8-2021

Exploration of Patient Variables and Characteristics Best Suited for Medical Marijuana Treatment for Anxiety and Depressive Disorders

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A Clinical Research Project submitted to the Faculty of the Florida School of Professional Psychology at National Louis University in partial fulfillment of the requirements for the degree of Doctor of Psychology in Clinical Psychology.

Tampa, Florida
August, 2021

The Doctorate Program in Clinical Psychology
Florida School of Professional Psychology
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CERTIFICATE OF APPROVAL

Clinical Research Project

This is to certify that the Clinical Research Project of

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has been approved by the
CRP Committee on August 13th, 2021
As satisfactory for the CRP requirement
For the Doctorate of Psychology degree
With a major in Clinical Psychology

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Abstract

Individuals with posttraumatic stress, anxiety and depressive disorders are currently being prescribed medical marijuana as a treatment in many states across the United States. However, marijuana is still considered a schedule one narcotic by the Drug Enforcement Administration and federal government, which provides several barriers and challenges to conduct research such as approval from the U.S. Food and Drug Administration and following guidelines from the National Institute on Drug Abuse issued by the DEA. Additionally, individuals prescribed medical marijuana for mental health disorders are not always thoroughly instructed on the type of medical marijuana, the dosage, and how frequently to use marijuana. This literature review's objective was to understand what mental health symptoms medical marijuana treats and what factors indicate medical marijuana is a suitable treatment for posttraumatic stress disorder, anxiety, and depression. Cannabidiol and tetrahydrocannabinol have been found to contribute to an acute reduction in both posttraumatic stress disorder and anxiety symptoms, although long-term efficacy is still unclear. Results have varied with depressive disorders regarding the successful reduction of depressive symptoms. Conversely, studies have shown that medical marijuana and recreational marijuana use may exacerbate depressive symptoms and psychosis, and tetrahydrocannabinol-based medical marijuana products may not be best suited for individuals with a history of substance abuse due to potential habit-forming qualities. In addition, medical marijuana can have an impact on the concentration of psychotropic medications. Studies to date have indicated that medical marijuana's effective dosage for treatment may differ across individuals depending on the disorder, individual factors, prior marijuana use, and time relative to experience symptoms.

EXPLORATION OF PATIENT VARIABLES AND CHARACTERISTICS BEST SUITED FOR MEDICAL MARIJUANA TREATMENT FOR ANXIETY AND DEPRESSIVE DISORDERS

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CHAPTER I: INTRODUCTION

Individuals who experience PTSD, anxiety, and depressive disorders are currently being prescribed medical marijuana as a treatment (Abizaid, Merali, & Anisman, 2019). Medical marijuana was first legalized in the United Stated in 1996 and since has been a controversial topic on local, state, and federal levels (Bridgeman & Abazia, 2017). There is limited data available indicating the best practices for prescribing medical marijuana based on patient characteristics such as diagnosis, chronic health conditions, and contraindications that would impact the effectiveness of medical marijuana. When an individual is prescribed medical marijuana, they have access to a medical marijuana dispensary (PA.Gov., 2020). At a dispensary, prescribed individuals can choose various cannabis options from edibles, vaporizing oils, and flower bud. They also can choose different strains of cannabis, which are predominantly *indica* and *sativa* or blends of the two. Beyond the route of administration and strain, individuals can then choose tetrahydrocannabinol (THC) or cannabidiol (CBD) products that also have different levels of blends and can also be administered individually (PA.Gov., 2020). As a consumer, it can be confusing what medical marijuana product may be right for them. Ideally, the doctor prescribing marijuana will help their patients navigate the challenges of finding the right product.

History of Medical Marijuana

"Cannabis genus" are flowering plants derivative from Central America, which humans have consumed for about 5,000 years (Hudak, 2016). There are three major cannabis species, sativa, indica, and *ruderalis*, and they have different chemical characteristics, uses, and look. Indica and sativa are common in cannabis production due to the high THC concentration in recreational and medical marijuana. Sativa is typically associated with feelings of euphoria, and indica is typically associated with the feeling of relaxation. Flower and particularly the bud are

common names for the highest concentration of chemicals that influence the brain. “Bud” delivered the ability to smoke the marijuana. Cannabinoids are a different part of the plant and contain some of the same chemical components as the flower and bud. The whole plant is used for commercial production to extract cannabinoids (Hudak, 2016). Cannabinoids can be psychoactive or non-psychoactive. THC is responsible for the psychoactive and euphoric responses associated with marijuana. CBD is typically associated with medical marijuana rather than recreational use. CBD has many therapeutic uses, such as anti-seizure and anti-inflammatory treatment. Medical marijuana has multiple delivery methods such as ointments, creams, lip balms, salves, massage oils, moisturizers, and hundreds more (Hudak, 2016).

