the method by which it was taken. Withdrawal can produce both psychological and physical symptoms, such as dysphoria, anxiety, insomnia, sweating, shaking, and diarrhea. Many of these physical symptoms are temporary, while several psychological symptoms can persist for months[6].

There are several replacement therapies available for opioid addiction. These drugs agonize, partially agonize, or antagonize the mu-opioid receptor. Many of these drugs are used as maintenance therapy or detoxification agents[11]. Psychosocial therapies such as counseling, therapy, and educational programs are also offered to patients who wish to overcome their addiction. The drugs that we aim to describe are methadone, Suboxone (buprenorphine and naloxone), naltrexone, and medical marijuana.

These Food and Drug Administration (FDA)-approved opioid replacement therapies have been effective at alleviating opioid dependence and helping to lessen withdrawal symptoms, however they are not always successful and do not come without risks. Various adverse effects to these drugs must also be considered, such as anxiety, cardiac effects, muscle aches, agitation, insomnia, nausea and diarrhea[9]. Access to these replacement therapies is also a challenge, as there are legal and logistical impediments to acquiring them. Often, the demand for these medications exceeds the supply. In this article, we examine the role of cannabis as a potential replacement therapy in treating opioid withdrawal symptoms and decreasing the probability of relapse. Cannabis and opioids share a common primary use of analgesia. Studies have shown that patients taking opioids for chronic pain who also have access to cannabis decrease their opioid use by 40-60%. Furthermore, cannabis has been shown to consistently decrease the dose of opioids needed to reach suitable pain relief[10].

Although current replacement therapies for opioid addiction seem ideal, there are several limitations which need to be considered, such as availability and potential side effects. The focus of this paper is fivefold. First, the mechanisms of action of methadone, buprenorphine, and naltrexoneare discussed. Second, an analysis of medical marijuana as a viable option for replacement therapy, including both THC and CBD, is considered. Third, the legal ramifications regarding the use of THC and CBD as replacement therapies are explored. Fourth, the implementation of a replacement therapy clinic in Philadelphia offering medical marijuana is presented, insofar that an established clinic could serve as a paradigm for those suffering from drug addiction to seek alternative therapy and treatment. Fifth, an ethical analysis of the problem and solutions is presented.

Pharmacotherapy For Opioid Use Disorder

Opioid Use Disorder (OUD), previously classified as opioid abuse, is defined as a problematic pattern of opioid use that leads to clinically substantial impairment[11]. Opioids have the potential to depress the central nervous system, which may lead to overdose and death. Replacement therapies, such as methadone, buprenorphine, and naltrexone, are used to decrease the symptoms of withdrawal and lower the risk of overdose.

Methadone

Methadone is a full, long-acting opioid receptor agonist. It acts by binding to the same mu receptors as other opioids, but is used to reduce withdrawal symptoms as well as cravings for opioids. This is because patients already addicted to opioids do not achieve a "high" while on methadone. Methadone is mostly used for heroin or other opioid dependence[12]. Because of its long half-life, its effects can last up to 24 hours and slowly taper off, so the withdrawal is less intense. This allows patients to be gradually weaned off of opioids entirely. Methadone is usually administered in a once daily dose in liquid or tablet form, though the latter is not as common[13]. This has long been a treatment of choice for chronic opioid addicts, albeit expensive[9].

Methadone is listed as a Schedule II drug. A Schedule II drug (i.e. cocaine, fentanyl) has a high potential for abuse, but has an approved medical use. The remaining Schedules (III, IV, V) are accepted for medical treatment, and have a low likelihood of abuse[14]. The potential for Schedule III drug abuse is lower than Schedule I and Schedule II drugs, but is higher than for Schedule IV[15]. Methadone is mostly ordered for OUD by licensed opioid treatment programs. These programs are required to provide counseling and social services for patients. Patients already on methadone from a licensed program may also be continued on methadone in an inpatient hospital setting to avoid withdrawal. Because the use of methadone is so strictly regulated to licensed centers, demand often exceeds availability[13].

Side effects of methadone include constipation, drowsiness, and overdose, very similar to other drugs in the class of opioids. Sexual dysfunction has also been reported in terms of reduced libido and erectile dysfunction. Lastly, though less frequently, methadone usage has been associated with life threatening arrhythmias in a dose-dependent fashion[13].

Meta-analysis studies have shown that patients receiving methadone are more likely to continue treatment and decrease opioid use compared to non-pharmacological treatment[16]. It has also been found that methadone is more effective than detoxification alone[17]. Methadone use has also reduced the spread of HIV, criminal behavior, and even long-term mortality. Treatment with methadone helps reduce psychological and social harms, as well[18].

Buprenorphine

Buprenorphine is a partial mu-opioid receptor agonist. Because

it is only a partialagonist, it has similar pharmacological effects to that of full agonists. Its affinity for the opioid receptor is so high that it has the ability to block the effect of other opioids. It can also reduce symptoms of withdrawal, does not give off the euphoria effect, and has been shown to be safer and better tolerated by patients than methadone[19]. However, because it is a partial agonist, it may require tighter doses to follow. It can be as effective as methadone if used in a dose-dependent manner[20]. Additionally, it demonstrates a "ceiling effect" in which exceeding a certain dose does not provide any added analgesic effect. Because of this, buprenorphine inherently carries a lower risk of overdose and associated adverse effects. However, if a patient is still experiencing the effects of a full opioid agonist, such as morphine, the addition of buprenorphine, a partial agonist, creates an antagonistic effect, thus actually precipitating a withdrawal[21].

Buprenorphine has approximately a 37.5-hour half-life. Because of this long half-life, its effects gradually diminish as it is tapered off; therefore any withdrawal symptoms are less severe. It is typically dosed every 24 hours usually through the sublingual route as this provides the greatest bioavailability[22]. The drug is available as a sublingual tablet or as a film strip that is dissolved under the tongue. Transdermal, intravenous, and intramuscular forms of buprenorphine have been approved for the treatment of acute and chronic pain. A new formulation of buprenorphine is the subcutaneous implant which has shown to be effective for 6 months and as such, increases patient compliance. Buprenorphine may also be administered in combination with naloxone as either a film strip, buccal film, or tablet form, known as Suboxone[21].

When initiated on buprenorphine therapy, the patient must abstain from short acting opioids for at least 12 hours, or 72 hours for long acting opioids, to the point where mild to moderate withdrawal symptoms have begun to manifest. The dose of buprenorphine may then be increased as needed based on degree of withdrawal and the patient's responsiveness to the drug[21].

Buprenorphine is a Schedule III drug, which, according to the DEA, has a moderate to low potential for physical and psychological dependence[15]. Physicians must be specially trained, certified, and registered with the US Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Service Administration (SAMHSA) and with the DEA in order to legally prescribe buprenorphine[23].

Adverse effects of buprenorphine are generally negligible due to its partial agonistic properties. Buprenorphine-related deaths occur secondary to respiratory depression and hypoxia. However, these deaths primarily occur when the drug is ingested concomitantly with another depressant such as benzodiazepines or alcohol[24].

In one study, buprenorphine was proven to be superior to placebo for maintenance therapy for opioid dependence in patients who use heroin at high doses (i.e. 16mg or more)[25]. Patients who received buprenorphine were found to have reduced use of illicit drugs and were more likely to adhere to treatments than those receiving placebo[26]. It was also determined that patients who received at least 12 week's worth of buprenorphine treatment were more successful in preventing relapse than those who received the same drug for only one to three months. Relapse rates in individuals only receiving one to three months was 90%[21].

In another meta-analysis comparing buprenorphine to methadone, researchers found that an 8-12 mg/day dose of buprenorphine was more effective than low dose methadone 40-50mg[26]. However, this study also found that patients were more likely to drop out of the study if they were on buprenorphine rather than methadone, which the researchers attributed to missing the "high" which methadone provides[19].

Despite some of the challenges associated with buprenorphine, it proves to have several advantages when compared to its counterparts. It is less likely to cause an overdose and physical dependence and is associated with easier detoxification than methadone[22].

Naltrexone

Naltrexone is a mu-opioid antagonist that prevents acute opioid intoxication or physiologic dependence with subsequent use, thus reinforcing abstinence[27]. This is an alternative option to the agonists, because instead of controlling withdrawals and cravings, it blocks euphoria[20]. However, despite these benefits, the first-line treatment for moderate to severe OUD is an opioid agonist medication (i.e., methadone or buprenorphine), rather than opioid-antagonist medications[27].

Two formulations of naltrexone exist. The first is a 50 mg tablet taken once daily, which is most effective in patients who are closely supervised or highly motivated. This tablet is equivalent to blocking 25mg of intravenous heroin for more than 24 hours[28]. The second formulation of naltrexone is an extended release or long-actinginjectable (LAI), at 380mg per 4 weeks[29-31].

Naltrexone is considered a Schedule II drug by the DEA, but it requires no special license or training to prescribe[31]. Common adverse effects of naltrexone include nausea, headaches, dizziness, fatigue, elevated ALT, increased creatine phosphokinase, and syncope. With supra-therapeutic doses, cases of liver damage have been reported, but can resolve with discontinuation of naltrexone. Patients who discontinue antagonist therapy and resume opioid use should be made aware of the risks associated with an opioid overdose, especially death. This is due to the loss of tolerance to opioids and a resulting misjudgment of dosage at the time of relapse[27].

Several clinical trials have assessed the efficacy of naltrexone, however results were limited due to poor adherence and high dropout rates[32]. Oral naltrexone was found to be more effective than placebo in sustaining abstinence in three trials in which patients were adherent to daily doses of the medication[27]. LAI naltrexonehas also been found to be more effective than placebo for opioid dependence in randomized trials[28,30,32,33].

As previously mentioned, several clinical trials have shown treatment with buprenorphine or methadone to reduce opioid use compared with placebo or other treatments. Studies comparing buprenorphine to naltrexone, however, were limited. One study comparing these determined that naltrexone required a much greater extent of full detoxification prior to initiating the drug than initiating buprenorphine-naloxone treatment. While it showed in this study that naltrexone can be effective for short term opioid abstinence, it requires patients who are highly motivated or under supervised medication administration[27,34].

Two recently published open-label clinical trials com-

paring monthly LAI naltrexone with daily sublingual buprenorphine found little evidence of a difference in abstinence rates, although it appeared that initial stabilization of buprenorphine may be easier to accomplish. The first clinical trial compared monthly LAI naltrexone and daily sublingual buprenorphine; it found the two medications to be comparable in reducing the use of heroin and other illicit opioids in opioid-dependent patients[34]. The second open-label clinical trial also compared LAI naltrexone with daily sublingual buprenorphine. It included patients who had entered inpatient programs for planned withdrawal from opioids but had not necessarily completed withdrawal at the time of enrollment. Less patients in the naltrexone group were successfully inducted onto medication compared with the buprenorphine group, however more patient staking naltrexone relapsed compared to patients taking buprenorphine[35,36].

Based on published data analysis, a valid approach to medication-assisted treatment with naltrexone for OUD should be as follows: For non-pregnant adults with mild OUD in the post withdrawal phase, naltrexone should be considered. If treatment fails, stop medication and initiate buprenorphine. If subsequent treatment with buprenorphine fails, change to methadone. For patients in the post-withdrawal phase with moderate to severe opioid use, treatment with buprenorphine should be initiated, as it is not an opioid antagonist[24,27].

