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Can Cannabis Solve the Opioid Epidemic?

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The Problems

The Opioid & Heroin Epidemic

The United States today is facing one its biggest drug crises historically, with death rates comparable the late 80's-early 90's HIV/AIDS crisis: the opioid and heroin epidemic (Park & Bloch, 2016). CDC reports found deaths from opioid overdose (OD) nearly quadrupled from 1999-2015. There were 52,404 deaths in 2015 from drug OD (144 per day), and 63.1% involved opioids (Dowell et al., 2016; Rudd et al., 2016). 500,000 deaths occurred in the U.S. due to drug abuse since 2000, amounting to approximately one every 20 minutes (Baker, 2016). Opioid pain medications (OPM) are most often used for non-cancer chronic pain and as CDC director at the time, Dr. Tom Frieden, put it best, "We know of no other medication used for a nonfatal condition that kills patients so frequently" (Frieden & Houry, 2016).

The rise in heroin use parallels OPMs use, nearly half of young heroin users report using OPMs prior to heroin, often citing cost and ease of access as reasons for switching (Baker, 2016). Though OPM overprescription is the root of the epidemic, diversion is another major issue; 12 of the 97 million+ Americans who took OPMs in 2005 reportedly did so with no prescription (Hughes et al., 2016).

OPM OD deaths have leveled off, but heroin and fentanyl (a painkiller 100 times more potent than morphine) OD deaths have skyrocketed since 2000 (Drug Enforcement Administration, 2016; Katz, 2017). Recent evidence divides the epidemic into two waves: In 2000, the most common age of drug-related deaths was about 40 years old and from OPMs, and more recently, these deaths are most commonly younger and dying from heroin and fentanyl OD instead (Unick & Ciccarone, 2017).

Chronic Pain

Chronic pain can result from numerous medical conditions, injuries, inflammation, medical treatments, or unknown causes (Institute of Medicine, 2011). Unlike acute pain, chronic pain can persist for weeks, months, or years. Though some causes (i.e. arthritis, cancer, injuries) are more obvious, some are less. Other chronic pain complaints include headache, back pain, neuropathic pain, and even psychological pain (i.e. anxiety, PTSD, etc.). Current treatments vary by condition, but range from acupuncture to brain stimulation, surgery, and most commonly, medication (National Institute of Neurological Disorders and Stroke, Accessed 2017).

The societal costs of chronic pain are shocking; in America, chronic pain costs society $560-$635 billion annually, including the total costs of health care due to pain and of lost productivity (including work days missed, work hours lost, and lower salaries) (Institute of Medicine, 2011). Individual consequences of chronic pain can lead to countless negative clinical, social, and psychological consequences, including sleep disruption, reduced quality of life, limitations in daily and/or work responsibilities leading to job loss, or long-term disability, isolation, and stigmatization (“Chronic Pain Statistics: Facts And Figures Behind This Epidemic,” 2017; Institute of Medicine, 2011). It's a major contributing factor for increased risks of opioid abuse (Blanco et al., 2016), depression (Blazer, 2009), and suicide (Calati, et al., 2015; M. T. Smith, et al., 2004).

More than 100 million Americans suffer from chronic pain (Institute of Medicine, 2011) and this isn't just an American issue. Market research estimates globally, approximately 1.5 billion people suffer from chronic pain. Approximately 3-4.5% suffer from neuropathic pain, which increases with age. Global trends show aging populations

and thus this epidemic threatens to continue to worsen (Global Industry Analysts, Inc., 2011).

Historical Context

History of Opioids and Heroin

Bayer pharmaceuticals first introduced heroin medically in 1898 as a “non-addictive” opioid pain medication (OPM) to replace morphine (addiction to which had become rampant.) However, patients discovered the amplified effects of injection. Reports of heroin addicted patients admitted to psychiatric institutes go back as far as 1910. The Harrison Narcotics Tax Act of 1914 imposed import, selling, and manufacturing taxes on any opium or coca leaf derivative, and the 1924 Heroin Act officially made heroin illegal (Beauchamp & Nelson, 2016; Moghe, 2016). The opioid addiction problem didn't disappear, it just went underground and into high-risk populations (i.e. minorities and low-income populations.) However, instead of addressing the epidemic, these communities were targeted by punitive measures based on the notion that addiction is caused by moral failings, rather than medical or societal factors. In addition, synthetic sedative (tranquilizers and barbiturates) and stimulant (amphetamines) addiction were on the rise; Barbiturate overdose killed more people by 1953 than prescription opioid OD in 2014. Because drug abuse had become so racially and economically stigmatized by that time, authorities were hesitant to acknowledge addiction among middle-class, doctor-visiting populations and even more hesitant to place restrictions on rich and powerful pharmaceutical companies (Herzberg, 2010, 2017).