Regulation of Marijuana in America

In 1906, Congress passed the Federal Food and Drug Act (currently Food and Drug Administration, FDA), which allowed the government to regulate and standardized commercial drugs, foods, and other products (Hudak, 2016). Robins (1995) indicated that in 1914 the Harrison Act was passed, and the United States made psychoactive drugs including marijuana illegal, and thus they were only made available by a prescribing physician. During the 1930s, Mexican immigrants crossing the border into the U.S. were deemed criminals with stereotypes that associate Mexicans with “marihuana” (Hudak, 2016). In 1937, Congress passed the Marihuana Tax Act, which was the first formal use of the word marihuana from the government. The law required individuals who import, manufacture, produce, compound, sell, dispense, prescribe, administer, or give away marijuana to register with the government (Hudak, 2016). The Controlled Substances Act was passed in 1970 to reduce abuse of drugs, and marijuana (THC) was categorized in the same was in the same class of drugs such as heroin, LSD, and ecstasy (El-Zein, 2017). El-Zein (2017) indicated that since the first state legalized marijuana in

1996 there has been a discrepancy between state and federal law. State law may permit recreational and medical marijuana use, and federal law states marijuana is an illegal substance. Possession of marijuana can result in a range of penalties from fines and imprisonment (El-Zein, 2017). The Drug Enforcement Administration (DEA) still considers marijuana a schedule one narcotic, which is defined as substances with no currently accepted medical use and a high potential for abuse (Drug scheduling, 2019).

Decriminalization and Legal Use of Marijuana and Medical Marijuana

Fichtner and Moss (2017) indicated that in 1985 THC was approved to treat vomiting and nausea for individuals receiving chemotherapy, which was the first time the U.S. government acknowledged potential therapeutic purposes for medical marijuana. California became the first state to have medical cannabis laws and medical cannabis for commercial use in 1996. There are several forms of medical marijuana, for example Sativex is an herbal extract with a THC:CBD ratio of 1:1 and was the first cannabis product to gain medical approval for multiple sclerosis in 2005 and for chronic cancer pain in 2006 (Fichtner & Moss, 2017).

Currently, 16 states have fully legalized marijuana use for medical and recreational use: California, Washington, Oregon, Nevada, Arizona, Colorado, Alaska, Michigan, Montana, South Dakota, Vermont, Maine, Massachusetts, New Jersey, and Illinois. Washington D.C. also has passed recreational marijuana use. Thirteen states have approved medical marijuana use but not decriminalized recreational use: Arkansas, Florida, Georgia, Indiana, Iowa, Kentucky, Louisiana, Oklahoma, Pennsylvania, Texas, Utah, West Virginia, Wisconsin. Of these, Georgia, Indiana, Iowa, Kentucky, Texas, and Wisconsin are only approved for CBD use. Fifteen states have approved medicinal use and decriminalization of marijuana: Connecticut, Delaware, Hawaii, Maryland, Minnesota, Mississippi, Missouri, New Hampshire, New Mexico, New York, North

Carolina, North Dakota, Ohio, Rhode Island, and Virginia; however, Virginia is approved for only CBD use. Two states have decriminalized recreational marijuana and but have not approved medical use of marijuana: Nebraska and South Dakota. Seven states have medical and recreational marijuana use designated as illegal: Idaho, Wyoming, Kansas, Tennessee, Alabama, and South Carolina ("Map of marijuana legality by state," 2021).

Medical Marijuana Treatment for Mental Health

Medical marijuana has been utilized by the medical profession to assist with ailments such as multiple sclerosis, seizures, and chemotherapy's harmful side effects (Bridgeman & Abazia, 2017). However, recreational marijuana is viewed differently from state to state. Many states are attempting to incorporate laws that decriminalize possession of marijuana, but conflicts persist between federal and state law (El-Zein, 2017). THC is a phytocannabinoid (cannabinoids that occur naturally in the cannabis plant) that can produce euphoric qualities in the consumers, but the disadvantages are that it has a potential habit-forming risk with continual use (Ligresti et al., 2016). Elms et al. (2019) conveyed that CBD is a phytocannabinoid and is viewed as an anxiolytic that can help reduce anxiety and hyperarousal and is a non-psychotomimetic (does not cause psychosis) cannabinoid compound. Elms et al. utilized a retrospective case study of 11 adult outpatient clients and examined the effect that oral CBD had on their PTSD symptoms over an eight-week duration. The 11 patients were also treated with psychiatric medications and psychotherapy and their symptoms were measured by PTSD Checklist for the DSM-5 (PCL-5; Weathers et al., 2013). A total of 10 out of the 11 patients showed a decrease in PTSD symptoms indicated by a reduction in their PCL-5 scores. Elms et al. concluded that oral CBD in combination with psychiatric care has shown reduction in PTSD symptoms such as reduction in nightmares. CBD has also shown promise in reducing anxiety and treatment for PTSD, although