Treatment Selection

As detailed above, there are a variety of medication options for alternative therapies, and in order to successfully prevent relapse, several factors should be considered [Figure 1]. Methadone, buprenorphine, and naltrexone are all approved by the FDA for long-term treatment to prevent relapse, with each medication having its unique outcomes, risks and benefits.

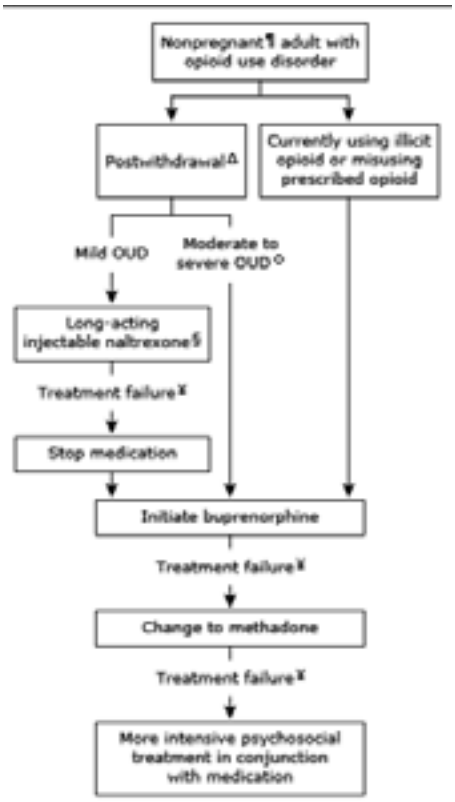

Figure 1: Treatment Selection Approach for OUD [12]

Severity of the OUD plays a key role in the selection, as buprenorphine and methadone are considered first line for patients who have moderate to severe OUD[24]. In deciding between the two, effectiveness, cost, and the availability need to be considered. Although both medications are effective (retaining patients in treatment and suppression of OUD), methadone is deemed slightly superior overall according to a meta-analysis comparing the two drugs[37]. Even though methadone has a higher efficacy, it is also a full agonist, thereby having a higher potential for abuse and lethal overdose. Taking into account this safety profile, buprenorphine is usually only recommended as the first line treatment[24]. It is reasonable to consider the usage of methadone in situations where buprenorphine is not feasible, such as failure of treatment to patients on buprenorphine or a history of buprenorphine misuse. Cost is also a crucial factor when deciding between the two maintenance therapies, as buprenorphine is more expensive than methadone[38]. Lastly, the regulation of methadone is more stringent than buprenorphine due to its higher schedule classification, and thus can only be given in specialized programs rather than office-based programs. The wider availability of buprenorphine and ease of access for patients makes it more appealing in terms of choice[39].

In patients with a mild OUD, naltrexone is a reasonable alternative to methadone or buprenorphine. Oral pills or LAI naltrexone can be used in patients who are highly motivated with mild opioid disorder, situations where medication use can be supervised, or circumstances in which the use of agonist medication is prohibited in certain occupations[24]. Apart from this, naltrexone should be administered once the patient is free of physiological opioid dependence, or greater than one week without symptoms of acute withdrawal[40].

Medical cannabis as treatment modality for opioid use disorder

Medical cannabis and its derivatives, known as cannabinoids, can serve as viable options for patients recovering from opioid addiction. The purpose of this section is threefold; first, to examine the preclinical and clinical evidence surrounding cannabidiol (CBD) and tetrahydrocannabinol (THC) on addictive behaviors as a whole; second, to highlight research establishing cannabidiol and the effectiveness of CBD in inhibiting opioid-seeking behavior; and third, to discuss the safety and pharmacokinetics of CBD when administered concomitantly with high-potency opioids.

Effect of CBD and THC on addictive and opioid-seeking behaviors

Despite numerous negative consequences, drug addiction continues to be an issue in the United States. Research has uncovered that the endocannabinoid system (ECBS) influences the acquisition and maintenance phase of drug addiction due to its function in reward and brain plasticity[41,42]. The endocannabinoid system is comprised of cannabinoids, endocannabinoid receptors, and various enzymes. CBD acts on the ECBS as a weak inverse agonist on CB1 receptors, stimulates vanilloid receptors, and alters the hydrolysis of anandamide by inhibiting fatty acid amine hydrolase[43-45]. These mechanisms, along with its 5-HT1A serotoninergic agonist properties, have led researchers to believe that CBD helps regulate the stress response as well

as compulsive behaviors, and thus can play an important role in substance abuse disorders[46].

CBD is the second most common chemical found in marijuana after THC. Currently, CBD is only approved for the treatment of a severe pediatric epileptic disorder[47]. Since CBD is non-psychoactive, it has not been shown to have any effect on cannabis intoxication when administered with THC[48]. Cessation of daily marijuana use leads to withdrawal symptoms such as increased irritability, anxiety, decreased quality and quantity of sleep, and reduced food intake[49]. Because CBD and THC have similar chemical structures, CBD may be used to bind to endocannabinoid receptors and aid in withdrawal from THC. One case study examined CBD oil and its ability to decrease addictive use of marijuana. The case study includes a twenty-seven-year-old male who was diagnosed with bipolar disorder and used marijuana daily. He self-reported that with the use of CBD oil, he was able to maintain a regular sleep schedule and decrease his overall anxiety. He also reported better relations with his family and friends, and additionally was able to obtain a stable occupation[50].

A 2015 systematic review searched existing preclinical and clinical data on CBD's effect on addictive disorders. Although there were a limited number of studies in this systematic review, many revealed that CBD may be a viable therapeutic solution for addictive behaviors from drugs such as opioids, cocaine, and psychostimulants[51]. One study included in this review investigated the effect of cannabinoids on morphine withdrawal syndrome. Morphine dependence was induced in rats, who were subsequently administered various doses of CBD. Withdrawal was precipitated with naloxone. During withdrawal, the dose of naloxone required to provoke 50% of the mice to jump off of a platform was recorded during the withdrawal, as were defecation and rearing behaviors. CBD was found to inhibit the naloxone withdrawal–induced jumping and reduced defecation and rearing behaviors[52]. Furthermore, a randomized, double blind, placebo-controlled study in the systematic review suggested that CBD may even be useful in reducing tobacco addiction. This study determined that in smokers who wanted to quit, those who used a CBD inhaler showed a 40% reduction in the number of cigarettes smoked compared to the placebo group. These results indicate that CBD may be effective helping active smokers reduce the number of cigarettes consumed[53].

Likewise, recent research exploring the use of CBD for drug and alcohol addiction is promising[54,55]. Individuals attempting to end their opioid use are at risk for relapse due to the craving induced by increased stress, anxiety, and impulsivity. The anxiolytic, antidepressant, anti-compulsive, and stress-reducing effects of CBD provide a basis for therapeutic benefit and a potential avenue to reduce the compulsive component of opioid seeking individuals[56,57].

Several studies have examined the effect of CBD on different phases of opioid addiction. One article found that CBD's influence on the intoxication phase of opioid addiction in animals reduces the reward-facilitating effect of morphine[51]. Another study examined the effects of CBD on self-administration and drug-seeking behavior using an experimental rat model. In these experiments, rats were able to self-administer heroin by pressing an active lever resulting in a drug infusion through catheter implantation. Rats who received a single injection of CBD 24 hours prior showed dramatically reduced active lever presses compared to placebo-treated rats. The influence of CBD on heroin-seeking behavior exhibited by the study proposes CBD as a potential treatment strategy to attenuate drug-seeking behavior[58].

Despite the findings in these studies, more research is needed to fully evaluate these relationships. Much of the existing literature suggests that CBD modulates several neuronal circuits involved in addictive processes. If these mechanisms are better understood, it could establish CBD as an effective and beneficial treatment modality for OUD[51].

Safety and Pharmacokinetics of Opioids and CBD

Heroin, Morphine, and Fentanyl

Heroin and morphine are opioid (mu, delta, and kappa) receptor agonists. Heroin is a semi-synthetic morphine derivative and a powerful opioid analgesic. Heroin can be injected intravenously or intramuscularly, inhaled into the lungs, absorbed intranasally (snorting), or administered and rectally. In order to synthesize heroin, morphine molecules are altered in order to make it more lipophilic than morphine. This molecular alteration allows heroin to pass the blood brain barrier much faster than morphine, resulting in a faster onset of action and a more intense pharmacodynamic effect. Heroin also binds opiate receptors with higher affinity compared to morphine. Heroine has a very short half-life, 1.3-7.8 minutes, and when injected intravenously, blood levels become undetectable after just 10-40 minutes. It is then hydrolyzed into 6-monoacetylmorphine, which is very lipophilic and is thought to have even higher opiate receptor affinity than heroin. Thus, it is considered responsible for all of the acute effects after heroin administration. 6-monoacetylmorphine is then metabolized by various enzymes into morphine, which is then conjugated and excreted in urine and bile[59].

Fentanyl is a man-made opioid that is 50-100 times stronger than morphine. Fentanyl quickly distributes into adipose tissue and is highly protein bound. Its onset of action begins almost immediately with intravenous administration and after 7–8 minutes with intramuscular administration. Fentanyl's half-life ranges from 6-32 hours. Peak effects of the drug are achieved in 5–15 minutes following intravenous injection. Analgesia after IM administration is observed for 1-2 hours. Thus, fentanyl has a faster onset of action but a shorter duration of action than morphine[60].

CBD

A 2017 World Health Organization report states that CBD is a naturally occurring cannabinoid found in cannabis plants that can also be produced synthetically. The report explains that CBD is generally well tolerated with a good safety profile, and that there had been no public health-related problems associated with the use of pure CBD since the time of the report. The naturally occurring CBD is a (-)-enantiomer and is the type of CBD receiving a majority of the attention for its potential therapeutic effects. In clinical trials, CBD is generally administered orally as a capsule or dissolved in an oil solution[61,62].

Oral CBD has low bioavailability due to its poor absorption in the gastrointestinal tract and significant first pass metabolism, which causes a varying pharmacokinetic profile[63]. Aerosolized CBD yields a quicker time to peak plasma concen-

tration (5-10 minutes) and has a higher bioavailability compared to oral administration[62]. Similar to THC, CBD is very lipophilic, causing it to preferentially accumulate in adipose tissue[64].

THC and CBD both act on the endocannabinoid system, as discussed earlier. Humans express at least two cannabinoid receptors. First, the CB1 receptor is present in many cell types throughout the body, functioning particularly in the nervous system. Secondly, CB_2 receptors are mainly expressed in immune cells, such as macrophages, B and T-cells, and monocytes. Recent studies have found that CB_2 receptors are often upregulated in non-immune cell types under certain pathological conditions[65].

The exact mechanisms of CBD and THC are not well-known. One study found that CBD demonstrates low affinity at CB_2 receptors but does not directly act on CB1 receptors. There is also evidence suggesting an inhibition of cytochrome p450 enzymes. Effects on the immune system are unclear, with evidence of suppression at high dosages and stimulation at low dosages[66]. However, studies have shown that CBD has several beneficial medical properties, such as anti-inflammatory, antioxidant, antipsychotic, antidepressant, and anti-nausea[61]. Based off of recent updates in the literature, CBD has shown to have a low toxicity[67,68]. Additionally, CBD has no observed effect on embryonic development or hormonal changes.