Pharmageddon: The Road to the Opiate Crisis

History of Cannabis

Evidence of cannabis use for medicinal purposes dates back to ancient times. It was used in ancient China (circa 2900-2700 BC) to heal over 100 ailments (Mack & Joy, 2014). Ancient Egyptians used cannabis for inflammation, glaucoma, and enemas (Moens & Manniche, 1992). Bhang, a mixture of milk and cannabis, was used as an anesthetic and later as a cure for leprosy in India. It was also used in ancient Greece for edema, earache, and inflammation (United States. Commission on Marihuana and Drug Abuse, 1972).

Cannabis in the U.S. dates back to the Jamestown settlers, who brought hemp to North America in 1611 (Segal, 2014). Founding fathers, George Washington and Thomas Jefferson's' journals document their use of hemp in the mid-late 1700's (Deitch, 2003). By 1850, the U.S. Pharmacopeia (the official standard for prescription and over-the-counter medicines) included MCB treatment for cholera, typhus, rabies, neuralgia, tetanus, dysentery, opiate addiction, alcoholism, incontinence, menstrual bleeding, insanity, tonsillitis, convulsive disorders, gout, and many more ailments (Boire & Feeney, 2007).

A large portion of the U.S. population was unknowingly addicted to easily accessible morphine and opium by the early 1900s. Once this public health crisis became known, things began to change: In 1906, the Pure Food and Drug Act created the FDA and put doctors in control of the regulation of drugs, a major shift in U.S. policy (Stack & Suddath, 2009). In 1930, Harry J. Anslinger, a rabid prohibitionist and propagandist who promoted the idea that cannabis caused insanity and criminal acts,

was appointed Federal Bureau of Narcotics commissioner. Anslinger's public fear mongering accompanied warnings against "reefers" pushed by jazz musicians/fans (aka African Americans) on schoolchildren that made them crazy and the release of propagandist films like *Reefer Madness* (1936), all of which misled and scared the country (Mann, 1999).

By 1937 23 states had enacted laws criminalizing cannabis possession and sale. Some states hoping to stop former addicts from picking up a new drug, and in some states it was racially fueled against new Mexican immigrants who had brought the plant with them and were the reason for the shift from cannabis to "marijuana" (Stack & Suddath, 2009). That same year, led by Anslinger, the federal government passed the Marihuana Tax Act, which put such a high tax on growers, sellers, and buyers, that it effectively made cannabis illegal without explicitly prohibiting it. The Act passed despite the American Medical Association's (AMA's) opposition and call for further MCB research (*Medical Marijuana: Review and Analysis of Federal and State Policies*, 2009). It still allowed medical use, but required prescribing doctors to register with authorities and pay annual taxes and fees, obstacles that led to a decline in MCB prescribing (Pacula et al., 2002). The day the Act was passed, the first two cannabis criminalization victims were arrested - the grower was sentenced to 4 years and the buyer (found guilty of possession) was sentenced to 18 months in prison (Bourrie, 2003).

In 1944, the LaGuardia Report, a 5-year study conducted by New York Mayor, Fiorella LaGuardia, and the NY AMA, concluded that cannabis does not lead to addiction or use of other drugs and isn't a causal factor in violent/criminal behavior (Mayor's Committee on Marihuana, 1944). Infuriated by the report, Anslinger

denounced it as “unscientific” and demanded no further cannabis research be conducted without his permission, interfering in all ongoing research to ensure their conclusions represented the government’s ideology (Mann, 1999). In the 1950s, the government established mandatory sentences for drug offenders (including cannabis) with the Boggs and Narcotics Control Acts. Though the laws were relaxed in the 1970s, the Reagan Administration's War on Drugs reinforced the criminalization of cannabis (Stack & Suddath, 2009). Nevertheless, the Baby Boomer generation experimented and realized cannabis wasn't the “demon weed” they had been warned about, sparking an anti-establishment popularity.