not proven at this point (Elms et al., 2019). Elms et al. have found significant results in their research although limitations include a small sample size, and thus additional research is needed to understand CBD's impact on PTSD symptoms.

Feingold et al. (2017) indicated that medical marijuana use has been shown to reduce anxiety and depression for patients with chronic pain compared to patients' prescription opioids. Feingold et al. examined 329 chronic pain patients prescribed medical marijuana compared to 474 chronic pain patients prescribed prescription opioids, 77 of whom were prescribed both. Patients were assessed for depression using the Patient Health Questionnaire (PHQ-9; Kroenke & Spitzer, 2001), and anxiety was screened using the Generalized Anxiety Disorder questionnaire (GAD-7; Spitzer et al., 2006). Depression and anxiety rates were highest among patients prescribed opioids compared to patients prescribed medical marijuana. Patients prescribed both medical marijuana and opioids were more likely to report depression compared to the medical marijuana group (Feingold et al., 2017). Limitations of this study include that the research was cross-sectional, which reduces the chances of causality because only correlations can be inferred from cross sectional data, and there are no variables that were manipulated.

Kosiba et al. (2019) conducted a systematic review and meta-analysis of empirical studies that included medical marijuana treatment for patient-reported symptoms of pain, anxiety, and depression. Kosiba et al. screened 2131 studies, which resulted in 109 full texts that were reviewed. Thirteen of the full text articles that only incorporated self-reported reasons for using medical cannabis were used, which included 6,759 participants from the thirteen self-report articles. Kosiba et al. reported that 50% of medical marijuana patients reported that they use it for anxiety, and 34% reported medical marijuana use for depression. The researchers several found methodological limitations in the studies. Patient recruitment was a limitation

because medical cannabis was only approved for certain medical conditions and may have influenced the patients to endorse medical marijuana use for approved conditions, which may not be the true reason for their use. Kosiba et al. highlighted Hawaii as an example of a state in which pain is the only condition legally approved for medical cannabis, which may have reduced the chances of an individual reporting medical cannabis use for reasons other than pain. Restrictive sampling was another limitation due to convenience sampling, which can be biased representations of a population. The last major limitation was the lack of randomized methods, which may overestimate the benefit of medical marijuana (Kosiba et al., 2019).

Piper et al. (2017) presented data from a New England dispensary that held an online survey about medical history and medical cannabis use. Piper et al. stated medical marijuana has shown a "substitution effect" for opioids for managing pain, and they hypothesized that there is an interaction between the cannabinoid and opioid neurotransmitter systems. The aim of the data examination was to explore whether the substitution effect of medical cannabis for opioids had similar result when substituting medical cannabis for psychoactive medications. There was a total of 1,513 participants in the online survey. Among the 308 patients who used anti-anxiety medication, 71.8% reported that they reduced their use of anti-anxiety medication, and 37.6% of the 237 patients using antidepressant medication reported that they reduced the number of antidepressants used after using medical marijuana. The substation effect for medical marijuana has not been extensively studied and is typically associated with a substitution for pain management (Piper et al., 2017).

Brain Anatomy and Neurotransmitters Involved in Medical Marijuana

There are several anatomical aspects of the brain to highlight in order to understand how medical marijuana impacts mental health. Fogaça et al. (2014) reported that the prelimbic medial

prefrontal cortex is a brain structure that influences the expression of emotional states, and 5HT1A is a serotonin receptor in presynaptic and postsynaptic neurons found in the prelimbic medial prefrontal cortex. Activation of 5HT1A may provide anxiolytic and antidepressant effects, and CBD is considered an agonist to the 5HT1A receptor. The activation of the 5HT1A receptor by CBD may have similar actions as anxiolytic, antipsychotic, and antidepressant medications (Fogaça et al., 2014).