A common concern regarding the use of CBD is its safety profile when taken with other high-potency opioids. One study has found that CBD, when administered concomitantly with fentanyl, was well tolerated with no significant pharmacokinetic changes. Fentanyl did not significantly alter plasma CBD concentrations, and there were no incidents of respiratory depression or cardiovascular compromise[66].

While the need for further research on the effects of CBD is great, there is at least evidence that suggests that the drug could function as an adjunctive treatment to assist patients struggling with OUD and opioid withdrawal, or possibly even as a primary treatment modality. Given the promising evidence that CBD is safe and well-tolerated, it is imperative that additional quality clinical trials be conducted to investigate what role CBD could play in the management of OUD. There is an extremely high level of need for OUD treatment in the U.S., making it critical that any novel therapeutic approaches be evaluated without delay.

Legal Analysis

The medical applications of cannabis cannot be fully discussed without mentioning the complex legal dimensions surrounding marijuana. While federal regulations pertaining to cannabis have remained steadfast for nearly five decades, state legislation has rapidly evolved over that same period, especially within the past 20 years. As a result, fierce political debate, not medical merits, has dominated the conversation regarding marijuana. In this section, the various legal aspects of medical marijuana in the U.S., including the evolution of federal legislation, the spectrum of state law, federal versus state law, and the influence of public opinion on marijuana legislation, will be discussed.

The birth of the federal government's legal history with marijuana dates back to more than a century ago[69]. The passage of the Pure Food and Drug Act of 1906 required all over-the-counter medicines containing cannabis, cocaine, morphine or opium that crossed state lines to list these ingredients on the label. This marked the first law identifying marijuana as a "dangerous" drug. However, at this time, physicians were still allowed to prescribe marijuana to patients for various ailments. This changed in 1937 when the U.S. legislature passed the Marihuana Tax Act[70]. This statute limited the possession of marijuana to individuals who paid an occupation (medical or industrial) excise tax to utilize the drug, essentially criminalizing marijuana. Subsequently, the 1950s saw the passage of the Boggs Act (1951) and Narcotics Control Act (1956), which included mandatory sentences for drug-related offenses, such as the possession or distribution of marijuana[71]. Under these laws, a first-time offender convicted of marijuana possession faced a minimum sentence of 2-10 years and a fine as much as $20,000[72].

The current day legal battles regarding marijuana take their roots in the 1970 Uniform Controlled Substances Act, which created five schedules of drugs (Schedule I, II, III, IV, and V), and classified marijuana as a Schedule I drug[73]. In addition to marijuana, other Schedule I drugs include heroin, lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote. As discussed earlier, the DEA defines Schedule I drugs as substances with no acceptable medicinal use and a high likelihood of abuse[74]. These drugs can only be used in a research setting, and possession of any Schedule I substance is illegal[75].

While the federal government has continued its prohibitory stance on cannabis, state laws vary drastically from prohibition to legal for recreational use. Following the Controlled Substances Act of 1970, the first state to pass legislation contradicting the federal policy was Oregon, which decriminalized the possession of small amounts of marijuana[75]. While several other states passed similar laws over the next decade, the first medical marijuana law was not passed until 1996 when California voted on the Compassion Use Act (Proposition 215), which afforded "seriously ill" patients the right to use marijuana for medical purposes[76]. Subsequently, 33 other states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands followed suit and enacted their own medical marijuana laws[77]. In 2012, Colorado became the first state to move beyond medicinal marijuana and legalize marijuana for recreational use[78]. Currently, ten states (Alaska, California, Colorado, Maine, Massachusetts, Michigan, Nevada, Oregon, Vermont, and Washington) and the District of Columbia have legalized both medicinal and decriminalized use of marijuana[14].

With respect to cannabis legislation, state laws have clearly taken steps that challenge federal policy. Consequently, this leads to the logical question about which policy (state or federal) holds more weight and should be followed. This question was first addressed by the Founding Fathers in the Supremacy Clause (Article VI paragraph 2) of the Constitution, which states that federal law supersedes state law[79]. Based on this legal precedence, it seems clear that the federal policy of marijuana illegality should trump conflicting state laws. However, the reality is not black and white. The federal government has jurisdiction over states like Colorado and Maine where the recreational use of marijuana is legal and can assert this authority to penalize individuals breaking federal law, but enforcement poses an issue. First, the resources necessary to apprehend, charge, and prosecute marijuana violations across the country would be vast; and

second, with public opinion supporting some form of marijuana legalization, political fallout could be extremely damaging to an individual politician or political party[80]. Furthermore, there are now protections for medical marijuana in place that prevents federal intervention at the state level.

New developments within the Trump Administration and Senate have been encouraging for legalization advocates. During his Senate confirmation hearing in January of 2019, AG William Barr vowed not to prosecute marijuana companies in compliance with state law[81]. Moreover, in a written response to questions from senators, AG Barr voiced support for an increased number of legal growers of marijuana for scientific research. AG Barr has also testified that he endorses the Strengthening the Tenth Amendment Through Entrusting States Act (STATES Act), a bipartisan bill aimed at granting states the right to enact the best approach to marijuana legislation within its borders[82,83]. The bill would amend the Controlled Substances Act such that it would no longer apply to any individual adhering to state or tribal marijuana laws[84]. A newly proposed version of this bill has gained significant support among Democrats and Republicans, but no vote in either chamber of Congress has happened yet. Additionally, as of November 2019, the House Judiciary Committee approved a bill that could legalize marijuana use at the federal level, allowing states to have more freedom in creating unique individual laws. The piece of legislature would also remove marijuana from Schedule I of the Controlled Substances Act[85]. We hope this bill will be approved by the House and Senate, and ultimately signed by the president.

Beyond the challenges of states passing their own laws, the federal government has also faced legal battles from groups of individuals advocating for an end to the Controlled Substances Act. In July 2017, a group of patients using cannabis for medical reasons and cannabis activists brought a lawsuit for legalization against the federal government, arguing that the Controlled Substances Act violates their constitutional rights[86]. The plaintiffs in the case of Washington, et.al v. Sessions, et.al. [87] contended that current federal law violated the 1st, 5th, 9th, 10th, and 14th Amendments because it threatened their rights to travel, engage in commerce, and due process. The five plaintiffs included Jose Belen, an Iraq War veteran with PTSD, Alexis Bortell, a 12-year-old with intractable seizures, Jagger Cotte, a seven-year-old with tremendous pain due to Leigh's Disease, Marvin Washington, a former NFL player and cannabis activist, and the Cannabis Cultural Association, an organization that advocates for minority leaders within the cannabis industry. The lawsuit argued its case for legalization from a collection of constitutional laws and from a plethora of historical examples of medicinal marijuana dating back to thousands of years ago. Judge Hellerstein of the Southern District of New York agreed with the plaintiff's argument that marijuana has medical benefits, but ultimately granted the federal government's motion to dismiss the case by concluding that Congress and the DEA have the right to regulate marijuana by classifying it as a Schedule I drug[88].

In response to numerous petitions requesting the rescheduling of marijuana from a Schedule I drug to a lesser Schedule, the DEA published its reasoning for the denial of these petitions in 2016[89]. The crux of their rationale was the recommendations of the FDA and Department of Health and Human Services (HHS). Based on the information provided to the DEA by the FDA and HHS, the DEA concluded that marijuana should remain a Schedule I substance for three main reasons: (1) "Marijuana has a high potential for abuse;" (2) "Marijuana has no currently accepted medical use in treatment in the United States;" and, (3) "Marijuana lacks accepted safety for use under medical supervision" [89]. The filing went on to note there are no studies establishing that marijuana is useful in the medical treatment a specific disorder. This position directly contradicts the numerous studies demonstrating the medical benefits of marijuana stated earlier. The DEA also used the FDA's conclusion that there is a lack of consensus among "qualified experts," or individuals "qualified by scientific training and experience to evaluate the safety and effectiveness of a drug"[89]. To support its third and final point for denial of reclassification, the DEA noted that there were no FDA-approved marijuana products. While true in 2016, this has changed recently. In June of 2018, the FDA approved Epidiolex (cannabidiol), a CBD-containing drug, to treat seizures caused by two forms of epilepsy. Epidiolex is the first FDA-approved drug to contain active ingredients from marijuana and is classified as a Schedule V drug under the Controlled Substances Act[90].

As the debate surrounding the legal status of marijuana has evolved, so too has public opinion. For example, a March 2019 Quinnipiac University Poll found that 93% of Americans supported medical marijuana prescribed by a doctor[91]. Support for recreational marijuana is at record highs, with nearly two out of three Americans supporting legalization in recent Gallup and Pew Research polls[93,94]. As more Americans continue to look favorably on marijuana for medical and recreational use, an important distinction must be made: these are two separate issues and should not be conflated. The research on the medical applications of marijuana and marijuana-related products is promising. Nevertheless, the caution shown by the federal government is warranted. The DEA's assertion that marijuana has a high potential for abuse is supported by recent federally funded studies that saw an increased prevalence of marijuana use disorder, particularly among adolescents[95,96]. This is a major concern in the US especially given the current opioid epidemic grappling the nation. This crisis began when pharmaceutical companies assured physicians that opioids (Schedule II drugs) did not have a high addiction potential, and physicians started prescribing at much higher rates[74,97]. However, before increased marijuana usage is viewed as the next opioid epidemic, it is important to highlight key differences between cannabis and opioids. First, opioid abuse is associated with a high risk of overdosing; marijuana has minimal risk of increased mortality[98]. Second, the addiction potential of opioids is great; developing marijuana use disorder is a concern, but the risk is much lower than that from opioids[99]. As discussed earlier, the efficacy of marijuana in the treatment of chronic pain and the decreased opioid use in patients using medical marijuana demonstrate that cannabis is a promising alternative to opioids[100-103]. The FDA now recognizes this fact and supports the investigation of medical marijuana through "adequate and well-controlled clinical trials"[90]. As long as physicians understand the wide array of benefits and harms associated with marijuana before prescribing, patients can make informed medical decisions.

Political momentum and public opinion are moving in a direction that favors not only marijuana for medical usage,

but for recreational use as well. The increasing number of states passing laws permitting the use of both decriminalized and medical marijuana necessitates an increase in quality research on marijuana[14]. If this is made possible and current federal restrictions are lifted, medical marijuana has great potential to benefit patients as replacement therapy for OUD.

Establishment of a Medical Marijuana Clinic in Philadelphia

Opioid Crisis in Philadelphia

Philadelphia is one of the cities greatly affected by the opioid epidemic. In May 2014, it was estimated that 50,000 people have overused prescription painkillers and opioids in one year and that there were about 70,000 heroin users in the Philadelphia area[104]. The population of people who inject drugs (PWID) in Philadelphia alone is as high as 26,400[105]. In 2017, there were 1,217 drug-related deaths documented, 1,074 of which involved the use of opioids[106]. Moreover, drug overdoses were the leading cause of death, killing four times as many people as homicides[107]. Even the AIDS epidemic, at its worse, fell 200 deaths short of the number of drug-overdose related deaths in 2017[104].

