Effect of Supplementing Methadone Maintenance Treatment with Delta-9-Tetrahydracanabinol on Reducing Withdrawal Symptoms and Increasing Patient Retention Rates.

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Abstract

Opioid addiction recovery is unique due to the highly addictive nature of opioids and their prevalence in society, both as pharmaceuticals and illicit substances. Recovering addicts are recommend to partake in a form of controlled detoxification due to the severity of withdrawal symptoms commonly experienced. Those with long histories of opioid abuse are frequently prescribed methadone maintenance therapy (MMT), an opioid engineered to be a competitive agonist by binding to the patient's mu opioid receptors. By first swapping the exogenous opioid for one that is not psychoactive patients can avoid withdrawal symptoms before steadily decreasing their dosage under doctor supervision. While in theory MMT allows patients a safe and controlled way to slowly detoxify from opioid addiction, patients tend to struggle with the transition from their opioid of choice to methadone. Frequently patients experience the full spectrum of withdrawal symptoms during the first week of treatment, leaving an especially vulnerable window known as the induction period. While patients normally partake in behavioral therapy to aid in the development of coping mechanisms, these skills are not learned by the induction period. I aim to prove that by supplementing MMT with a rapid acting, relatively non-addictive, non-opioid based analgesic and anxiolytic, delta-9-hydrocannabinol (THC), during the induction period patients will express fewer withdrawal symptoms with lesser intensity than those without this supplementation. Additionally, I will prove the aforementioned THC supplemented patient group will express better patient retention rates throughout the duration of the 18-month treatment. 200 participants currently addicted to opioids and seeking MMT for the first time in the greater Philadelphia area will be randomized into two groups for a double-blind placebo study, where they will be asked to self-report their withdrawal symptoms and severity twice daily for three weeks. Participants will be given full doctor supervised MMT with additional behavioral therapy once a week, with patient retention measured as attendance at

said therapy sessions and medicine distribution appointments. I hypothesize that by supplementing patients' MMT program with delta-9-tetrahydrocannabinol will result in a reduction in number and severity of withdrawal symptoms as well as higher patient retention rates.

Keywords: methadone, opioid, addiction, THC, delta-9-tetrahydracannabinol, withdrawal

Introduction and Background

The United States is currently experiencing a massive opioid abuse crisis, leaving researchers searching for the best possible methods for aiding patients in breaking these addictions. With 47,600 deaths due to some form of opioid overdose in 2017 alone, the addictive nature of both these legal and illegal opioids has taken hold of persons from all walks of life (National Institute on Drug Abuse, 2019). As recently as 2012 due to massive doctor overprescribing there was an average rate of 81.3 opioid prescriptions written per 100 people; only dropping to 58.7 prescriptions per 100 persons in 2017 after intense public backlash (Centers for Disease Control and Prevention, 2018a).

The rates of opioid overdose rates in the United States are representative of the highly addictive nature of these chemicals. Due to their endogenous roles in a plethora of human functions including but not limited to reward and emotion processing, motivation and arousal, doctors have worked to develop methods of gradual opioid detoxification in hopes to prevent some of the side effects of abruptly terminating exogenous opioid consumption (Nummenmaa & Tuominen, 2018). In relapse studies conducted by Chalana, Kundal, Gupta, & Malhari (2016) it was found that when abruptly terminating opioid consumption without a slow titration to lower dosages between 72-88% of patients were found to relapse within 12 to 36 months after completing opioid detoxification. This has forced the "lesser of the two evils" approach to helping patients break their dependencies on exogeneous opioids. By using a process of Medication Assisted Treatment (MAT) where behavioral counseling is supplemented by a doctor controlled dose titration using one of two pharmokinetically engineered opioids with a long half-life designed to lessen the intensity of withdrawal symptoms without providing the psychoactive

"high" obtainable from the more abused opioids (National Institute on Drug Abuse, n.d.) For patients with a shorter history of addiction, especially non intravenous users, a weaker opioid buprenorphine is recommended; while those with a long term history of abuse and or intravenous usage methadone is preferred. With a half-life of approximately 24 hours in an opioid tolerant patient methadone allows for easier regulated administration via a doctor or clinic (Grissinger, 2011).