The late 1980’s-early 1990’s HIV/AIDS crisis created a surge of anecdotal evidence of MCB's therapeutic effects on HIV/AIDS symptoms, symptoms of other chronic illnesses, and cancer. Underground MCB dispensaries and “social clubs “emerged in cities like San Francisco, and California ultimately became the first U.S. state to establish an MCB program in 1996 (Penn, 2014). At least 28 states and countries throughout the world have since followed, yet in many places MCB still remains illegal.

A Comparison

Opioids

Opioid drugs like morphine, heroin, and OPMs like Oxycontin and Vicodin, are derivatives of opium, a narcotic found in poppies. There are also synthetically created drugs, like methadone and fentanyl. Together, they make up the drugs called “opioids” (Katz, 2017). In 2010, in an effort to combat OPM abuse, pharmaceutical companies released “addiction deterrent” OMPs designed to reduce the likelihood abuse (i.e.

snorting or injecting) (Dreisbach, 2016; Raffa & Pergolizzi, 2010). There are several types of abuse-deterrent formulae including: a form in which the opioid cannot be crushed and extracted, like Purdue's newer version of OxyContin); mixing the opioid with an antagonist like naltrexone, that interferes with the effects if the drug is injected but not if taken orally; mixing the opioid with a substance that causes an adverse response if tampered with or used at a higher than prescribed dose; and another formula now in development, a prodrug with a chemical block against in-vitro conversion, in which the opioid would need enzyme-induced activation (Raffa & Pergolizzi, 2010; Volkow & McLellan, 2016).

Opioids affect mu-opioid receptors in the brain that regulate the body's pain and reward system. Mu 1 receptors are responsible for producing analgesia while Mu 2 receptors are responsible for euphoria (also sedation, respiratory depression, vomiting, pruritus, urinary retention, and dependence). This makes them effective painkillers but simultaneously extremely addictive (Ng & Di Renna, 2017; Volkow & McLellan, 2016). Tolerance to the euphoric and analgesic effects builds rather quickly, some from a single dose while others take longer to develop. Therefore, chronic pain patients require higher and higher doses for effective pain management (Buntin-Mushock et al., 2005).

Typically, OPMs are prescribed for a defined pain condition that limits daily function and hasn't responded to non-opioid treatments, cancer, and during end-of-life care. OPMs are contraindicated for those with headaches, lower back pain, and fibromyalgia, those with a history of or current substance abuse issues, social and/or mental instability, pregnant women, those without a pain condition, and for illegal activity. Current prescription protocol recommends beginning treatment with low dose,

short-acting, “weak” OPMs (like codeine and tramadol) before increasing strength and dose if proven to be ineffective (Ng & Di Renna, 2017).

Cannabis

Cannabis is the most commonly used illicit drug worldwide; approximately 181.8 million people, ages 15-64 years, used cannabis for nonmedical reasons in 2013 (United Nations Office on Drugs and Crime, 2015; WHO, 2016). There are various methods of cannabis consumption including: cigarettes (joints), pipes, glass (bowls/bongs), edible products, beverages, vaporizers, pills, oils/wax, tinctures, lotions, and resin (i.e. hashish) (National Academies of Sciences, Engineering, and Medicine, 2017a). Cannabis is made of two main compounds: THC, the psychoactive component, which produces the “high” feeling but can also induce anxiety, psychosis, and cognitive impairment (Colizzi & Bhattacharyya, 2017), it has, however, been shown to have immunosuppressive properties (Jamontt et al., 2010); and CBD, the pain relieving component, which has anti-oxidative and anti-inflammatory properties (Cheng et al., 2014), and may alleviate THC’s psychotic-like effects (Morgan et al., 2012).