At the epicenter of this epidemic is Kensington, a once bustling working-class neighborhood where immigrants could find affordable housing and stable factory jobs; now, it is one of the East Coast's largest "open air" drug markets[108]. Originally, the main focal point of the crisis was Kensington, but it has now spread throughout the city where no subpopulation has remained unaffected. With estimates nearing 1,200 lives cut short in 2017, Philadelphia takes its place as the number one major city hardest hit in the United States[109].

One way for individuals with substance use disorder to pursue sobriety is through pharmacotherapies. As of January 2019, the Mayor's Task Force has begun a four-part series of initiatives to combat the opioid crisis which includes prevention and education, treatment, overdose prevention and harm reduction, and involvement of the criminal justice system. One recommendation is to increase the provision of MAT, or medication-assisted treatment[110]. The Department of Behavioral Health and Intellectual Disability Services (DBHIDS) issued three policies in an attempt to increase education, individual choice and availability of MATs[110]. As of December 2018, the total DBHIDS in-network MAT Program capacity was 12,479 slots, 2,906 of which were available[110].

Most of these programs implement opioid maintenance treatments using methadone or Suboxone. However, less than 25% of all individuals affected by substance abuse disorder who quit opioids are able to remain sober without relapsing[111]. Even though these maintenance therapies help lower the amount of heroin used by individuals with substance use disorder, many individuals remain on methadone or Suboxone treatment for months or years. Additionally, approximately 40-60% is expected to relapse at least once within the first year[111]. Thus, these pharmacological therapies are usually unsuccessful for long-term sobriety and are not enough. This section will propose a replacement therapy clinic that integrates standard pharmacological treatments (i.e. methadone, Suboxone) with medicinal cannabis in conjunction with psychological and social avenues that could help individuals in Philadelphia with substance use disorder[112].

Planning

Clinic Layout

The Medical Marijuana for Opioid Replacement Therapies Clinic (MMORT Clinic) is intentionally designed in a manner that promotes safety, effectiveness, and community worth. This comprehensive treatment center will incorporate Suboxone, methadone, and medical marijuana and will be stationed in the heart of Philadelphia, particularly in Kensington. The general design of the MMORT Clinic will be adapted from Coatesville Comprehensive Treatment Center in Coatesville, PA. A kiosk will be present at the entrance which patients can enter an ID code, which will allow entry into the waiting room. Patients will wait there for a nurse or receptionist to assist them with their prescriptions. Once inside, there will be window bays staffed by a nurse to provide safe administration of the treatment. Beyond the area of drug administration are rooms where the patient can receive treatment and counseling from other members of the overall care team such as psychiatrists, physicians, counselors, and social workers.

The clinic will have additional services for the patients as well as several safety features. The clinic's layout must be wheelchair accessible, providing ramps in place of stairs. Next to the care team offices will be a play area for children so they can be supervised while the patients are being seen. The MMORT Clinic will have security checkpoints throughout the facility to ensure its safety. The first entrance will have a basic lock-and-key and metal gate to be secured at night, but open during designated hours. A second door will be placed prior to entry to the bay windows requiring a provided member ID. Once inside the clinic, there will be surveillance in all of the general spaces. Lastly, there will be keypads in each of the private rooms, record rooms, and the drug storage rooms. Only the clinic staff will have the pass codes to these rooms.

Staff

The MMORT Clinic must be composed of an interdisciplinary treatment team devoted to serving their patients. This team will consist of psychiatrists, physicians, nurses, counselors, social workers, receptionists, and security guards. Psychiatrists provide the initial evaluation of the patient, gauging the amount of medical, psychological, and social needs of the patient. Physicians provide wound care and address any major health concerns for the patient. A psychological counselor provides sessions to address the patient's mental health needs. The nurse provides the drug regimen for patients and any immediate needs of the patient. The social worker assists with the familial, communal, and economical dimensions of the patient. Each member of this unit will work together cohesively to develop a safe, efficient, and effective environment and care plan for the patient.

Types of Treatment

The MMORT Clinic would offer a holistic treatment approach to best care for its patients, which would include wound care, psychopharmacological treatment, and psychological counseling.

Wound care

Chronic repeated injections of IV drugs can lead to venous sclerosis, in which the vein is no longer patent and a viable route to

administer the drugs[113]. Individuals typically resort to intramuscular and subcutaneous methods of using opioids. Compounded with the effects of opioids, wounds and lacerations can be inflicted from improper technique[113]. As a result, comorbid conditions can arise via the use of needles such as necrotizing fasciitis, wound botulism, gas gangrene, and tetanus. Additionally, a high prevalence of sharing needles has led to an increase in spread of HIV, Hepatitis B, Hepatitis C, and tuberculosis in this population[113]. Therefore, the MMORT Clinic would have wound care service staff alongside healthcare personnel to provide immediate care for the wounds at the site to minimize the spread and progression of secondary infections.

Psychopharmacology

The psychopharmacological approach at the clinic seeks to create a collaborative effort between the healthcare staff and the patients. Psychopharmacology incorporates the use of medications and psychology to monitor the pharmacokinetics and pharmacodynamics of the drugs that impact an individual and their mental health. Psychopharmacology plays a crucial role in the detoxification and minimizing withdrawal symptoms that individual's experience. The focus is to eliminate the effects of opioids in a safe and effective manner. Here, physicians will work with the patients to create a treatment regimen that consists of opioid agonists or antagonists with medical marijuana. The aim for this combination is to wean patients off of opiates initially with the use of methadone or Suboxone. The methadone or Suboxone would be paired with medical marijuana until patients would eventually be transitioned to non-steroidal anti-inflammatory drugs (NSAIDS) for pain management.

Psychological Counseling

There is a high prevalence of mental illness among patients with substance abuse issues. Studies indicate that of the individuals with substance use disorder, 28% had co-occurring anxiety disorders, 26% had mood disorders, 18% had antisocial personality disorder, and 7% suffered from schizophrenia[114]. Individuals with mood disorders are more susceptible to succumb to drug abuse and addiction due to underlying brain deficits, genetic disposition, and/or early exposure to stress or trauma[115]. Furthermore, social determinants of health, socioeconomic factors, and the physical environment can have a strong impact on a patient's mental health. The NIDA states that stress is the leading cause of relapse while in recovery[116]. However, mental illness and substance abuse are treated separately as opposed to a dual-diagnosis program in the U.S. In 2016, only 6.9% of adults were treated for both mental illness and substance abuse[114]. Therefore the implementation of psychological counseling is pertinent in order to address the co-morbid conditions of mental illness and substance use disorder. Psychological counseling will consist of individual and group therapies as well as cognitive-behavioral therapy and dialectical-behavior therapy to address the harmful beliefs and maladaptive behaviors to reduce harmful behaviors and drug abuse. The psychological counselors will also work closely with social work to address the background of the individual in recovery to help mitigate stress.

Phases of Treatment

Initial assessment

If no immediate wound care is needed, individuals would be examined for history of abuse, and patterns of consumption. Triggers and the patient's attitude towards abstinence and motivation for change will also be evaluated. After assessment, the patient and the team can develop a plan consisting of detoxification and a pharmacological regimen. Psychological co-morbities and socioeconomic factors would also be considered. It is also important to offer or establish a support group and community network in which that the patient feels comfortable during and even after treatment.

Detoxification and maintenance

Although opioid detoxification is a crucial first step in the recovery process, it alone is not sufficient to free a dependent person from addiction. However, the detoxification process is vital for the complete rehabilitation and ultimately abstinence. The detoxification process, for our purposes, will serve as bridge between overcoming withdrawal and beginning replacement therapy. As discussed earlier, the symptoms experienced from opioid withdrawal can be severe and quick acting. Therefore, the best method of action to cope with these symptoms are to enroll in inpatient treatment programs that can closely monitor the individual's vitals as they progress through the pharmacological and psychological treatment plans.

Preventative care and support

Preventative care plays an essential role in addiction recovery, providing information and counseling on addiction and the recovery process. For recovering individuals, the program seeks to address their individual needs physically, mentally, and emotionally. It helps patients understand the intricacies of opioid addiction and provide a regimented plan to taper them from the dependency of substances using psychopharmacology. For the family and/or support group, it enhances the understanding of the disease concept, dependency, and the effect on relationships. The support counseling also addresses the implications behind their role as caregivers and allows the unit to seek advice in order to give proper support. The aim of preventative care is to 1) keep individuals from relapsing, 2) provide information and counseling on the overall impact of addiction and the psychopharmacology that the clinic provides, 3) establish concrete goals of care, 4) open the dialogue between parties, and 5) strengthen both individuals and their supportsystems. After interacting with individuals alone and within support groups, counselors will assess and provide realistic short and long-term goals so that the patient can achieve his or her desired quality of life.

Rehabilitation and integration

Other determinants that affect the overall health of patients and their propensity for drug use are low socioeconomic status, low income, lack of education, unemployment, inaccessibility to resources, community disorder, etc.[117]. According to recent studies, 75% of homeless patients were also suffering from substance abuse. Furthermore, those homeless individuals were nine times more likely to overdose than those who had a form of stable housing[118]. The opioid Crisis Response Act of 2018 not only aims to expand access to rehabilitation and recovery centers, but also pushes for Medicaid-funded housing for those

suffering from substance abuse[119]. While this is a step in the right direction, more can be done. This clinic will help serve as a resource for individuals to be informed on housing opportunities at shelters or programs that specifically house people with substance abuse disorder. The MMORT Clinic will partner with programs such as Project HOME to help these individuals in getting back on their feet by providing affordable and safe housing, education, employment opportunities, the option to rebuild resumes and practice interview skills, and the support they need to recover. Social work can also assist with the reintegration of individuals back into society through both community service and providing resources to help assist in their milieus. Additionally, it is important to connect individuals with safe housing and vocational supports to facilitate healthy and positive outcomes. The focus of these rehabilitation and integration options is to work closely with patients in order to keep them in recovery and lay a solid foundation so that they can achieve positive outcomes and qualities of life.

Additional Services

Hepatitis-C Screenings

Hepatitis C virus infections are one of the most commonly acquired blood-borne diseases among IV drug users. In Philadelphia, it is estimated that between 20,000 and 45,000 of residents are living with hepatitis. In 2018, 928 new cases were documented, 60% of which reported IV drug use[120]. Prolonged exposure to the virus can lead to fatigue, fever, jaundice, muscle aches, and liver cirrhosis[121]. Treatment for symptomatic chronic hepatitis entails a relatively new 12-week antiviral regiment that ranges from $63,000 to $94,500 per person[122]. Therefore, the clinic will offer Hepatitis C screenings as proactive measure andencourage patients to seek treatment early to minimize costs for both the patient and the healthcare system.

HIV Screenings

HIV (human immunodeficiency virus) is another virus that can be spread through sharing needles and unsafe injections. In Philadelphia, the rate of newly acquired HIV infection is five times the national average[123]. HIV infects the body's CD_4^+T cells which help the immune system fight infections. If left untreated, the reduction of CD_4 cells leaves the body defenseless and susceptible to secondary infection or cancers that can lead to acquired immune deficiency syndrome (AIDS)[124]. No effective cure for HIV currently exists, but there are treatment plans that reduce the HIV viral load.