While methadone is pharmokinetically similar to the commonly abused opioids, patients tend to not feel the full effects of the methadone maintenance treatment (MMT) for the duration of the initiation period, which commonly lasts from five days to one week, and are subject to the full effects of opioid withdrawal (Grissinger, 2011). The common symptoms patients experience include but are not limited to: anxiety, intense drug cravings, increased raspatory rate, sweating, runny nose, lacrimation, dilated pupils, heightened sensitivity, confusion, nausea, vomiting, diarrhea, insomnia, muscle cramping, fatigue, pain, depression, anhedonia, agitation, tremors, tachycardia, chills and muscle twitches (O'Malley & O' Malley, 2018); (Peles, Schreiber, Naumovsky & Adelson, 2007); (World Health Organization, 2009). Patients enrolled in a MMT program are additionally ineligible for withdrawal management programs further enforcing the severity of the gap until onset of methadone's full effects (World Health Organization, 2009). Due to the myriad of terrible symptoms experienced by patients during the initial onset period of MMT, a need for better developed therapies to aid in patient retention has arisen (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 present in humans potentially opening the door for combination therapy and improvement on the current "lesser of two evils" treatment model that

MMT currently provides. As highlighted by a plethora of studies delta-9-tetrahydrocannabinol (THC), the naturally occurring psychoactive compound found in cannabis, has been shown to not only increase the potency of exogeneous opioids but to also provide analgesic effects while aiding in reduction of the psychological symptoms associated with MMT (Chicewics, 2004); (Mayet et. al., 2015); (Abrams et. al., 2007); (Kahan, Srivastava, Spithoff, & Bromley, 2014); (Scavone, et. al., 2013). Abrams et. al. (2007) measured non-HIV linked pain reduction inn patient administering cannabis cigarettes vs. placebo cigarettes to find an average of 34% pain reduction in the cannabis group vs 17% in the control group with no serious side effects seen. Further studies by Kahan et. al. (2014) optimized THC dosage for pain moderation with minimal unwanted cognitive impairment as 400mg of smoked cannabis containing 9% THC by weight. 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 (Cichewics, 2004). Cannabinoids, including THC, 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.

In a study conducted by Epstein and Preston (2003) the outcome of cannabis use for heroin dependent patients undergoing MMT was examined to find that cannabis use showed no associated differences in patients' treatment retention. 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 (Scavone et al., 2013). 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 providing further evidence for the potential success of THC supplemented MMT (Scavone et al., 2013).

Additional precautions to this approach 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 (Reisfield et al., 2009). Positive metabolite urine testing 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 susceptibility of relapse in these patients with comorbid psychiatric diagnoses. This correlation was not found in patients lacking psychiatric diagnoses.

Supplementing MMT with an additional substance with analgesic and anxiolytic properties that also presents patients with a low potential for addiction during the initiation phase of treatment will not only increase patient retention but lower subjective experienced symptoms. In order to determine if supplementation with THC lowers patient reported withdrawal symptoms and increases patient retention, I propose a study that will examine the effects of such

supplementation on new patients undergoing MMT for the first time. In order to evaluate the subjective withdrawal symptoms experienced patients will be asked to self-report symptoms twice daily as well as any additional drug usage to prevent confounding factors. Additionally data on the patient's treatment duration will be collected to measure mean patient retention time.

Methods

Study Design

This proposed study will utilize a random double-blind placebo method to divide study participants into two groups. This randomization will be done via computer software to prevent any experimental bias. Utilizing a patient pool of 200 participants, with an approximately 1:1 ratio of males to females to remove and confounding factors due to patient sex, participants will be randomly assigned to one of two treatment groups, THC supplementation and control. The 100 participants assigned to the THC supplementation group will receive a standard MMT program, including behavioral therapy, paired with THC supplementation administered via tablet. The other 100 participants assigned to the control group will also receive a standard MMT program including behavioral therapy but will be administered placebo tablets. All participants will be asked to keep a journal of self-reported withdrawal symptoms, recording their symptoms twice daily for the first three weeks of MMT initiation. Participants will also be asked to record any and all additional drug usage, including but not limited to alcohol, cannabis, opioids, cocaine, benzodiazepines, and amphetamines. Treatment retention will be measured by patient attendance at therapy visits and medication administration appointments over an 18 month period as this is the standard duration of MMT for patients (Chao, Hung, Lee, Lin, & Peng, 2015).