Over the past 20 years, both medical and recreational cannabis policy has changed. Today, countries across the globe including Canada, Israel, 28 states in the U.S., and many other countries have legalized cannabis use for medical purposes, and many of those (including 8 states and D.C.) have also legalized recreational cannabis (National Academies of Sciences, Engineering, and Medicine, 2017).

Medical cannabis (MCB) is associated with a number of therapeutic health effects and has been used to treat various chronic conditions. The full range of conditions is still unknown but they most commonly include: relief of nausea and

vomiting due to chemotherapy; neuropathic and cancer-related pain; spasticity from MS, Tourette's syndrome, and Parkinson's disease; epileptic seizures; anxiety and depression; sleep disorders and insomnia; glaucoma; anorexia; menstrual cramps; psoriasis; inflammatory bowel disease and other gastrointestinal conditions; and many more (Lahat et al., 2012; Satterlund et al., 2015; Whiting et al., 2015).

However, there's still quite a bit of uncertainty of MCB's full potential, due to a lack of controlled studies and definitive evidence regarding its exact indications, doses, strains, and adverse effects. A comprehensive systematic review and meta-analysis of 79 studies by Whiting et al. (2015) found moderate-quality evidence associating MCB with reductions in nausea and vomiting, pain, and spasticity, and low-quality evidence of associations with increased weight gain in HIV+ patients, improvement in sleep disorders/insomnia, and a significant improvement in tic severity in Tourette's syndrome. Their analyses were unable to find sufficient evidence of therapeutic uses for depression, anxiety disorders, psychosis, or glaucoma.

The uncertainty about the overall efficacy of MCB still continues. In a more recent systematic review and meta-analysis of randomized controlled trials conducted by Aviram and Samuelly-Leichtag (2017), though they found evidence of a larger pain reduction among chronic pain patients compared to those treated by placebo (especially for neuropathic pain), the evidence was limited and thus uncertainty of the clinical significance of the results remains.

Adverse Effects

To determine a preferable treatment, it's important to not just consider the efficacy but to also consider the risks.

Opioids

Known opioid side effects include sedation, constipation, respiratory depression, cardiac arrhythmias, nausea, opioid induced hyperalgesia, negative hormonal and immune effects, a high rate of opioid abuse behaviors, and unknown risks of addiction and overdose (Ballantyne, 2006). Physical dependence is responsible for common withdrawal symptoms including insomnia, chills, diarrhea, muscle aches, nausea and vomiting, which typically last between 1 to 14 days, depending on type, duration, and prescribed dose of opioids (Volkow & McLellan, 2016). Opioid use is also associated with birth defects, and those with mental illness are especially at risk of dependency (Dowell et al., 2016).

When opioids activate mu-opioid receptors repeatedly, it creates learned associations between the drug and these effects (Miguez et al., 2014). Eventually addiction to the drug develops to satisfy an acquired craving for these effects (Ewan & Martin, 2013). While addiction isn't a certainty with OPM use (Volkow & McLellan, 2016), the CDC estimates the prevalence of opioid abuse among primary care non-cancer pain patients to be as high as 26% (Dowell et al., 2016; Frieden & Houry, 2016).

The switch to abuse deterrent formulae in 2010 had severe unintended consequences. A study published in the New England Journal of Medicine (Cicero et al., 2012) collected data from 2566 opioid dependent patients before and after switching to abuse-deterrent formulas and found no evidence that the switch deterred drug abuse. Rather, they (66%) changed to a different opioid. Although respondents who reported OxyContin as their drug of choice decreased, patients reporting oxycodone-based drugs rose slightly and those reporting other opioid-based drugs, most commonly heroin, rose significantly. Patients reported switching to heroin not only due to difficulties extracting

the opioid in the abuse deterrent form, but also due to the new drugs' high cost. In addition, 24% of patients reported finding a way to tamper with the abuse-deterrent component.

An unfortunate real-life example of this is the case of Endo Pharmaceutical's switch to abuse-deterrent Opana, meant to deter users from *snorting* the drug. However, people learned they could inject the opioid, which sparked an HIV outbreak. 190 people have tested positive for HIV in Scott County, Indiana since 2015, making it the largest HIV outbreak in Indiana history (Dreisbach, 2016).