The next anatomical structure of focus is the endocannabinoid system (eCB). Hill et al. (2013) indicated that the endocannabinoid system (eCB) is composed of a central CB1 receptor and two endogenous ligands, which serve as a means to activate the cannabinoid receptor (*N*-arachidonylethanolamine [anandamide; AEA] and 2-arachidonoylglycerol [2-AG]). There are also CB2 receptors, the expression of which is primarily restricted to immune cells of macrophage lineage but may also be expressed in the central nervous system (CNS). The eCB system is believed to constrain activation of the stress response through distributed actions in limbic and hypothalamic circuits in the brain. The eCB system is responsive to glucocorticoids, which regulate physiological actions of these hormones such as modulation of emotional and cognitive processes. The eCB system is involved in extinction of negative emotional memories, habituation, and adaptation to stress. Hill et al. believed that reduction in circulating concentrations of eCB increase the likelihood of stress vulnerability. PTSD may be a result of low concentrations of eCB signaling, which can help explain the reason some individuals are more likely to develop PTSD symptoms after an event (Hill et al., 2013). Zhang and Ho (2015) conveyed that CB1 receptors are most populated in the hippocampus, cortex basal ganglia, spinal cord, and cerebellum, and CB2 receptors have the highest concentration in cells responsible for

immune mediation, which helps to illuminate benefits and side effects of cannabis use (Zhang & Ho, 2015).

Potential Physical Side Effects of Medical Marijuana

Medical marijuana that contains THC or CBD may have impacts on various medications and may produce a number of side effects. For example, THC can have side effects such as headaches, nausea, hallucinations, increased heart rate, increased appetite, fatigue, drowsiness, dry mouth, red eyes, and dizziness (Mayo Clinic, 2020). THC may decrease concentrations of various medications including clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine. CBD may increase concentrations of various pharmaceutics including macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil, antihistamines, haloperidol, and antiretrovirals. CBD may also increase concentrations of various medications including SSRIs, tricyclic antidepressants, antipsychotics, beta-blockers, and opioids (Fugh-Berman et al., 2020).

Individuals who also experience psychosis and/or depression may be at risk of exacerbating depressive symptoms, hallucinations, or psychosis when using nabilone, which is synthetic THC used for the treatment of PTSD. Nabilone is a C1 receptor agonist spread throughout the brain that has limited interaction with cardiorespiratory areas in the brain stem. The implications of limited cardiorespiratory interaction reduce the risk of cardiorespiratory suppression, which can be a concern with use of other treatments such as opioids (Cameron et al. 2014). When focusing on nabilone use with women who are pregnant, nabilone has not been studied on women during pregnancy and has only been studied on pregnant animals, where it was shown to increase embryo lethality, fetal resorptions, decreased fetal weight, and pregnancy disruptions (U.S. FDA pregnancy category C). Therefore, when considering treatment for PTSD

on pregnant women, the FDA does not recommend breastfeeding while on nabilone because some cannabinoids are excreted in breast milk (Fugh-Berman et al., 2020).

Zhang and Ho (2015) conducted a review and reported that individuals who smoke cannabis usually have the peak effect after 30 minutes after use, and the effects typically last for 2 to 4 hours. They found that cannabis use may potentiate anxiety or agitation, hallucinations, paranoid ideations, impaired attention and judgment, and feelings of depersonalization. Individuals who use edible marijuana may not experience the intensity of the above symptoms, although high amounts of consumed marijuana can result in acute confusion, hypotension, hypothermia, and experience of psychosis (Zhang & Ho, 2015).

Statement of Problem

Individuals with mental health diagnoses are starting to be prescribed marijuana as a treatment. Prior to marijuana prescriptions, the treatment for mental health disorders primarily consisted of antidepressants, antipsychotics, benzodiazepines, and psychotherapy. The effectiveness of medical marijuana for individuals with mental health disorders and how it compares with traditional medical and psychological interventions is unknown. Medical marijuana may also have negative health ramifications and addiction potential. Although marijuana has been approved for medical use in many states, there are conflicting perspectives about whether medical marijuana should be used to treat mental health disorders. In addition, the existing literature often does not specify or compare the same types of medical marijuana in the available research, making it challenging to discern the efficacy. Finally, marijuana is still considered a schedule one narcotic under federal law, which may complicate use in treatment as well as broad based research on efficacy.

Purpose of CRP Literature Review

The purpose of this literature review is to investigate medical marijuana treatment for the symptoms of PTSD, anxiety, and depression. The review's major goal is to provide clinicians with an additional research tool to help inform psychotherapeutic interventions with individuals who have been prescribed medical marijuana for PTSD, anxiety, and depression. This review addressed the following research questions:

How may medical marijuana treat PTSD, anxiety, and depression?

What information supports and contraindicates medical marijuana as a suitable treatment for PTSD, anxiety, and depression?