PWID have a tendency to seek emergency medical attention once the symptoms have progressed to later stages, putting a substantial burden on healthcare systems. Additionally, according to the CDC, the cost for one treatment over a lifetime for an HIV infection is estimated at $379,668 per individual[125,126]. One article compared the lifetime cost of patients infected with HIV at age 35 (antiretroviral medications and other treatments) to that of non-infected individuals who are at high risk for infection. It was estimated that approximately $229,800 is saved by avoiding one HIV infection, which highlights the significance of HIV prevention[127]. Therefore, offering HIV screenings in addition to Hepatitis C screenings would be beneficial for both PWIDs and healthcare systems in reducing healthcare costs.

Recovery/Support Groups

Clinics will offer support groups for those seeking further help. The clinic will provide various options for recovery groups, including but not limited to community, outpatient, inpatient and sober living community programs[128]. These sessions, if applicable, will be held directly at the facility. If a patient is seeking a more permanent home-style facility, the clinic will connect the individual with options that satisfy their needs. If patients choose to utilize a community recovery group outside of the clinic, various locations and times of the meetings will be provided. It is important to remember that it is only up to the individual to get the help they want.

Recovery group meetings held at the clinic or a facility nearby will have a tight, regulated schedule. There will be multiple group meetings throughout the week at varying times to give options to those with different schedule conflicts. Trained leaders will direct the sessions and reward members with "recovery chips" as they achieve milestones in their sobriety. Members involved with the program will be appointed a sponsor to act like a guide in the recovery process. Any individual that does not participate in a recovery program provided by the clinic will have to abide by any procedures and processes set forth by that facility.

Childcare and Youth Education

A safe space will be provided for children while their parents are receiving counseling or administering their dosage. This space will be secluded from the waiting room and will include a childcare specialist to watch over the area and activities to keep children occupied (puzzles toys, books, movies, etc.). The clinics will also partner with various universities to offer responsible student volunteers the opportunity to babysit, assist the children with schoolwork, and provide general company.

Furthermore, the childcare specialist will monitor children for repercussions of Adverse Childhood Experiences (ACEs). ACEs encompass all types of abuse, neglect and traumatic experiences that occur to individuals under the age of 18[129]. Children who encounter ACEs have a higher propensity to engage in risky health behaviors such as alcohol and drug abuse and are more susceptible to chronic health conditions, low life potential, and early death[129]. Therefore, it is also important to provide resources to address the physical and psychological needs of children of guardians with substance use disorder, as well.

It is also important to educate the younger generation of the implications behind substance use and the prevalence of opioid addiction. The Department of Education in Ohio has implemented its own educational curriculum from kindergarten to twelfth grade, which emphasizes substance recognition, resistance, and navigation based upon age groups[130]. From kindergarten to third grade, students are taught the differences among foods, poisons, medications and drugs. In the fourth and fifth grades students are taught about the numerous effects of a variety of drugs. The sixth to eighth graders are introduced to addiction, abuse and misuse, impacts on family and peers, and how the media can influence substance abuse. In high school, the students are taught the responsibility of proper handling of prescription medications and recognizing symptoms of drug

overdose[130]. Thus, the implementation of a substance abuse curriculum in Pennsylvania schools would also be beneficial in the prevention of an opioid crisis for future generations.

Implications to establishing a replacement therapy clinic

There are many barriers to establishing a methadone clinic. For example, many opponents of methadone clinics do not see the value added for their community and assert that the clinics do not fit the pattern of businesses and professional offices in the area[131]. The clinics may have a negative connotation in certain communities and deter their construction, especially in wealthier areas.

The goals of the replacement therapy clinic are not just designed to benefit the individuals who are enrolled but are also aimed to benefit the community at large as well. The clinic will attempt to improve the surrounding area by making it cleaner and safer. Many communities do not wish to harbor drug replacement therapy clinics for fear of increasing rates of crime, drug use, and litter. In fact, replacement therapy clinics do not cause rates of crime to increase in the surrounding area; studies have shown that the same number of violent crimes occur near convenience stores as to drug replacement therapy clinics[132]. In reality, these centers are public health facilities that are necessary for the rehabilitation for the individuals of a community. Our program will also strive to decrease rates of crime by providing our members with behavioral cognitive therapy. By implementing this in tandem with pharmacological medications, we hope to rehabilitate these individuals from both addictions and also prevent violent crimes.

As part of the community outreach program, clinic members will have the opportunity to go into the surrounding area and engage in community service programs. This will provide the public with assurance that this facility will serve as a community pillar, rather than an establishment that depreciates property values. Certain areas of Philadelphia, especially Kensington, have become a refuge for broken needles, abandoned cars, mattresses, and litter. By employing our recovering individuals to go out and to better their community, we are demonstrating their self-worth as assets to the public while simultaneously restoring an area deeply affected by the opioid epidemic.

Another issue facing patients, rather than the clinic itself, is Pennsylvania's driving law. Chapter 38 Title 75 under controlled substances states that individuals cannot drive a vehicle if their blood contains any amount of Schedule I, Schedule II, or Schedule III drugs[133]. Unfortunately, methadone is classified as a Schedule II controlled substance[133]. Those in violation of that law are subject to a list of penalties. First time offenders are set to undergo a mandatory minimum term of six months' probation, pay a fine of $300, attend an alcohol highway safety school, and comply with all drug and alcohol treatment requirements[133]. This proves to be problematic for those who are seeking an alternative method of treatment to combat an opioid addiction. Clinics are often opened early in the morning to allow individuals to come to treatment without being stigmatized. As many of the individuals are coming before work, they may need to drive to that destination if they cannot secure a ride. Even though the dosage that is given will not cause any impairment, it is still risky for an individual to receive treatment and leave the clinic driving a vehicle. Although medical marijuana has been studied in various medical conditions, its effects on driving performance remain uncertain[134]. A 2018 study that compared differences in driving performance between chronic medical marijuana users and nonusers found that chronic users had more impairments[135]. As a result, public transportation resources will be given at the MMORT Clinic to ensure the safety of patients after receiving treatment.

Ethical Perspective

Society, in general, has always recognized that in our complex world there is the possibility that we may be faced with a situation that has two consequences--one good and the other evil. The time-honored ethical principle that has been applied to these situations is called the principle of double effect. As the name itself implies, the human action has two distinct effects. One effect is the intended good; the other is unintended evil. As an ethical principle, it was never intended to be an inflexible rule or a mathematical formula, but rather it is to be used as an efficient guide to prudent moral judgment in solving difficult moral dilemmas[136]. The principle of double effect specifies four conditions which must be fulfilled for an action with both a good and an evil effect to be ethically justified:

1. The action, considered by itself and independently of its effects, must not be morally evil. The object of the action must be good or indifferent.
2. The evil effect must not be the means of producing the good effect.
3. The evil effect is sincerely not intended, but merely tolerated.
4. There must be a proportionate reason for performing the action, in spite of the evil consequences[125].

The principle of double effect is applicable to the issue of whether it is ethical for a physician to prescribe marijuana as an adjunctive treatment to assist patients struggling with OUD and opioid withdrawal, or possibly even as a primary treatment modality because it has two effects, one good and the other evil. The good effect is that marijuana is more effective than conventional therapies in helping patients in the treatment of chronic pain and decreases opioid use. The evil effect is that marijuana smoke has toxic effects and as a Schedule I illegal drug it has been argued it could lead to more serious drug abuse and sends a wrong message that illegal drug use is safe and even condoned. To determine if it is ethical for physicians to prescribe medical marijuana for patients as a medical therapy, this issue will be examined in light of the four conditions of the principle of double effect.

The first condition allows for the medical use of marijuana because the object of the action, in and of itself, is good. The moral object is the precise good that is freely willed in this action. The moral good of this action is to stop an individual's cravings for opioids and the onset of withdrawal symptoms. Some of the main withdrawal symptoms include nausea, muscle pains, cramping, and anxiety. Two of the main components present in cannabis, cannabidiol (CBD) and tetrahydrocannabinol (THC) have been shown to effectively relieve these symptoms. The immediate goal is not to endorse, encourage or promote illegal drug use. Rather, the direct goal is to relieve patients of their unnecessary pain and suffering[1] [127]. The second condition permits the medical use of marijuana because the good effect

of relieving an individual's cravings and withdrawal symptoms is not produced by means of the evil effect. The two effects happen simultaneously and independently. The third condition is met because the direct intention of medical marijuana is to give patients suffering from opioid addiction relief from the effects of withdrawal and as a possible replacement therapy. Recent studies have shown that cannabinoids and CBD in particular, modulate addictive processes in some way, and if these mechanisms are better understood through future research, then it could establish cannabinoids as being beneficial in helping to treat addictive disorders as a replacement therapy. To deny a physician the right to discuss, recommend, and prescribe marijuana to patients is a direct violation of the physician-patient relationship. To make an informed decision about their treatment, patients have the right to expect full disclosure and discussion of all available treatment options from their physicians. Failure to do this violates the patient's right of informed consent[138].

The hypothesized foreseen but unintended consequences of legalizing medical marijuana are two-fold. First, the smoke from marijuana is highly toxic and can cause lung damage. The intention of smoked marijuana is not to cause more health problems but to remedy the effects of existing treatments. Second, some members of the federal government believe that legalizing medical marijuana may lead to harder drug usage and may be seen as condoning and encouraging recreational drug use. Nevertheless, this has not been proven to be true. The March 17, 1999 report by the Institute of Medicine found no evidence that the medical use of marijuana would increase illicit use in the general population, nor was it a "gateway drug" that would lead to the use of harder drugs like cocaine or heroin[139]. A 2003 study by Jan van Ours of Tilburg University in the Netherlands, found that cannabis users typically start using the drug between the ages of 18 and 20, while cocaine use usually starts between 20 and 25. But it concludes that cannabis is not a stepping stone to using cocaine or heroin. Four surveys, covering nearly 17,000 people, were carried out in Amsterdam in 1987, 1990, 1994 and 1997. The study found that there was little difference in the probability of an individual taking up cocaine as to whether or not he or she had used cannabis. Although significant numbers of people in the survey did use soft and hard drugs, this was linked with personal characteristics and a predilection to experimentation[140]. The National Institute on Drug Abuse states, "the majority of people who use marijuana do not go on to use other, 'harder' substances. Also, cross-sensitization is not unique to marijuana. Alcohol and nicotine also prime the brain for a heightened response to other drugs and are, like marijuana, also typically used before a person progresses to other, more harmful substances. It is important to note that other factors besides biological mechanisms, such as a person's social environment, are also critical in a person's risk for drug use. An alternative to the gateway-drug hypothesis is that people who are more vulnerable to drug-taking are simply more likely to start with readily available substances such as marijuana, tobacco, or alcohol, and their subsequent social interactions with others who use drugs increases their chances of trying other drugs. Further research is needed to explore this question" [141-145]. If officials in the federal government are worried that the legalization of medical marijuana will send the wrong message to our children about drugs, then why have 33 states and the District of Columbia, Puerto Rico and the Virgin Islands enacted medical marijuana laws making it legal for medical purposes? It has been proven medically effective in treating pain, nausea, severe weight loss associated with AIDS and to combat muscle spasms associated with multiple sclerosis that cannot be treated adequately by traditional medicines, etc. These treatments are firmly grounded in medical research. If medical marijuana is effective in treating withdrawal symptoms and as a possible replacement therapy for opioid addiction, then it will send a message to our children that we must give their mothers, fathers, brothers, sisters and cousins the best possible medicine available to overcome this disease. Will some people view the legalization of medical marijuana as the condoning and encouraging of marijuana for recreational drug use? The answer is "yes." But this is not the direct intention of legalizing medical marijuana as a possible replacement therapy for opioid addiction. The direct intention is to relieve pain and suffering that cannot be relieved by presently approved medications. This misinterpretation of the legalization of medical marijuana can be corrected through public education. Finally, the argument for the ethical justification of marijuana for medical use by the principle of double effect focuses on whether there is a proportionately grave reason for allowing the foreseen but unintended possible consequences. Proportionate reason is the linchpin that holds this complex moral principle together[146-149].

