Examining the Supplementation of Methadone Maintenance Therapy with Delta-9-tetrahydrocannabinol to Aid in Patient Comfort and Increase Treatment Retention Rates.

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April 28, 2019

Introduction

As classified by the National Institute on Drug Abuse, opiates are derivatives of opium, a naturally occurring chemical from the poppy plant, including but not limited to morphine, codeine, and thebaine. Semi-synthetic and synthetic variants of opiates are known as opioids and are either hybrids from chemical modifications to opiates or chemically manufactured respectively. Both opiates and opioids interact with the opioid receptors of the nervous system, yet the remainder of this paper will examine opioids only as they currently present a significantly greater risk to society due to their high levels of availability (National Institute on Drug Abuse, n.d.). The most infamous opiates currently circulating amongst the U.S. population are heroin and fentanyl, the latter of which has most recently appeared in the world of illegal drug use (Centers for Disease Control and Prevention, 2018b). As reported by the DEA National Drug Threat Assessment in the 2018 annual publication there has been a strong relationship noted between the number of synthetic opioid deaths and the number of cases in which forensic laboratories encounter fentanyl (Drug Enforcement Administration, 2018). Classified as a schedule II substance, deemed to possess some medicinal value, fentanyl is prescribed as a high-power analgesic used in situations of palliative care. With a potency fifty times greater than heroin and one hundred times that of morphine the illegal sale and manufacture of fentanyl has spiked in recent years (Centers for Disease Control and Prevention, 2018b). In response to the April 2005 to March 2007 spike in fentanyl overdoses the Drug Enforcement Administration (DEA) recorded 1,013 non-pharmaceutical fentanyl related deaths (Drug Enforcement Administration, 2018). This illicitly manufactured fentanyl, commonly referred to as IMF, is then used as a low-cost cutter that increases potency of low grade heroin and counterfeit home-pressed pills which are in turn sold to unaware users and has effectively caused an increase in the already staggering overdose rates (Centers for Disease Control and Prevention, 2018b). To curb

the production of IMF the DEA passed regulations to prevent the sale of precursors to unregulated individuals (Drug Enforcement Administration, 2018). Responding to the increased regulation attempting to thwart the production of IMF, many clandestine labs have begun working on synthetic fentanyl analogs, most of which do not appear on traditional toxicology reports and are thus under reported in current data. The most potent fentanyl analog detected in the U.S. to date is known as Carfentanil, a substance with an estimated potency 10,000 times that of morphine (Centers for Disease Control and Prevention, 2018b).

According to data published by the National Institute on Drug Abuse 15,482 heroin related overdose deaths were recorded in 2017. Approximately 10,000 of those deaths were attributed to persons consuming a combination of heroin and at least one other synthetic opioid, the most frequent of which being fentanyl. While these overdose rates are staggering and present significant problems alone, when paired with the rapidly increasing rate of overdoses due to prescription opioids, 17,029 in 2017 alone, the true weight of this problem becomes palpable. In 2012 overprescribing of opiates by doctors hit its peak with the average prescribing rate of opiates at a staggering 81.3 prescriptions per 100 persons. Due to nationwide backlash and the increased rate of addictions due to legitimately prescribed opioids the prescribing rate dropped to a ten year low of 58.7 prescriptions per 100 persons in 2017 (Centers for Disease Control and Prevention, 2018a). Even with this drop in prescribing rates, out of the 70,237 overdose-based deaths in the 2017 year, just above two thirds at 47,600 total, were attributed to some form of opioid overdose (National Institute on Drug Abuse, 2019).

The rates of opioid overdose deaths in the U.S. are representative of the highly addictive nature of opioids. Due to the human body's use of endogenous opioids for a plethora of functions including but not limited to reward and emotion processing, motivation, and arousal,

the introduction of exogeneous opioids creates a high potential of wreaking havoc on these processes resulting in behaviors characteristic of addiction (Nummenmaa & Tuominen, 2018). These interactions with and disruptions of the body's natural homeostatic function cause the high relapse rate characteristic of opiates, with a range of 72-88% persons relapsing between 12-36 months after completing opioid detoxification (Chalana, Kundal, Gupta, & Malhari, 2016).