Death due to OD is the most serious side effect of opioids. Mu-opioid receptors are also responsible for respiratory depression, the cause of most OD deaths (Volkow & McLellan, 2016). One reason is tolerance to the analgesic and euphoric effects builds faster than tolerance to opioid-induced respiratory depression, which explains why dose increases for chronic patients increase their risk of OD (Ling et al., 1989). During a study (Kaplovitch et al., 2015) following 32,499 chronic opioid therapy patients from their first use of OPMs, 1 in 550 patients died of opioid-related causes a median of 2.6 years after the first prescription. 1 in 32 died among those prescribed 200 MME or more. The CDC also found the risk of death by OD is dose-dependent and those who died from opioid OD were more likely to have obtained opioids from multiple physicians and pharmacies (Dowell et al. 2016). Other studies (Chou et al. 2014; Miller et al. 2015; Edlund et al. 2014; Kaplovitch et al. 2015) similarly determined dose and duration to be major factors in both addiction and overdose.

Cannabis

According to the National Institute of Drug Abuse (NIDA), the short term AEs of recreational cannabis use include altered sense of time, impaired movement and memory, difficulty thinking and problem solving, altered senses, changes in mood, higher risk of breathing problems, increased heart rate, and temporary hallucinations and/or paranoia (NIDA, 2017; Waltermaurer et al., 2017). A meta-analysis by Whiting et al. (2015b) found increased risk of dizziness, dry mouth, fatigue/drowsiness, nausea and/or vomiting, somnolence, hallucinations, disorientation, confusion, and loss of balance. Aviram and Samuelly-Leichtag (2017) likewise, found central nervous system AEs to be most common in their meta-analysis; adding apprehension, attention disturbance, increased awareness, lack of alertness or awareness, numbness, and vertigo, among other symptoms. They also found gastrointestinal AEs to be the second most common, including abdominal pain and discomfort, anorexia, constipation, decreased/increased appetite, heartburn, nausea, oral irritation, and dry mouth.

Other potential short-term effects may impact peripheral vision, balance, motor control, and executive functioning, factors necessary for driving. The U.S. National Roadside Survey has seen a 47% rise in THC positive drivers since the cannabis legalization in Washington and Colorado (Davis et al., 2016). However, the data's significance is unclear because it's difficult to assess the relationship of THC blood levels and driving accidents due to various factors. THC is fat soluble and depends on how often and recently one has smoked, making it difficult to determine after the fact, and different levels affect people differently. Additionally, an increased prevalence of

MCB users driving would be expected in the case of any recently legalized drug (Waltermaurer et al., 2017).

A more serious health concern associated with cannabis use is the possibility of developing schizophrenia-like disorders, found to be seven times more likely in daily users with one of three AKT1 gene variations and with *any* use among individuals with one or two copies of the Val variant in the COMT gene (NIDA, 2017; Waltermaurer et al., 2017).

Other common MCB related events reported by emergency rooms include pediatric intoxication, cannabis hyperemesis syndrome (CHS) in which MCB causes severe abdominal pain and cyclical vomiting, lighter burns, and negative reactions to synthetic cannabinoids, like “spice” or “K2” (Heard et al., 2017).

The risk of fatal cannabis OD is relatively impossible. It would require the consumption of at least 15g of THC within a short time span, more than even a heavy user would consume in a whole day (Gable, 2004); a prospective cohort study of cannabis for pain management determined the average daily dose to be 2.5g of THC for a chronic user (Shah et al., 2017). It's possible to experience acute MCB intoxication, but this typically results in “passing out;” it's never itself fatal (Heard et al., 2017).

Efficacy as Analgesic

Opioids

OPMs are among the most common chronic pain treatments, with an estimated 20% of non-cancer related pain patients receiving a prescription (Dowell et al., 2016). In a survey of chronic pain patients using OPMs, only 23% found them effective (American Pain Foundation, 2008). A review of randomized controlled trials lasting at least 4

weeks evaluated the efficacy of opioids for chronic, non-cancer pain and found a statistically significant reduction in pain, but the reductions were small to modest and there was no consistent improvement in functioning (Van Zee, 2009). A summary of 3 systematic reviews found unclear or weak evidence of the effectiveness of opioids for chronic pain, and either a limited or no evidence for the efficacy of other OPMs, like Vicodin and Oxycontin (Trescot et al., 2008). Furthermore, a Cochrane review of methadone (another opioid) also found insufficient high quality evidence for use in chronic non-cancer pain (McNicol et al., 2009). Additionally, a CDC review found patients who don't experience analgesia early in treatment are unlikely to benefit from long-term use (Dowell et al., 2016). Unfortunately, there are insufficient methodologically rigorous studies, lasting more than 6 weeks, to prove the efficacy and risks of long-term opioid therapy (Chou et al., 2014; Dowell et al., 2016; Frieden & Houry, 2016).