Subject Recruitment

The participants will be recruited from the greater Philadelphia area by the distribution of flyers, radio advertisements, and through doctor recommendations. The flyers and advertisements will contain the patient inclusion criteria outlined below as well as the necessary contact information for the research facility. In order to reach participants of equal walks of life flyers will be distributed throughout the greater Philadelphia area entirely with special focus in primary care physicians' offices, pharmacies, treatment clinics, as well as psychiatry and psychology offices with doctors specializing in addiction recovery. All participants will be compensated financially for their time and travel in addition to the free treatment provided as the basis of this study. Prior to the start of the study the main investigator will prescreen all applicants and explain in detail the procedures and aim of this investigation. Participants will asked in their prescreening questionnaire if they are comfortable possibly consuming THC over the duration of this study, as some workplaces test for this substance, thus preventing patients from potentially losing their employment.

Subjects

The 200 participants will be randomly assigned to placebo or THC supplemental groups after completion of prescreening processes. Any age, height, gender, or weight participant will be considered for this experiment; however, there will be strict inclusion/exclusion requirements enforced as outlined below.

Inclusion Criteria

- Participants must be currently addicted to some form of opioid (both obtained legally or illegally) following the DSM-V's qualifications for opioid addiction.

- Participants must be seeking addiction treatment for themselves.
- Participants must have a long history of opioid addiction that requires treatment with methadone rather than buprenorphine.
- Participants must have never participated in a MMT program in the past.
- Participants must be currently using opioids at the start of the experiment.

Exclusion Criteria

- Individuals who have previously initiated an MMT program, even if not successfully completed.
- Individuals with preexisting psychiatric conditions.
- Individuals with a history of cannabis abuse.
- Individuals with comorbid substance abuse disorders (ex. patients addicted to opioids and cocaine).
- Family members or friends of individuals seeking treatment for a loved one without their consent.
- Individuals who have begun the withdrawal and detox process before the start of the study.

Procedure

Participants will attend a preliminary psychiatric evaluation paired with self-reported questionnaires to obtain baseline levels for self-reported withdrawal symptoms before the initiation of the MMT. It will be noted if patients consumed any opioids that day prior to arrival at the research facility. Following this evaluation and a meeting with a doctor, patients will begin their respective MMT program. Those in the THC supplemented group will receive oral

capsules containing 36mg of THC to be taken three times daily during the first three weeks of MMT. Those in the control group will be given oral capsules containing sugar also to be taken three times daily. All participants will be asked to keep a journal self-reporting their specific withdrawal symptoms as well as their respective intensities on a 1-10 scale. Participants' retention will be measured by their attendance at the provided once weekly behavioral therapy appointments and medication distribution appointments over the full 18 week duration of the MMT program.

Statistical Analysis

The data will be represented as means and standard errors of the mean. The number of withdrawal symptoms experienced each day by the THC supplementation and control groups will be compared using a 2 tailed z-test. The relative intensities of each weekly cataloged withdrawal symptom will be compared using a 1 tailed z-test. Lastly patient retention times of the control and THC supplementation groups will be compared with a two tailed z-test. Z-tests will be used due to the high sample size of this study. Statistical significance will be noted at $p \leq 0.05$.

Predicted Results and Discussion

I hypothesize that utilization of THC supplemented MMT for patients undergoing a MMT program for the first time will reduce the number and severity of patient experienced withdrawal symptoms during the initiation period of therapy compared to those undergoing this program without supplementation. Additionally, I believe the utilization of THC for withdrawal symptom mitigation will result in greater patient retention rates during the full 18-month duration of methadone treatment. This study holds great value to physicians and medical

researchers as it presents a potential new treatment methodology opioid addiction, a public health issue that is ravaging lives worldwide. By providing patients with a form of symptom mitigation via a chemical with low addictive potential this study will allow researchers to explore THC supplemented MMT as well as supplementation with other non-opioid based substances; a breakthrough that could potentially help those ill fit for THC supplementation, such as those with psychiatric co-morbidities.

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