What are the client characteristics that make a good fit and characteristics that make a client a poor fit for treatment with medical marijuana once diagnosed with PTSD, anxiety disorders, and depressive disorders?

Research Procedure

Various databases such as Google Scholar, ProQuest, and EBSCOhost were utilized to locate psychological and scientific journals and relevant information presented in books, conference presentations, and dissertations that address medical marijuana, medical cannabis, recreational marijuana, nabilone, CBD, and THC as a treatment for PTSD, anxiety disorders, and depressive disorders. The research procedures were intended to identify patient characteristics that would deem them advantageous or disadvantages in medical marijuana treatment, identify health and legal barriers surrounding prescribing medical marijuana, and highlight the interactions of medical marijuana and comorbid mental health disorders.

CHAPTER II: RESEARCH FOR USING MEDICAL MARIJUANA TO TREAT PTSD, ANXIETY, AND DEPRESSIVE DISORDERS

Supportive Research on Medical Cannabis for PTSD

PTSD is classified as a trauma and stressor-related disorder in the DSM-5. *The Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; American Psychiatric Association, 2013) has seven criteria that must be met to receive a diagnosis of PTSD. Each of the categories for PTSD has several criteria that help delineate a diagnosis. The following are the diagnostic categories for PTSD: (a) exposure to actual or threatened death, serious injury, or sexual violence; (b) presence of one (or more) of the following intrusion symptoms associated with traumatic event(s); (c) persistence avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred; (d) negative alterations in cognitions and mood associated with the traumatic event(s) beginning or worsening after the traumatic event(s) occurred; (e) marked alternation in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred; (f) duration of the disturbance (criteria b, c, d, and e) is more than a month; (g) disturbance causes significant distress or impairment in social, occupational, or other important areas of functioning; and (h) disturbance is not attributable to the physiological effects of a substance or another medical condition (American Psychological Association, 2013).

LaFrance et al. (2020) conducted a study to understand the short- and long-term effects of cannabis on symptoms of PTSD. The study was conducted over a 31-month period from March 2017 to October 2019. Data were acquired from a medical cannabis technology platform that contains a journaling app and allows users to monitor changes in symptom severity and cannabis use. Participants “self-identified” as having PTSD. The participants using the app can identify

which mental health condition they are using cannabis to treat and provide their symptom severity on a scale from 0 (no symptoms) to 10 (extreme experience of symptoms). The app measures PTSD in terms of four components: intrusive thoughts, irritability, flashbacks, and anxiety. The users also track their route of administration (e.g., smoke, vape, dab bubbler, dab portable, oil, edible, pill, spray, transdermal, tincture). The users also indicated the strain of cannabis and the producer/distributor, so the researchers then could obtain verified cannabinoid content for each strain of cannabis. Only lab verified marijuana and inhaled method of administration were included in the results for the LaFrance et al. study. Following use, the app allows recording the dosage of marijuana (number of puffs) consumed, route of administration, and measurement of PTSD symptoms. The participants are then provided a notification after a period of 20 minutes to re-rate the severity of symptoms. This rating was recorded within 4 hours of marijuana use for all participants (LaFrance et al., 2020).

LaFrance et al. (2020) chose 404 medical cannabis users (220 women, 176 men, and 8 other) who identified as having PTSD on the app. Symptom severity was measured prior to marijuana use and 20 minutes after use (latent change score); this approach assisted in examining changes in PTSD symptoms within subjects across time and allowed the researchers to compare gender, dose, and cannabinoid content. The study found that irritability, anxiety, intrusive thoughts, and flashbacks were significantly reduced after marijuana use. A high number of puffs of cannabis was the strongest predictor of symptom relief for anxiety and intrusive thoughts. Women reported higher rates of flashback severity reduction and anxiety reduction compared to men. Men reported significantly higher rates of irritability reduction compared to women. The results found no gender differences in intrusive thoughts. Overall, individuals with PTSD reported a 62% reduction in intrusive thoughts, a 51% reduction in flashbacks, a 67% reduction