Cannabis

Chronic pain is the most common condition among MCB patients. Many studies and meta-analyses (Deshpande et al., 2015; Lynch & Campbell, 2011; National Academies of Sciences, Engineering, and Medicine, 2017; Sexton et al., 2016; Shah et al., 2017; WHO, 2016) have found evidence of cannabinoid involvement in analgesia, though the evidence tends to be somewhat limited. One systematic review (Lynch & Campbell, 2011) found 15 of 18 good-quality studies showing medical cannabis to have a significantly analgesic effect, especially for neuropathic pain. Another review by Whiting et al. (2015b) analyzed 28 randomized trials of medical cannabis use for chronic pain and found that medical cannabis increased the odds of improvement by

40% compared to control groups. Most commonly, the conditions were related to neuropathy, cancer and/or chemotherapy-related pain, multiple sclerosis, rheumatoid arthritis, and musculoskeletal issues. Again, further research is required to determine the extent of MCB's analgesic effects.

Barriers

Legal Status

The War on Drugs, including cannabis, has led astronomical incarceration rates in the U.S. (2nd only to Russia) (NORML Foundation, n.d.). 8.3 million marijuana related arrests occurred from 2000-2010 and 88% (over 690,000) were for simple possession. Racial trends in cannabis arrests are discriminatory, with arrests of blacks being 3.73 times more likely than whites, despite similar rates of use (ACLU, n.d.).

Under federal law, cannabis of any kind, for recreational or medicinal purposes, remains illegal. Cannabis's classification as a Schedule 1 drug (same as heroin) has impeded researchers, doctors, and patients for decades (National Academies of Sciences, Engineering, and Medicine, 2017; Williams, 2016). Regardless of the number of states that have legalized or decriminalized cannabis, still 574,641 arrests for small quantity possession occurred in 2015 (Williams, 2016).

Stigma

Despite recent policy changes and relative efficacy and safety of MCB, researchers, patients, and health professionals still face obstacles in accessibility, standardization, and legality (Lucas et al., 2012). Unfortunately, insufficient understanding and legal ambiguity have blurred the lines between medical and

recreational/illicit use. A review of Canadian newspapers' reporting on cannabis use (not specifically medical) between 1997-2007 revealed a discourse of "privileged normalization" that frames cannabis use as acceptable for certain people at specific times and places, but "use by those without power and status is routinely vilified and linked to deviant behavior" (Haines-Saah et al., 2013, p. 1). This has resulted in stigmatization of MCB users, labeling them as "stoners," "potheads," or simply "illicit drug users" and "criminals." This can have lasting negative socioeconomic, legal, and health effects (Bottorff et al., 2013).

The negative effects of health-related stigma are well documented, especially for conditions like obesity, HIV/AIDs, and drug use. These conditions are often attributed to "lifestyle choices," a result of irresponsibility and thus avoidable. Therefore, patients often face discrimination and barriers to treatment, and receive lower quality healthcare (Link et al., 1997; Satterlund et al., 2015). MCB patients in several studies reported seeking a license from private "medical cannabis clinics" or cultivating their own, rather than speaking to a physician. Patients even admitted to lying to a doctor or hiding their use. Those who did ask physicians only did so when the physician or nurse brought up the subject, while others faced scrutiny or criticism and were offered counseling for cannabis addiction. Some felt the need to exaggerate conditions when questioned about their symptom severity to secure access to medication (Belle-Isle et al., 2014; Bottorff et al., 2013; Satterlund et al., 2015; Sznitman, 2017).