There are several recommended therapies to aid in opiate detoxification and relapse prevention, the most common involving utilization of what the World Health Organization considers "essential medicines" such as buprenorphine and methadone. The current widely accepted treatment for opioid addiction is use of an essential medication supplemented with a form of behavioral counseling, a process defined by the National Institute on Drug Abuse as Medication Assisted Treatment, MAT. Buprenorphine is used in patients with a lesser history of abuse where Methadone Maintenance Therapy, MMT, is more common and effective at treating addicts with long term abuse and addiction histories (National Institute on Drug Abuse, n.d. b). Buprenorphine is only a partial mu opioid receptor agonist resulting in its decreased efficacy and its observed apparent ceiling effect. Individuals with a history of addiction greater than three months or those who used intravenous opioids have a greater tolerance causing the partial agonist to be insufficient in maintaining withdrawal symptoms. Unlike methadone, buprenorphine is will cause displacement of any other exogenous opioids causing precipitated withdrawal (Remski & Whelan, 2012).

MAT is aimed at lessening the physical symptoms of withdrawal and aiding cessation of illegal opioid use. By introducing methadone, a pharmokinetically different opioid with a longer half-life, approximately 24 hours in an opioid-tolerant patient, via regulated administration by a doctor or clinic MMT meets the goals of MAT (Grissinger, 2011). If conducted properly the

patient can slowly work down their dependence while the methadone lessens the intensity of the withdrawal symptoms without providing the same level of psychoactive "high" obtainable from other more abused opiates (National Institute on Drug Abuse, n.d. b).

Even with effective MMT the full effects of this replacement therapy are normally not observed in the first five days of use with patients commonly experiencing the full effects of opioid withdrawal (Grissinger, 2011). This initial onset period is considered the most difficult part of starting an MMT, creating the need for better developed therapies to aid in patient retention (Mayet et al., 2015; Scavone, Sterling, Weinstein & Vockstaele, 2013). Recent research has begun to highlight the potential interactions between the human endocannabinoid and opioid systems potentially opening the door for combination therapy. Currently delta-9-tetrahydrocannabinol, the naturally occurring psychoactive compound found in cannabis more commonly referred to as THC , has been shown to not only increase potency of opioids but to also provide analgesia and aid in reduction of the psychological symptoms associated with MMT (Cichewics, 2004; Mayet et al., 2015; Abrams et al., 2007; Kahan, Srivastava, Spithoff & Bromley, 2014; Scavone et al., 2013). This hypothesized link between the endocannabinoid system and the opiate system in the brain provides potential for supplementation of MMT with detla-9-tetrahydrocannabiniol allowing for lower methadone dosage, lessened withdrawal symptoms, and greater early treatment retention rates.

Opioids: Mechanism of action, Addiction, Withdrawal, and Relapse

Before analysis of the addictive nature of opioids can begin a working definition of opiate addiction needs to be developed. The American Society of Addiction Medicine (n.d.) outlines addiction as a primary, chronic disease of brain reward, motivation, memory and related circuitry. Characterized by an inability to consistently abstain from use, impairment of

behavioral control, cravings for drugs or similarly rewarding experiences, diminished recognition of behavioral and interpersonal relationship issues, and dysfunctional or aberrant emotional responses (American Society of Addiction Medicine, n.d.). In accordance with this definition the fifth edition of the Diagnostic and Statistical Manual (DSM-V) goes further to define opioid use disorder, which in the case the remainder of this review will serve as the working definition of opioid addiction (American Psychiatric Association, 2013). The criteria outlined by the DSM-V requires that a patient have a pattern of opioid use leading to clinically significant impairment or distress occurring within a twelve month period, observable as at least two of the following symptoms: patient consumes opioids in greater frequency and/or in doses greater than prescribed, persistent desire or unsuccessful efforts to reduce usage, large amounts of time are spent to obtain, use, and recover the opioids in question, a strong craving or desire to consume opioids, recurrent use resulting in failure to maintain responsibilities at work, school, and or home, continuation of opioid use despite recurring social or interpersonal problems resulting from or exacerbated by use, frequent opioid use in physically dangerous environments, continuation of opioid use despite having knowledge of a physical or psychological problem likely to be the direct result of or intensified by opioid usage, tolerance, and withdrawal.