in irritability, and a 57% reduction in anxiety when measured before and after inhaling cannabis. Individuals with a higher severity of symptoms showed a larger reduction in symptom severity. There was no significant difference in symptom changes when comparing THC to CBD. Thus, cannabis use appeared to assist in temporary relief from PTSD symptoms. The results also indicated that higher doses were used to manage anxiety, but individuals' baseline PTSD symptom ratings did not change over time (LaFrance et al., 2020). Thus, marijuana did not appear to have an impact on the presence of PTSD symptoms and only served as acute relief from PTSD symptoms. LaFrance et al. acknowledge that the implications of the results are that marijuana may reduce PTSD symptoms in short-term and may not have long-term effectiveness in sustained PTSD symptom reduction. There are a number of limitations of this study. The research did not utilize confirmed PTSD diagnosis and relied on "self-identified" PTSD. The research also did not use a validated measure of PTSD. Thus, all participants may not meet the actual criteria for PTSD. LaFrance et al. did not utilize a randomized placebo control group, which reduces the ability to make accurate predictions of the effectiveness of marijuana on PTSD symptoms. The study was also conducted from voluntary participants on a journaling app, which calls into question the reliability of the data. The strength of the study is based on utilizing a quantitative longitudinal cohort study with a considerably large sample size of over 400 cannabis users, which allowed the researchers to analyze PTSD symptoms over a 31-month period with multiple ratings for each participant. The 404 medical cannabis participants produced 11,797 ratings within that 31-month period. Also, lab-verified cannabis was utilized, which increased the control the researchers had to compare potency and concentration of THC and CBD.

Treatment for PTSD with THC

There has been a limited amount of research focusing on THC treatment for PTSD. In order to compare studies explaining the effectiveness of THC treatment, this review focused on the type of THC, the dosage, participants' individual differences, route of administration, what measures were utilized to track changes in symptoms, comorbid mental health disorders, and identifying any other treatment being implemented during the time of THC treatment.

Roitman et al. (2014) conducted research to determine the use of orally absorbable THC for chronic PTSD. The study was a 3-week preliminary evaluation of the safety, tolerance, and efficacy of THC (Roitman et al., 2014). The study was considered "open label," which means that the participants and the researchers were aware of the drug (THC) being administered in the study. The participants consisted of 10 adult individuals (7 male and 3 female) from a mental health outpatient clinic in Jerusalem, Israel. Each participant had been diagnosed with PTSD for at least 1 year it had been and at least 3 years or longer since they experienced their traumatic event. Each participant was currently on psychotropic medication and continued the medication throughout the trial. Each participant was taking an average of more than four different psychotropic medications, including Duloxetine, Escitalopram, Mirtazapine, Bupropion, Clonazepam, and Lorazepam. The researchers used the Clinicians-Administered PTSD Scale (CAPS; Blake et al., 1995) to validate the PTSD diagnosis. CAPS is considered a structured clinical interview that surveys the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*) criteria based on frequency and intensity on a 0-4 Likert scale. The CAPS assisted the researchers in determining the presence or absence of PTSD, in which higher ratings indicated increased levels of PTSD symptomology and severity. The researchers also utilized the *DSM-IV* to confirm PTSD diagnosis. The Clinical Global Impression Scale (CGI; Guy, 1976)

was utilized to measure the severity of illness and global improvement. The Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) was utilized to quantify sleep disturbances and sleep quality. The researchers also utilized the Nightmare Frequency Questionnaire (NFQ; Krakow et al., 2002), which identified the frequency of the participants' dreams. The Nightmare Effects Survey (NES; Krakow et al., 2000) was implemented to examine work, relationships, sleep, daytime energy, mood, school, sex life, mental health, diet, leisure activities, and physical health and to determine the level of impairment accounted for by the participants' nightmares (Roitman et al., 2014).

Roitman et al. (2014) excluded individuals who displayed dissociative symptoms or endorsed alcohol or drug abuse, individuals experiencing psychosis, and women who were pregnant or nursing. Individuals were also excluded if they had used cannabis within the last 6 months; however, they allowed one patient who "reported such a condition" to participate in the study. Neither the particular condition endorsed nor the reason why the participant was not excluded was explained. Each participant underwent physiological measures such as heart rate and blood pressure ratings and were assessed for body mass index at the beginning and throughout the study (Roitman et al., 2014).

Roitman et al. (2014) administered 2.5 mg of THC beneath the tongue twice per day and after two days they raised the dosage to 5mg of THC twice per day until the end of the 3-week trial if the participants did not endorse adverse side effects. Roitman et al. found a statistically significant decrease in PTSD hyperarousal symptoms, CGI, sleep quality, frequency of nightmares, and total NES scores. Two participants reported they did not experience any nightmares in the 3-week trial. As for side effects, two participants reported dry mouth, one participant endorsed headaches, and one participant reported dizziness (Roitman et al., 2014).