Proportionate reason refers to a specific value and its relation to all elements (including premoral evils) in the action[153]. The specific value in legalizing medical marijuana is to relieve withdrawal symptoms that include nausea, muscle pains, cramping and anxiety and as a possible replacement therapy. The premoral evil, which can come about by trying to achieve this value, is the foreseen but unintended possibility of the potential harmful effects of the smoke and the possibility that some may view this as condoning and even encouraging illegal drug use. The ethical question is: does the value of relieving pain and suffering outweigh the premoral evil of the potential harmful effects of the smoke and the possibility of scandal? To determine if a proper relationship exists between the specific value and the other elements of the act, ethicist Richard McCormick proposes three criteria for the establishment of proportionate reason:

1. The means used will not cause more harm than necessary to achieve the value.
2. No less harmful way exists to protect the value.
3. The means used to achieve the value will not undermine it[150-154].

The application of McCormick's criteria to the legal use of medical marijuana for OUD supports the argument that there is a proportionate reason for allowing physicians to prescribe marijuana. First, maintenance treatment for opioid users, such as methadone and buprenorphine, can lower the amount of opioids used by those addicted but they will remain on these therapies for years and there is a 40%-60% relapse rate. It is clear that these MAT therapies are not enough. The main goal of opioid maintenance therapy is to stop an individual's cravings and the onset of withdrawal symptoms. Medical marijuana is effective in decreasing the withdrawal symptoms and with further research could be a new replacement therapy. The point is that the benefit of the medical marijuana outweighs the burdens[155]. The focus should be on encouraging the federal government to

direct its research resources toward examining medical marijuana through adequate and well-controlled clinical trials. The FDA is encouraging this and the NIH and other research organizations should adequately fund these clinical trials. The Institute of Medicine study also reported that there was no evidence that prescribing medical marijuana would increase illicit drug use or that it is a "gateway drug" that prompts patients to use harder drugs like cocaine or heroin. Second, at present, there does not seem to be an alternative medication that is as effective as medical marijuana in controlling the treatment of chronic pain and withdrawal symptoms. Thousands of patients who have smoked marijuana illegally for medical purposes have attested to its effectiveness. Those patients who were and are involved in the government sponsored compassionate care program also attest to smoked marijuana's effectiveness. In addition, scientific studies have shown that Marinol, Nabilone and Sativex are less effective, more difficult for nauseous patients to consume, and more expensive than smoked marijuana. There are also other approved antiemetic drugs or combinations of these drugs which have been shown to be effective in relieving pain and suffering in some cancer patients [156]. However, for others these medications have proven ineffective. To date, the only therapy that relieves the withdrawal symptoms is medical marijuana. Third, using marijuana for medical reasons does not undermine the value, which is the relief of pain and withdrawal symptoms. Many of the patients on replacement therapies like methadone and buprenorphine need to integrate them with medicinal cannabis for withdrawal symptoms and other psychological and social supports in the best interest of those addicted. Since this seems to be the only therapy to date that relieves the pain and withdrawal symptoms of these patients, one can argue convincingly that it is a medical necessity. The federal government's concern that legalizing medical marijuana could lead to the possibility of the slippery slope in regards to drug use is a real fear. But, this has not occurred with other prescription psychoactive drugs (e.g., morphine, codeine, cocaine, etc.) and there is no evidence it would occur with marijuana. Therefore, it is ethically justified under the principle of double effect for the federal government to legalize marijuana for patients with OUD at a minimum as an adjunctive treatment to assist patients struggling with opioid withdrawal and also, with further research, as a possible primary treatment modality. Seriously ill patients have the right to effective therapies. To deny them access to such therapies is to deny them the dignity and respect all persons deserve. The greater good is promoted in spite of the potential evil consequences.

Conclusion

The current opioid epidemic is a continuing national crisis and public health issue; thus, it creates an ongoing need for additional solutions. Recovering opioid users are still at risk for relapsing while solely using pharmacotherapies, such as methadone, buprenorphine, and naltrexone. In essence, these medications are not suitable for long term sobriety. Instead, medical marijuana has been found to serve as a viable treatment option for OUD, as it has several beneficial effects. It could be used to manage addictive behaviors that could lead to less relapse risk during recovery. While complex legal issues surrounding medical marijuana have hindered its research, recent political momentum is headed in the right direction for medical usage, which could yield great potential benefits in replacement therapies for OUD. Additionally, advancement in OUD rehabilitation therapy can be made with the petition of the replacement therapy clinic modeled for Philadelphia. The MMORT Clinic will aim to foster a safe, efficient, and effective environment, integrate current pharmacotherapies (methadone and Suboxone) with medical cannabis, and offer an integrative combination of treatments to holistically care for each individual patient. Furthermore, it is justifiable under several ethical principles to legalize marijuana as not only an adjunctive treatment for patients experiencing opioid withdrawal, but also, with further research, as a possible primary treatment method for patients suffering from OUD. In conclusion, medical marijuana should be offered as a viable replacement therapy option for patients struggling and recovering from OUD during this ongoing opioid epidemic.

References

1. Scholl, L., Seth, P., Kariisa, M., et al. Drug and Opioid-Involved Overdose Deaths — United States, 2013–2017. (2018) MMWR Morb Mortal Wkly Rep 67: 1419–1427.
   PubMed | CrossRef | Others
2. Understanding the Epidemic. (2018, December 19). Retrieved May 1, 2019, from Centers for Disease Control and Prevention.
   PubMed | CrossRef | Others
3. Haffajee, R.L., Frank, R.G. Making the Opioid Public Health Emergency Effective. (2018) JAMA Psychiatry 75(8): 767–768.
   PubMed | CrossRef | Others
4. Prescription Opioids. (2018, June). Retrieved May 1, 2019, from National Institute on Drug Abuse.
   PubMed | CrossRef | Others
5. Pergolizzi, J.V., Jr, LeQuang, J.A., Berger, G.K., et al. The Basic Pharmacology of Opioids Informs the Opioid Discourse about Misuse and Abuse: A Review. (2017) Pain Ther 6(1): 1–16.
   PubMed | CrossRef | Others
6. Evans, C.J., Cahill, C.M. Neurobiology of opioid dependence in creating addiction vulnerability. (2016) F1000Research 5: F1000 Faculty Rev-1748.
   PubMed | CrossRef | Others
7. Gupta, M., Attia, F.N. Withdrawal Syndromes. (2019) Stat Pearls Publishing LLC.
   PubMed | CrossRef | Others
8. Kosten, T.R., George, T.P. The neurobiology of opioid dependence: implications for treatment. (2002) Sci Practice Perspect 1(1): 13–20.
   PubMed | CrossRef | Others
9. Stotts, A.L., Dodrill, C.L., Kosten, T.R. Opioid dependence treatment: options in pharmacotherapy. (2009) Exp Opinion Pharmacother 10(11): 1727–1740.
   PubMed | CrossRef | Others
10. Wiese, B., Wilson-Poe, A.R. Emerging Evidence for Cannabis' Role in Opioid Use Disorder. (2018) Cannabis and Cannabinoid Res 3(1): 179–189.
    PubMed | CrossRef | Others
11. Assessing and Addressing Opioid Use Disorder (OUD),

(n.d.).
PubMed | CrossRef | Others
12. Ward, J., Bell, J., Mattick, R.P., et al. Methadone Maintenance Therapy for Opioid Dependence. (1996) CNS Drugs 6(6): 440–449.
PubMed | CrossRef | Others
13. Legislatures NCoS. Marijuana Overview.
PubMed | CrossRef | Others
14. DEA (n.d.). Drug Scheduling.
PubMed | CrossRef | Others
15. National Academies of Sciences, Engineering, and Medicine. (2017). The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.
PubMed | CrossRef | Others
16. Auriacombe, M., Fatséas, M., Dubernet, J., et al. French field experience with buprenorphine. (2004) Am J Addict 13(Suppl 1): S17-S28.
PubMed | CrossRef | Others
17. Ball, J., Lange, W., Myers, C., et al. Reducing the Risk of AIDS Through Methadone Maintenance Treatment. (1988) J Health Social Behav 29(3): 214-226.
PubMed | CrossRef | Others
18. Mattick, R.P., Breen, C., Kimber, J., et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. (2009) Cochrane Database of Systemic Reviews (3): CD002209.
PubMed | CrossRef | Others
19. Whelan, P.J., Remski, K. Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds. (2012) J Neurosci Rural Pract 3(1): 45-50.
PubMed | CrossRef | Others
20. Opiate and Opioid Withdrawal. (2019). MedlinePlus Medical Encyclopedia U.S. National Library of Medicine.
PubMed | CrossRef | Others
21. Ling, W. Buprenorphine implant for opioid addiction. (2012) Pain Manag 2(4): 345-350.
PubMed | CrossRef | Others
22. Bart, G. Maintenance medication for opiate addiction: the foundation of recovery. (2012) J Addict Dis 31(3): 207-225.
PubMed | CrossRef | Others
23. Chanell.Baylor. Buprenorphine Training for Physicians. Stages of Community Readiness | SAMHSA.
PubMed | CrossRef | Others
24. Uptodate.com. (2018). Up To Date.
PubMed | CrossRef | Others
25. Mattick, R.P., Breen, C., Kimber, J., et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. (2014) Cochrane Database of Systematic Reviews (2): CD002207.
PubMed | CrossRef | Others
26. Barnett, P., Rodgers, J., Blocha, D. Meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. (2001) Addiction 96(5): 683–690.
PubMed | CrossRef | Others
27. Minozzi, S., Amato, L., Vecchi, S., et al. Oral naltrexone maintenance treatment for opioid dependence. (2011) Cochrane Database Syst Rev (4): CD001333.
PubMed | CrossRef | Others
28. Krupitsky, E., Nunes, E.V., Ling, W., et al. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. (2011) Lancet 377(9776): 1506-1513.
PubMed | CrossRef | Others
29. Tiihonen, J., Krupitsky, E., Verbitskaya, E., et al. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. (2012) Am J Psychiatry 169(5): 531-536.
PubMed | CrossRef | Others
30. Sullivan, M., Bisaga, A., Pavlicova, M., et al. Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine. (2017) Am J Psychiatry 174(5): 459-467.
PubMed | CrossRef | Others
31. Lee, J.D., Friedmann, P.D., Kinlock, T.W., et al. Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. (2016) N Engl J Med 374: 1232-1242.
PubMed | CrossRef | Others
32. Comer, S.D., Sullivan, M.A., Yu, E., et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. (2006) Arch Gen Psychiatry 63: 210.
PubMed | CrossRef | Others
33. Tanum, L., Solli, K.K., Latif, Z.E., et al. Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. (2017) JAMA Psychiatry 74:1197.
PubMed | CrossRef | Others
34. Lee, J.D., Nunes, E.V. Jr, Novo, P., et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. (2018) Lancet 391(10118): 309-318.
PubMed | CrossRef | Others
35. Strang, J., McCambridge, J., Best, D., et al. Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. (2003) BMJ 326: 959.
PubMed | CrossRef | Others
36. Mattick, R.P., Kimber, J., Breen, C., et al. Buprenorphine Maintenance versus Placebo or Methadone Maintenance for Opioid Dependence. (2003) Cochrane Database of Systematic Reviews.
PubMed | CrossRef | Others
37. Whelan, P.J., Remski, K. Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds. (2012) J Neurosci Rrural Pract 3(1): 45-50.
PubMed | CrossRef | Others
38. Ling, W. Buprenorphine for opioid dependence. (2009) Expert Rev Neurother 9(5): 609–616.
PubMed | CrossRef | Others
39. Schuckit, M.A. Treatment of Opioid-Use Disorders. N Engl J Med 375(4): 357–368.
PubMed | CrossRef | Others
40. Gardner, E.L. Endocannabinoid signaling system and brain reward: emphasis on dopamine. (2005) Pharmacol Biochem Behav 81(2): 263–284.