These behavioral symptoms characteristic of opioid addiction are direct results of neurological changes induced by long term introduction of exogeneous opioids. When exogeneous opioids are consumed in an acute fashion by a patient without a previous history of opioid addiction the mu (μ) opioid g-protein coupled receptor is stimulated activating the G_i subunit cellular firing rate is suppressed by direct activation of K^+ channels and by inhibition of synthesis of adenylyl cyclase leading to the downstream inhibition of the cAMP pathways and altered gene expression. In contrast the patterns of opioid addiction result in chronic exposure

that yields an increased production of adenylyl cyclase and upregulation of the cAMP pathway increasing electrical excitability of locus coeruleus neurons characteristic of tolerance and dependence. This response is theorized as a homeostatic response to the continued presence of opioids in order to return firing processes to the patient's baseline levels prior to addiction (Koob & Nestler, 1997).

Opioid tolerance as further defined by the DSM-V is either a consistent need for increased dosage or frequency of opioid consumption in order to obtain the desired effects or a markedly diminished effect with continued usage of the same dosage of opioid. This model of tolerance has been corroborated by self-administration studies conducted in mice, illustrating a positive correlation between rates of self-administration and duration of use. These exhibited tolerance symptoms are likely due to the upregulation of cAMP pathway to counteract continuous exogenous opioid stimulation of the mu opioid receptors. Upon removal of the opioid from the receptor, causing the patient to "come down", these cells experiencing upregulated cAMP are left unopposed and cause a significant spike of firing rates above baseline levels leading to the symptoms described as withdrawal (Koob & Nestler, 1997). This cAMP hypothesis of opioid addiction developed by Klee, Nerenberg, and Sharma (1975) has been widely regarded as the mechanism for these symptoms of tolerance, a defining characteristic of opioid addiction. By subjecting neuroblastoma cells to morphine Klee et al. (1975) observed a decrease in cellular cAMP, yet after continued exposure cAMP levels first returned to baseline and continued to rise with each repeated exposure indicating cAMP's role in tolerance formation.

While opioid withdrawal is experienced as a combination of a myriad of symptoms varying in intensity, in almost all cases it first manifests as anxiety coupled with intense drug cravings (O'Malley & O'Malley, 2018). Additional symptoms include: increased respiratory

rate, sweating, runny nose, lacrimation, dilated pupils, heightened sensitivity, confusion, nausea, vomiting, diarrhea, insomnia, muscle cramping, pain, fatigue, depression, anhedonia, agitation, tremors, muscle twitches, tachycardia, and chills (O'Malley & O'Malley, 2009; Peles, Schreiber, Naumovsky & Adelson, 2007; World Health Organization, 2009). Many studies have underlined the commonality of patients experiencing depression when undergoing MMT. By studying depression rates in patients undergoing MMT, Peles et al. (2007) found the severity of an individual's depression is directly correlated with the patients' daily methadone dose in those individuals who additionally abuse other drugs. A highly significant correlation was also found between depression rates and use of methadone in conjunction with benzodiazepines compared to those who abstained from additional drug usage (Peles et al., 2007).

While MMT is commonly employed with the end goal of aiding the patient in breaking their addiction, the methodology of this treatment lies in withdrawal symptom maintenance. By acting as a competitive antagonist methadone occupies the mu receptors, stopping some of the physical withdrawal symptoms without providing the same euphoria provided by other opioids. The initiation period of MMT, how long it takes for the methadone to lessen symptoms, can take from five days to one week leaving patients vulnerable to relapse in that period (Grissinger, 2011). While those undergoing MMT while living in an in-patient facility exhibit a low rate of relapse at 20%, individuals attempting out-patient methadone substitution exhibit an 80% relapse rate (Kleber, 2007). Those who are not enrolled in an in-patient facility but are undergoing MMT are not considered for withdrawal management (WM) programs further heightening the severity of the gap until onset of methadone's full effects (World Health Organization, 2009). Patients have been shown to seek out additional substances to aid in the stress management associated with MMT. Smoking tobacco is the most commonly abused substance by patients