Roitman et al. (2014) concluded that oral THC did not cause harsh side effects and viewed oral THC as relatively safe. The researchers noted that ingesting oral THC was associated with improved sleep quality and reduced nightmares by reducing rapid eye movement sleep and increasing non-REM phase 4 sleep, which appear to be consistent with Fraser's (2000) research. Roitman et al. indicate that their pilot study had a relatively small sample size, which decreases the ability to generalize their findings. The researchers used a cross-sectional quantitative design, which decreases the ability to analyze behavior over an extended period of time and determine causality. The researchers acknowledged that the use of an open label design that lacks randomized placebo-controlled trials makes determination of changes in PTSD symptoms difficult to assign to oral THC use versus variability during the course of PTSD. Therefore, oral THC cannot be determined to be the cause of the reduction in PTSD symptoms and results are correlational at best. The researchers appeared to conduct a thorough assessment of PTSD symptoms through five objective measures and utilizing the *DSM-IV* criteria, which increases the likelihood of an accurate PTSD diagnosis.

Several researchers investigated the impact the endocannabinoid system has on emotional learning. Greer et al. (2014) completed a statistical analysis of psychometric data for 80 psychiatric evaluations of individuals applying to New Mexico medical cannabis programs. The Clinician-Administered Posttraumatic Scale for *DSM-IV* (CAPS; Blake et al., 1995) was utilized to measure PTSD symptoms based on a retrospective chart review of symptoms. The CAPS measures reexperiencing, avoidance, and arousal. Greer et al. used telephone screening to determine who would move forward with an evaluation, and to exclude individuals who did not meet the *DSM-IV* criteria for PTSD. Greer et al. also examined and included only individuals who endorsed symptom reduction in PTSD symptoms while using cannabis, and presence of

PTSD symptoms when not using cannabis. Greer asked patients to utilize the CAPS questions during a time they were not using cannabis and also answer the same questions on the CAPS during a time when they were using cannabis. Analysis determined that there was a significant reduction in symptoms related to reexperiencing, avoidance, and hyperarousal for individuals using cannabis compared to no cannabis use. Of cannabis users, 75% showed an overall reduction in CAPS scores (Greer et al., 2014). However, there were several limitations in this study. The researchers reported that they did not collect any information on the length of time with or without cannabis use, which significantly reduces the validity for determining how effective cannabis use is on reducing PTSD symptoms. Also, using a retrospective design and having patients evaluate their symptoms with and without marijuana use raised questions regarding how accurate individuals are at remembering the severity of their symptoms potentially months or years after. The researchers also screened for individuals who endorsed experiencing reduction in PTSD with the use of cannabis, which can increase the likelihood of participants showing significant results in PTSD symptom reduction and therefore be less representative of individuals with PTSD in general. Greer et al. utilized a within subject correlational design that appeared to find statistically significant results although the generalizability appeared low due to only evaluating patients who reported benefiting from cannabis.

Treatment for PTSD with Nabilone

Cameron et al. (2014) conducted a retrospective study on the effects of nabilone (a synthetic cannabinoid) on treating insomnia and nightmares related to PTSD symptoms. Cameron et al. surveyed 104 males, with an average age of 32.7 years, who were inmates at a dual correction center and mental health center for persistent and serious mental illness. On

arrival, all inmates were screened for PTSD, sleep time, nightmares, and substance use. Pretreatment and posttreatment sleep hours per night and nights with nightmares per week were measured by the self-report Posttraumatic Checklist-Civilian version (PCL-C; Weathers et al., 1994), and the Global Assessment of Functioning and PTSD criteria from the *DSM-IV-TR* (GAF*; Aas, 2011; DSM-IV-TR*, American Psychological Association, 2000). Every inmate participated in weekly psychiatric sessions that monitored symptomology (Cameron et al., 2014).

Cameron et al. (2014) reported that prior to incarceration, chronic pain, cannabis dependence, and trauma were prevalent among inmates. The study involved a retrospective chart review of inmates who had been prescribed nabilone over a 3 year and 7-month period. The average initial dosage was 1.4 mg daily, and the average final dose was 4.0 mg daily, with the average length of 11.2 weeks on nabilone. One hundred one inmates reported an increase in average hours slept, and 90 inmates reported a reduction in nightmares experienced per week. Sleep quality, sleep time, and reduction in nightmares were reported within the first 2 weeks of treatment. Fifty-eight inmates who had "moderate" PTSD symptoms improved to "borderline mild" PTSD symptoms based on their GAF score. One hundred three inmates reported significant improvements in functioning on the GAF scale. With the initiation of starting nabilone, 90 medications were discontinued (antidepressants, benzodiazepines, cyclopyrrolones, antiadrenergic, methadone codeine, anticonvulsants, and prednisone) by various inmates due to either an indication from the inmates that nabilone was an adequate substitute or when the medications were found to be of limited efficacy. Antipsychotics, sedative hypnotics, and opioids were stopped because of the risk of serious adverse effects or abuse. Ten inmates who had preexisting psychotic disorders showed a reduction in PTSD symptoms with the use of nabilone while remaining on their antipsychotic medications. Adverse effects were noted in a