Insufficient Research

Recently, the notion of MCB as a substitute and/or treatment for OPMs has begun to gain popularity. In 2017, Maine attempted to add opioid addiction to the list of

MCB treatable ailments, but the health department ultimately denied the proposal (Sifferlin, 2016). Nevertheless, unofficial substance addiction and withdrawal treatment still exists in the state (*Meet the Opiate Addicts Getting Clean with Cannabis*, 2016).

Unlike other medications, the legalization of MCB has preceded the science. It's the first substance in U.S. history determined effective by the public and politicians, rather than the medical community. Normally, years of pre-clinical and clinical trials are required, followed by federal agency evaluation for approval of the substance itself and the specific diseases it may treat (Hurd, 2017). However, due to its legal status, there's a limited amount of rigorous clinical research, and thus uncertainties remain regarding the scope of MCB's therapeutic value, dosage amounts, and adverse effects (Sexton et al., 2016).

Therefore, further research is necessary to better understand these factors to establish clear health guidelines for patients, medical professionals, and producers, for safe and effective use (Deshpande et al., 2015; National Academies of Sciences, Engineering, and Medicine, 2017). Additionally, although MCB may not be a proven cure for substance abuse, it's certainly a safer option.

Recommendations

Legalize

Reports from the U.S. of reduced opioid prevalence after cannabis legalization have begun to emerge. Comparing the prevalence of opioid-related deaths in Colorado after the retail availability of cannabis, researchers found a 6.5% decrease in monthly opioid deaths, translating to 0.7 fewer deaths per month (Livingston et al., 2017). A review of opioid mortality rates in the U.S. from 1999-2010 showed a 25% lower rate of

deaths in states with legal MCB (Bachhuber et al., 2014). Another study analyzed driver fatality records from 1999-2013 for opioids at the time of death and found a reduction in opioid positivity among drivers ages 21-40 after cannabis legalization (Kim et al., 2016).

Federal legalization would be an important step, primarily, in fighting stigmatization and criminalization of MCB users. It would also reduce incarceration rates, remove major barriers to improving accessibility and availability, encourage research, and improve treatment options. Not to mention the enormous revenue potential of taxing recreational cannabis and savings on prison spending. Ideally, this would increase available funding for further research and available treatment options, ultimately resulting in reduced opioid addiction and related deaths.

However, regulations must be put in place to avoid cannabis diversion to children or those predisposed to psychiatric conditions, unless prescribed. Additionally, regulations MCB prices are needed to insure affordability. Already, a secretive company of unknown investors, BioTech Institute LLC, has been registering utility patents (the strongest crop patents available) on cannabis plants. If enforced, once legalized, any grower, seller, or researcher would need to pay a licensing fee for plants and seeds. A loophole in patenting laws allows for the patent of any item regardless of its legal status (Lewis & Cutler, 2017). To combat this, the loophole must be addressed *before* federal legalization and antitrust laws should be enacted to avoid losing cost and regulatory control.

Cannabis as A Substitute for OPMs

As an analgesic, MCB is a potential a substitute for OPMs. In small studies (350-404 MCB patients), 66%-67.7% reported using MCB to substitute OPMs and 26%-

36.1% used as a substitute for illicit drugs (Reiman 2009; Lucas et al. 2012). In studies of larger samples, 46-60% reported substituting cannabis for OPMs (Corroon et al., 2017; Sexton et al., 2016), Interestingly, a study in New England found a significantly higher reduction in regular OPM use than reductions in antidepressant or alcohol use among 1,513 MCB patients (Piper et al., 2017). In addition, an analysis of opioid-mortality rates in states with and without medical cannabis policies and/or prescription drug monitoring programs (PDMPs) found PDMPs may be more effective if combined with availability of medical cannabis as an alternate analgesic treatment (Phillips & Gazmararian, 2017). However, without further research, it's difficult to tell to what extent this phenomenon is a result of changes in costs, policy, legal status, and other external factors (Lucas et al., 2012).

Regardless, there's enough evidence to show patients are indeed using MCB to supplement, or at least improve, the efficacy of OPMs, making it a worthwhile approach to consider. MCB would be a much less harmful and less addictive pain treatment than OPMs (Sifferlin, 2016). Furthermore, the CBD compound, has no psychoactive component so it does not trigger similar rewarding sensations, and therefore has little potential for misuse and diversion (Katsidoni et al., 2013; Vann et al., 2008).