PubMed | CrossRef | Others
41. Heifets, B.D., Castillo, P.E. Endocannabinoid signaling and long-term synaptic plasticity. (2009) Annu Rev Physiol 71: 283–306.
PubMed | CrossRef | Others
42. Bisogno, T., Hanus, L., De Petrocellis, L., et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. (2001) Br J Pharmacol 134(4): 845-852.
PubMed | CrossRef | Others
43. Thomas, A., Baillie, G.L., Phillips, A.M., et al. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. (2007) Br J Pharmacol 150(5): 613–623.
PubMed | CrossRef | Others
44. Pertwee, R.G. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. (2008) Br J Pharmacol 153(2): 199–215.
PubMed | CrossRef | Others
45. Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. (2005) Neurochem Res 30(8): 1037–1043.
PubMed | CrossRef | Others
46. Hurd, Y.L. Cannabidiol: Swinging the marijuana pendulum from 'Weed' to medication to treat the opioid epidemic. (2017) Trends Neurosci 40(3): 124–127.
PubMed | CrossRef | Others
47. Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. (2010) Neuropsychopharmacology 35(9): 1879–85.
PubMed | CrossRef | Others
48. Crippa, J.A., Hallak, J.E., Machado-de-Sousa, J.P., et al. Cannabidiol for the treatment of cannabis withdrawal syndrome: a case report. (2013) J Clin Pharm Ther 38(2): 162–164.
PubMed | CrossRef | Others
49. Shannon, S., & Opila-Lehman, J. (2015). Cannabidiol Oil for Decreasing Addictive Use of Marijuana: A Case Report. Integrative medicine (Encinitas, Calif.) 14(6): 31–35.
PubMed | CrossRef | Others
50. Prud'homme, M., Cata, R., Jutras-Aswad, D. Cannabidiol as an Intervention for Addictive Behaviors: A Systematic Review of the Evidence. (2015) Subst Abuse 9: 33–38.
PubMed | CrossRef | Others
51. Bhargava, H.N. Effect of some cannabinoids on naloxone-precipitated abstinence in morphine-dependent mice. Psychopharmacology. 1976;49(3):267–70.
PubMed | CrossRef | Others
52. Morgan, C.J., Das, R.K., Joye, A., et al. Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings. (2013) Addict Behav 38(9): 2433–2436.
PubMed | CrossRef | Others
53. O'Connell, B.K., Gloss, D., Devinsky, O. Cannabinoids in treatment-resistant epilepsy: a review. (2017) Epilepsy Behav 70: 341–348.
PubMed | CrossRef | Others
54. Russo, M., Naro, A., Leo, A., et al. Evaluating sativex(R) in neuropathic pain management: a clinical and neurophysiological assessment in multiple sclerosis. (2016) Pain Med 17(6): 1145–1154.
PubMed | CrossRef | Others
55. Campos, A.C., Ferreira, F.R., Guimaraes, F.S. Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: possible involvement of 5HT1A receptors. (2012) J Psychiatr Res 46(11): 1501–1510.
PubMed | CrossRef | Others
56. Zanelati, T.V., Biojone, C., Moreira, F.A., et al. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT(1A) receptors. (2010) Br J Pharmacol 159(1): 122–128.
PubMed | CrossRef | Others
57. Ren, Y., Whittard, J., Higuera-Matas, A., et al. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. (2009) J Neurosci 29(47): 14764–14769.
PubMed | CrossRef | Others
58. Rook, E.J., Huitema, A.D.R., van den Brink, W., et al. Pharmacokinetics and pharmacokinetic variability of heroin and its metabolites: Review of the literature. (2006) Curr Clin Pharmacol 1(1): 109–118.
PubMed | CrossRef | Others
59. Vardanyan, R. S., & Hruby, V. J. Fentanyl-related compounds and derivatives: current status and future prospects for pharmaceutical applications. (2014) Future Med Chem 6(4): 385-412.
PubMed | CrossRef | Others
60. Fasinu, P.S., Phillips, S., ElSohly, A.M., et al. Current Status and Prospects for Cannabidiol Preparations as New Therapeutic Agents. (2016) Pharmacotherapy 36(7): 781-796.
PubMed | CrossRef | Others
61. Hawksworth, G., McArdle, K. Metabolism and pharmacokinetics of cannabinoids. The Medicinal Uses of Cannabis and Cannabinoids. (2004) Pharmaceutical Press, London p: 205-228.
PubMed | CrossRef | Others
62. Ohlsson, A., Lindgren, J.E., Andersson, S., et al. Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration. (1986) Biomed Environ Mass Spectrom 13(2): 77-83.
PubMed | CrossRef | Others
63. McPartland, J.M., et al., Are cannabidiol and Δ9-tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. British Journal of Pharmacology, 2015. 172(3): p. 737-753.
PubMed | CrossRef | Others
64. Manini, A. F., Yiannoulos, G., Bergamaschi, M. M., et al. Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. (2015) Journal of Addiction Medicine 9(3): 204–210.
PubMed | CrossRef | Others
65. Bergamaschi, M.M., et al., Safety and side effects of cannabidiol, a Cannabis sativa constituent. (2011) Current drug safety 6(4): 237-249.
PubMed | CrossRef | Others

66. Iffland, K., Grotenhermen, F. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. (2017) Cannabis and Cannabinoid Research 2(1): 139-154.
PubMed | CrossRef | Others
67. Booth, M. Cannabis: A History. (2003) New York: St. Martin's Press.
PubMed | CrossRef | Others
68. Pub L No. 75-238, 50 Stat 551. In.
PubMed | CrossRef | Others
69. Stack P, Suddath C. A Brief History of Medical Marijuana. In. *Time*2009.
PubMed | CrossRef | Others
70. Pub L No. 82-255, 65 Stat. 767. . In.
PubMed | CrossRef | Others
71. Thomas, J. The Past Present, and Future of Medical Marijuana in the United States. (2010) Psychiatric Times 27(1).
PubMed | CrossRef | Others
72. United States Drug Enforcement Administration. (2019) Drug Scheduling.
PubMed | CrossRef | Others
73. Pacula, R.L., Chriqui, J.F., King, J. Marijuana Decriminalization: What does it mean in the United States? (2003) National Bureau of Economic Research Working Paper Series: 9690.
PubMed | CrossRef | Others
74. Health and Safety Code, Section 11362.5. (1996) In: California So, ed.
PubMed | CrossRef | Others
75. Press, T.A. Georgia Gov. (2019) Kemp Signs Medical Marijuana Bill.
PubMed | CrossRef | Others
76. Coffman K, Neroulias N. Colorado, Washington first states to legalize recreational pot. 2012;.
PubMed | CrossRef | Others
77. Senate US. Constitution of the United States. https://www.senate.gov/civics/constitution_item/constitution.htm. Accessed April 22, 2019.
PubMed | CrossRef | Others
78. Angell T. Government Shutdown Could Allow Sessions To Launch Marijuana Crackdown. 2017; https://www.forbes.com/sites/tomangell/2017/12/04/government-shutdown-could-allow-sessions-to-launch-marijuana-crackdown/#7fb3805f6d59. Accessed April 22, 2019.
PubMed | CrossRef | Others
79. Angell T. Trump Attorney General Pick Puts Marijuana Enforcement Pledge In Writing. 2019; https://www.forbes.com/sites/tomangell/2019/01/28/trump-attorney-general-pick-puts-marijuana-enforcement-pledge-in-writing/#3c1799c85435. Accessed April 22, 2019.
PubMed | CrossRef | Others
80. Wingerter, J. New Trump attorney general endorses Gardner's marijuana legalization bill. (2019)
Pubmed| Crossref| Others
81. Senators Gardner, Warren and Representatives Blumenauer, Joyce Reintroduce Bipartisan, Bicameral Legislation to Protect States' Marijuana Policies. (2019).
Pubmed | Crossref | Others
82. Hansen, C. Bipartisan Bill Would Give States Control Over Marijuana Laws. (2019).
Pubmed | Crossref | Others
83. Burns, J. Lawsuit Argues That Feds' Cannabis Ban Violates Our Constitutional Rights. (2018)
Pubmed | Crossref | Others
84. 1:17-cv-05625, July 24, 2017 (United States District Court Southern District of New York 2018).
PubMed | CrossRef | Others
85. Feuer A. Judge Rejects Lawsuit Seeking to Legalize Marijuana Nationwide. 2018
PubMed | CrossRef | Others
86. Administration DE. Denial of Petition To Initiate Proceedings To Reschedule Marijuana. (2016).
Pubmed | Crossref | Others
87. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. (2018) U.S. Food and Drug Administration.
Pubmed | Crossref | Others
88. FDA-approved drug Epidiolex placed in schedule V of Controlled Substance Act. (2018) United States Drug Enforcement Administration.
Pubmed | Crossref | Others
89. Voters Oppose Trump Emergency Powers On Wall 2-1 Quinnipiac University National Poll Finds; 86% Back Democrats' Bill On Gun Background Checks. (2019)
Pubmed | Crossref | Others
90. McCarthy, J. Two in Three Americans Now Support Legalizing Marijuana. (2018) Pubmed | Crossref | Others
91. Hartig H, Geiger A. https://www.pewresearch.org/fact-tank/2018/10/08/americans-support-marijuana-legalization/. 2018; https://www.pewresearch.org/fact-tank/2018/10/08/americans-support-marijuana-legalization/. Accessed April 22, 2019.
PubMed | CrossRef | Others
92. Hasin, D. S., Saha, T.D., Kerridge, B.T., et al. Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013. (2015) JAMA psychiatry 72(12): 1235-1242.
Pubmed | Crossref | Others
93. Winters, K.C., Lee, C. Y. Likelihood of developing an alcohol and cannabis use disorder during youth: association with recent use and age. (2008) Drug alcohol depend 92(1-3): 239-247.
Pubmed | Crossref | Others
94. Opioid Overdose Crisis. (2019).
Pubmed | Crossref | Others
95. Sidney, S., Beck, J.E., Tekawa, I.S., et al. Marijuana use and mortality. (1997) Am J public health 87(4): 585-590.
Pubmed | Crossref | Others
96. Harris, R. Opioid Use Lower In States That Eased Marijuana Laws. (2018)
Pubmed | Crossref | Others
97. The health effects of cannabis and cannabinoids. *(*2017) Nat Academies Sciences Eng Med.
Pubmed | Crossref | Others
98. Boehnke, K. F., Litinas, E., Clauw, D. J. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. (2016) 17(6): 739-744.