participating in MMT and is frequently cited as a form of stress relief for those addicted to nicotine. Some studies have measured tobacco usage rates amongst those suffering from opioid addictions at rates as high as 91% (Clarke, Stein, McGarry & Gogineni, 2001). This gap in treatment efficacy paired with high comorbidity of tobacco addiction illustrates the need for a fast-acting supplemental treatment in conjunction with MMT to increase its effectivity.

Delta-9-tetrahydrocanabiniol

A substance of increased study for a host of medical conditions has high potential for being a successful addition to MMT as well. Many know delta-9-tetrahydrocanabiniol as THC, the psychoactive compound naturally occurring in *Cannabis sativa*, and until recently this powerful molecule was overlooked for its potential medicinal benefit. One of the most well studied effects of THC is analgesia. Abrams et al. (2007) measured non-HIV-linked pain reduction in patients by administering cannabis "cigarettes" versus a form of placebo "cigarette". The cannabis group was given 3.56% THC "cigarettes" to smoke three times daily and saw an average 34% reduction in pain compares to the 17% observed pain reduction in the placebo group. No serious adverse effects were reported, and smoked cannabis was well tolerated. These findings were comparable to oral drugs used for the same purpose (Abrams et al. 2007). Additional studies by Kahan et al. (2014) set out to optimize THC dosage for pain moderation with minimal to no cognitive impairment. Recommended dosage was measured to be 400mg per day of smoked cannabis containing 9% THC by weight and was found to provide significant pain relief without unwanted cognitive impairment. Additional cannabinoid compositions were not measured. The analgesic properties of THC coupled with its fast acting and minimally addictive properties make it an ideal candidate to supplement methadone during the initiation period of MMT.

One of the main concerns surrounding THC usage is depression. Bovasso (2001) conducted a study comparing if cannabis abuse is a risk factor for depression or if cannabis abuse is indicative of self-medication for depression. Those who measured baseline depressive symptoms with a diagnosis of cannabis abuse were 4x more likely to have depressive symptoms at follow up than non-cannabis abuse patients. Particularly suicidal ideation and anhedonia were the main symptoms witnessed. Those with no abuse diagnosis at baseline failed to significantly predict cannabis use at follow up. Long term cannabis abuse has been theorized to induce depression by increasing interferon-gamma, which inhibits aromatase inhibiting conversion of androgens to estrogen, thus creating a deficiency in estrogen a hormone that augments the synthesis of serotonin. This was not found to be a long-term concern in those not exhibiting cannabis-use disorder, underlying the potential safety of using THC as supplementation to traditional MMT without inducing additional anhedonia or depression in patients (Bovasso, 2011).

Methadone Maintenance Therapy and delta-9-tetrahydrocannabiniol Use and Interactions

Utilization of THC by patients undergoing MMT is not uncommon nor understudied, and additional research currently being conducted due to the increased rate of doctors prescribing some form of THC or cannabis to patients for various ailments. The main push for additional research on THC supplemented MMT is rooted in the recently identified links between the endocannabinoid and opiate systems. In a highly replicated study by Welch and Stevens (1992) highlighted that spinal administration of various cannabinoids, including THC, with morphine induced effects greater than the sum of each individual component's effects, demonstrating synergy. With this discovery, the next logical focus of study was the mechanism of this interaction. As discussed by Chicewicz (2004), the analgesic effect of THC is partially mediated

via delta and kappa opioid receptors indicating a connection between systems in the modulation of pain perception. Cannabinoids exhibit a similar binding distribution of opioids, and receptors for both opioid and cannabinoid receptors are co-distributed in areas of the dorsal horn of the spinal cord, raphe nuclei, central-medial thalamic nuclei, and the periaqueductal gray areas. This illustrates the potential of using low doses of THC to enhance the potency of opioid drugs and minimize the adverse effects of both. When optimized correctly this successfully reduces the need to escalate opioid dose while increasing opioid potency (Cichewicz, 2004).