Cannabis and Substance Abuse Treatment

A growing body of evidence is emerging showing cannabis, specifically the CBD cannabinoid, can be a useful tool in substance addiction treatment, abuse, and withdrawal; It functions as an “exit drug” to wean addicts off of other, more harmful substances, like alcohol, opiates, and other hard drugs (Hurd, 2017; Lucas et al., 2012;

Meet the Opiate Addicts Getting Clean with Cannabis, 2016; Mikuriya, 2004; Socías et al., 2017; Vyas et al., 2017).

There are several ways in which cannabinoid receptors play a moderating role in addiction and dependence. First, cannabinoid receptors interrupt the opioid receptor systems signals that affect cravings and withdrawal symptom severity (Blume et al., 2015; Hine et al., 1975; Ramesh et al., 2013). For example, reproducible studies on mice and humans have shown endocannabinoid system involvement in moderating certain behavioral and motivational effects of nicotine (Balerio et al., 2006; Merritt et al., 2008). Drug cravings increase over time - another study found CBD caused a direct reduction in heroin-seeking behavior by normalizing the heroin-induced brain receptor damage, which reduces heroin cue-induced cravings (Ren et al., 2009).

Additionally, cannabinoids can modulate negative emotional states and disruptions in cognition characteristic of addiction, that trigger cravings and fuel opioid use (Hurd, 2017). The strongest evidence of this is CBD's effect on the amygdala, the brain region that mediates anxiety, fear, and stress response. More specifically, CBD infusion into the amygdala nucleus reduces anxiety-like behaviors in animal models (Hsiao et al., 2012), and studies of neuroimaging have shown CBD decreases activation of the amygdala during negative emotion processing (Fusar-Poli et al., 2009). This translates to an improved quality-of-life, as a systematic review of studies found among chronic pain patients using MCB (Goldenberg et al., 2017).

Though it may seem contradictory to use a substance to treat substance addiction, such is the current practice with methadone, another addictive substance. Reassuringly, studies have found MCB to have no causal influence over use of hard

drugs (Morral et al., 2002; Waltermaurer et al., 2017). Furthermore, a small study of authorized MCB users admitted to substance abuse treatment in California found no negative effect of MCB use on treatment outcomes (Swartz, 2010).

Dispensaries

Historically, underground dispensaries in cities like San Francisco played an activist role in ensuring access to and availability of MCB treatment for individuals suffering from HIV/AIDS. Not only did they provide the medication itself but they provided spaces to nurture a collective illness (Jones & Hathaway, 2008) and provided alternate services such as counseling, support groups, substance abuse counseling, advocacy, and eventually research (Penn, 2014).

Further development of these “social club” model MCB dispensaries (Grinspoon, 1999) would provide a professional facility to help wean existing opioid abusers off OPMS and prevent new patients from becoming addicted. Indeed, a recent cross-state study found a 20% decrease in OPM administration and suggestive evidence of a reduction in drug-induced mortality rates over the first two years of dispensary operations (R. A. Smith, 2017).

Additionally, dispensaries can be activist organizations as they have been in the past. By placing cannabis use into a framework of compassionate care for the dying or chronically suffering, the early underground dispensaries helped reduce stigma, defining a morally legitimate user. More recently, a wellness framework emerged, broadening the legitimate conditions for use to include less serious conditions like anxiety, pain, and even non-medical conditions like creativity and quality-of-life (Dioun, 2016).

Conclusion

Both opioids and cannabis have a long, racially, and economically complicated history in the United States. However, the current situation has brought to light the dangers of opioids, while the full therapeutic potential of MCB has yet to be unlocked. In search of a safer treatment, it's clear MCB has infinitely less dangerous side effects than OPMs but its efficacy in pain management is still unclear and needs further research. Enough anecdotal evidence suggests MCB’s potential in opioid use reduction to believe it can save lives. Legal protections, activism, research, increased treatment options and accessibility, and de-stigmatization campaigns are just some basic steps necessary to further explore how MCB may help end the opioid epidemic.

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