Pubmed | Crossref | Others
99. Reiman, A., Welt, M., Solomon, P. Cannabis as a substitute for opioid-based pain medication: patient self-report. (2017) Cannabis Cannabinoid Res 2(1):160-166.
Pubmed | Crossref | Others
100. Bellnier, T., Brown, G.W., Ortega, T. R. Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis. (2018) Ment Health Clin 8(3): 110-115.
Pubmed | Crossref | Others
101. Larson, S., Padron, N., Mason, J., et al. Supervised Consumption Facilities-Review of the Evidence. (2017).
Pubmed | Crossref | Others
102. The Epidemic of Overdoses from Opioids in Philadelphia. (2016) CHART. 1(1).
Pubmed | Crossref | Others
103. Lubrano, A. How Kensington got to be the center of Philly's opioid crisis. (2018) *The Philadelphia Inquire*.
Pubmed | Crossref | Others
104. Kenney, J., & Krasner, L: Criminalizing crack addiction was a mistake. (2018).
Pubmed | Crossref | Others
105. The Opioid Epidemic of Philadelphia: Implementation of the Mayor's Task Force Recommendations. (2019).
Pubmed | Crossref | Others
106. Stuckert, J. How is Suboxone Treatment Different than Drug Abuse? (2018).
Pubmed | Crossref | Others
107. Jacobson, R. Medical Marijuana: How the Evidence Stacks Up *Scientific American*. (2014)
Pubmed | Crossref | Others
108. Balhara, S. Infections from IV Drug Use. Rehabs.
PubMed | CrossRef | Others
109. Villa, Lauren. In 2016, only an estimated 6.9% of adults with mental illness and substance abuse disorder received the mental health and substance abuse care they needed. Mental Health & Drug Abuse.
Pubmed | Crossref | Others
110. Comorbidity: Addiction and Other Mental Illnesses. (2010) *NIDA*.
Pubmed | Crossref | Others
111. Stress Management
Pubmed | Crossref | Others
112. Catherine, S., Hetherington, K. Social Determinants of Drug Use. (2004) Nat Drug Alcohol Res Cent.
Pubmed | Crossref | Others
113. Addressing the Opioid Epidemic: How the Opioid Crisis Affects Homeless Populations. (2017)
Pubmed | Crossref | Others
114. Crawford, C. The Opioid Crisis Response Act of 2018: What does it Mean for People Experiencing Homelessness? (2018)
Pubmed | Crossref | Others
115. Hepatitis B & C Surveillance.
Pubmed | Crossref | Others
116. Hepatitis C. (2018).
PubMed | CrossRef | Others
117. Annual Report. (2016) Division of Disease Control.
PubMed | CrossRef | Others
118. "HIV/AIDS Facts.
Pubmed | Crossref | Others
119. "What Are HIV and AIDS? (2018).
Pubmed | Crossref | Others
120. HIV/AIDS Cost Effectiveness.
Pubmed | Crossref | Others
121. Kelly, G. Medico-Moral Problems. (1958).
Pubmed | Crossref | Others
122. Finding the Best Private Inpatient or Outpatient Recovery Program.
Pubmed | Crossref | Others
123. About Adverse Childhood Experiences. (2019).
Pubmed | Crossref | Others
124. "Ohio Prevention and Education Conference: The Power of Collaboration. (2006) PsycEXTRA Dataset.
PubMed | CrossRef | Others
125. Miller, M. court gives win to opponents of methadone clinic that would aid heroin.
Pubmed | Crossref | Others
126. Patients and Caregivers.
Pubmed | Crossref | Others
127. Schackman, B. R., Fleishman, J. A., Su, A. E., et al. The lifetime medical cost savings from preventing HIV in the United States. (2015) *Med Care 53*(4): 293-301.
Pubmed | Crossref | Others
128. Neavyn, M. J., Blohm, E., Babu, K. M., et al. Medical marijuana and driving: a review. (2014) J Med toxicol 10(3): 269-279.
Pubmed | Crossref | Others
129. Doroudgar, S., Mae Chuang, H., Bohnert, K., et al. Effects of chronic marijuana use on driving performance. (2018) *Traffic Inj Prev 19*(7): 680 - 686.
Pubmed | Crossref | Others
130. Mangan, J. An Historical Analysis of the Principle of Double Effect. (1949) Theological Studies 10: 41-61.
Pubmed | Crossref | Others
131. Janssens, L. Ontic Evil And Moral Evil. Readings In Moral Theology, No. 1: Moral Norms And Catholic Tradition, ed. Curran CF and McCormick RA. (1979) Ramsey (NJ): Paulist Press 60.
PubMed | CrossRef | Others
132. Annas, G.J. Reefer Madness – The Federal Response to California's Medical-Marijuana Law. (1997) N Engl J Med *337*(6): 435-439.
Pubmed | Crossref | Others
133. Gay, S. S. Government Study on Marijuana Sees Medical Benefits. (1999) The New York Times
Pubmed | Crossref | Others
134. Van Ours, J. C. Is Cannabis a Stepping-Stone for Cocaine. (2003) *J Health Econ* 22(4): 539-554.
Pubmed | Crossref | Others
135. Marijuana: Is Marijuana a Gateway Drug. (2018).
Pubmed | Crossref | Others
136. Walter JJ. Proportionate Reason and Its Three Levels Of Inquiry: Structuring The Ongoing Debate. (1984) *Louvain Studies* 1032.
PubMed | CrossRef | Others
137. McCormick's criteria for proportionate reason first appeared in McCormick R, *Ambiguity In Moral Choice*. Milwaukee

(WI): Marquette University Press, 1973. He later reworked the criteria in response to criticism. His revised criteria can be found in *Doing Evil To Achieve Good*, eds. McCormick R, Ramsey P. Chicago (IL): Loyola University Press, 1978.
Pubmed | Crossref | Others

138. Examples include drugs called serotonin antagonists which include ondansetron (Zofran) and granisetron (Kytril), used alone or combined with dexamethasone (a steroid hormone); metoclopramide (Reglan) combined with diphenhydramine and dexamethasone; high doses of methylprednisolone (a steroid hormone) combined with droperidol (Inapsine); and prochlorperazine (Compazine).
PubMed | CrossRef | Others

139. Nordrum, A. Why is marijuana A Schedule I Drug? (2015).
Pubmed | Crossref | Others

140. Lopez, G. (2018 November 14). Marijuana is illegal under federal law even in states that legalize it. Retrieved from https://www.vox.com/identities/2018/8/20/17938372/marijuana-legalization-federal-prohibition-drug-scheduling-system
PubMed | CrossRef | Others

141. Governor Wolf Signs Medical Marijuana Legalization Bill into Law. (2016)
Pubmed | Crossref | Others

142. Furr-Holden, C. D., Milam, A. J., Nesoff, E. D., Johnson, R. M., Fakunle, D. O., Jennings, J. M., & Thorpe, R. J., Jr (2016). Not in My Back Yard: A Comparative Analysis of Crime Around Publicly Funded Drug Treatment Centers, Liquor Stores, Convenience Stores, and Corner Stores in One Mid-Atlantic City. *Journal of Studies on Alcohol and Drugs*, *77*(1), 17–24. doi:10.15288/jsad.2016.77.17
PubMed | CrossRef | Others

143. Ling, Walter, Mooney, Larissa, and Torrington, Matthew. (2012). Buprenorphine implant for opioid addiction. Pain management, 2(4), 345-50.
PubMed | CrossRef | Others

144. Chanell, B. Buprenorphine Training for Physicians. Stages of Community Readiness SAMHSA.
Pubmed | Crossref | Others

145. Sees, K.L., et al. Methadone maintenance vs. 180-day psychosocially enriched detoxification for treatment of opioid dependence. (2000) JAMA 283:1303-1310.
PubMed | CrossRef | Others

146. Caplehorn, J.R., Dalton, M.S., Haldar, F., et al. Methadone maintenance and addicts' risk of fatal heroin overdose. (1996) Subst Use Misuse 31(2): 177-196.
PubMed | CrossRef | Others

147. Ward, J., Bell, J., Mattick, R.P., et al. Methadone Maintenance Therapy for Opioid Dependence. (1996) CNS Drugs 6(6): 440–449.
PubMed | CrossRef | Others

148. Lenné, M., Lintzeris, N., Breen, C., et al. Withdrawal from methadone maintenance treatment: prognosis and participant perspectives. (2001) Australian and New Zealand Journal of Public Health 25(2): 121–125.
PubMed | CrossRef | Others

149. Tanum, L., Solli, K.K., Latif, Z.E., et al. Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. (2017) JAMA Psychiatry 74:1197.
PubMed | CrossRef | Others

150. Tiihonen, J., Krupitsky, E., Verbitskaya, E., et al. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. (2012) Am J Psychiatry 169(5): 531-536.
PubMed | CrossRef | Others

151. Gonzalez-Cuevas, G., Martin-Fardon, R., Kerr, T.M., et al. Unique treatment potential of cannabidiol for the prevention of relapse to drug use: preclinical proof of principle. (2018) Neuropsychopharmacology 43(10): 2036-2045.
PubMed | CrossRef | Others

152. Katsidoni, V., Anagnostou, I., Panagis, G. Cannabidiol inhibits the reward-facilitating effect of morphine: involvement of 5-HT1A receptors in the dorsal raphe nucleus. (2013) Addict Biol 18(2): 286–296.
PubMed | CrossRef | Others

153. Clark, J.D. Understanding Methadone Metabolism: A Foundation for Safer Use. (2008) Anesthesiology. 108(3): 351–352.
PubMed | CrossRef | Others

154. Institute of Medicine (US) Committee on Federal Regulation of Methadone Treatment; Rettig RA, Yarmolinsky A, editors. Federal Regulation of Methadone Treatment. Washington (DC): National Academies Press (US); 1995. 2, Pharmacology and Medical Aspects of Methadone Treatment.
PubMed | CrossRef | Others

155. World Health Organization. (2017, November 6). Cannabidiol a pre-review report. Retrieved from
PubMed | CrossRef | Others