As mentioned previously, the primary goal of MMT programs is to reduce the symptoms of withdrawal an individual experiences while titrating down their opioid consumption. By increasing the potency of methadone THC would synergistically enhance withdrawal mitigating effects, especially in the induction period of therapy, without causing the need for an increased dosage. This desire to limit methadone dosage is self-explanatory, the fewer exogenous opioids needed for therapy results in fewer side effects and a shorter duration of MMT treatment. Additionally, THC has been shown to posses a low potential for addiction, which presents a comparative advantage to the addiction potential presented by any opioid (Cichewicz, 2004). The end goal of MMT is to provide patients with a complete detox of all opioids and allow them the return to functional life. While THC is a psychoactive compound its effects are minimal, and proper dosage for analgesic function without impairment has been determined, allowing for its use as a safe and inexpensive supplement for patients undergoing MMT (Kahan et al., 2014).

In a study conducted by Epstein and Preston (2003) the outcome of cannabis use on treatment retention rates in heroin dependent patients undergoing MMT was investigated to find that cannabis use showed no associated differences in patients' treatment retention rates. Cannabis users were shown to have no special propensity to relapse after the conclusion of

MMT. Usage of cannabis, a source of THC, was found to account for no more than 10% of the heroin usage in the population, indicating a low level of influence on heroin use due to cannabis consumption (Epstein & Preston 2003). Objective rates of patients' cannabis use were high during induction of MMT and dropped significantly post dosage stabilization of methadone dosage. Cannabis use did not negatively impact the methadone induction process further underlying the low potential for THC consumption to cause relapse (Scavone et al., 2013); (Mayet et al., 2015). Relapse shown to alcohol and cocaine use in cannabis users has been shown but no correlation between cannabis use and heroin relapse was identified (Scavone et al., 2013). Cannabis shown to be less helpful then benzos in withdrawal reduction but more effective than cocaine, alcohol, and nicotine.

Additional precautions have been outlined for patients with psychiatric comorbidity or additional physical ailments when undergoing MMT as this has additional effects on the patient's propinquity to experience enhanced withdrawal symptoms (Reisfield, Wasan & Jamison, 2009); (Mayet et al., 2015). Cannabis use is thought to differently predict relapse to heroin in patients with psychiatric co-morbidity. Psychiatric co-morbidity is determined as an active opioid addiction as well as diagnoses with psychotic, bipolar, personality or major depressive disorders. Additional implications for those with diagnoses with an anxiety disorder are hypothesized but not yet studied (Epstein & Preston, 2002). As illustrated by Reisfield et al. (2009) positive tests for THC metabolites in urine illustrated a significantly higher THC consumption rate in those undergoing MMT with psychiatric co-morbidities and has been associated with the 13.8% of cannabis positive patients that self-reported partaking in aberrant opiate behaviors such as doctor shopping. This is predicted to be due to chronic THC administration inducing cross tolerance to opioids increasing these patients with additional

comorbidities susceptibility of relapse. This correlation was not found in patients lacking psychiatric diagnoses (Reisfield et al., 2009). Those with higher levels of physical health problems were found by Mayet et al. to more frequently use cannabis during MMT indicating the potential for self-medication (Mayet et al., 2015).

Conclusion

MMT is an effective treatment method for those attempting to recover from an opioid addiction, yet there is still room for improvement in this treatment plan. Special care should be taken to aid patients in the transition from terminating their aberrant opioid use through the initiation period of MMT. Utilization of THC for pain mediation has proven as effective as oral drugs and has been shown to not cause depression in users unless there is a preexisting psychiatric co-morbidity (Abrams et al., 2007); (Reisfield et al., 2015). While this treatment methodology requires additional research the early literature on the interactions between the endocannabinoid and opioid systems has outlined a safe and effective way to potentiate MMT in the initiation phase of treatments effectively lessening patient side effects without requiring an increase in dosage.

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