portion of the inmates as a result of nabilone treatment. Thirty-one inmates reported adverse effects including dry mouth, feeling “stoned”, hypotension, agitation, and headache. Two patients reportedly experienced psychosis; each had a preexisting psychotic illness. Twenty inmates discontinued the nabilone trial, 10 of which were due to adverse effects, four due to abuse of other medications, and two inmates were going to a treatment center that did not allow for nabilone use. Inmates who had no cannabis experience appeared to experience a higher rate of adverse effects, suggesting these individuals may require a lower initial dose to counterbalance adverse effects (Cameron et al., 2014).

Overall, Cameron et al.’s (2014) research has shown reduction in PTSD related nightmares and insomnia has shown that nabilone may help reduce the number of medications needed to manage PTSD symptoms. Reducing the number of medications with the use of nabilone may reduce the risks associated with taking multiple medications, but more research would be needed to prove this phenomenon. The question of whether cannabis dependent individuals may benefit is mentioned by Cameron et al., although there is no data from the study that suggests that cannabis dependent individuals may benefit and in what way. The study has several limitations. A retrospective chart review has several disadvantages such as relying on the accuracy of previous records, which provides lack of control in the scoring and interpretation of the assessments administered to the participants. The research is a within-subject design that can allow observation of changes within the participants over time, in which Cameron et al. were able to find significant results for the benefits of nabilone. In order to confirm their finding, a randomized placebo-controlled studies would be necessary. Cameron et al.’s utilization of inmates allows for certain control for environmental factors although how applicable their

findings would translate to an uncontrolled environment and other non-forensic populations is not able to be determined.

Additional research has found similar results regarding the positive effects nabilone had on sleep issues related to PTSD. Jetly et al. (2015) conducted a study that involved the efficacy of nabilone capsules on 10 Canadian male military personnel diagnosed with PTSD. The design of the study was double blind placebo controlled, in which the men either received .5 mg of nabilone orally or a placebo. The participants were administered the Clinical Global Impression (CGI; Guy, 1976) and the Clinicians-Administered PTSD Scale (CAPS; Blake et al., 1995). Each participant received nabilone or placebo for 7 weeks, and the doses were adjusted for nightmare suppression to a level that they determined was an effective dose. The maximum dosage administered to the men was 3.0 mg. The study found a significant reduction in nightmares when comparing pre and post CAPS scores for both the nabilone and placebo groups, and a reduction in frequency and intensity of nightmares for both the nabilone and placebo groups. The nabilone group was found to have a larger decrease in nightmares, frequency, and intensity than the placebo group. The improvement in CGI scores was similar to CAPS results in that improvement was seen in both nabilone and placebo groups and the nabilone showed a larger improvement in CGI scores. The nabilone group reportedly had five out of 10 participants in the “much improved” range on their CGI scores (5 out of 10) compared to the placebo group, which had one out of nine in the “much improved” range. (Jetly et al., 2015). Jetly et al. indicated that the sample size of their study was small, and stated further exploration is needed to understand the effect of nabilone. Jetly et al.’s study does utilize a double-blind placebo-controlled design, but the study will need to be recreated on larger sample sizes to get closer to data that can link cause and effect. The results also show reduction in nightmares measured by CAPS scores for both the

placebo and nabilone group but does not provide a clear indicator that nabilone is the only factor that is allowing for improvement in nightmare reduction. The nabilone group did show a larger improvement in their CAPS, which may indicate that there are confounding variables that are a factor in nightmare reduction.

The commonality among nabilone research studies appears to be the reduction of nightmare frequency and intensity with individuals diagnosed with PTSD. Fraser (2009) conducted a review on an open label clinical trial to evaluate the effect of nabilone on treatment resistant nightmares for individuals diagnosed with PTSD. The 47 individuals who had PTSD-related nightmares were recruited from a psychiatric specialist outpatient clinic between 2004 and 2006. The participants were required to experience at least one nightmare per week to be eligible for the study. PTSD diagnosis was confirmed by the Posttraumatic Stress Diagnostic Scale (Foa, Cashman, Jaycox, & Perry, 1997), and each participant had at least a 2-year history of PTSD related nightmares. Each participant was classified as "treatment-resistant" to antidepressants and hypnotic medications. However, current use of medication regiments was continued during the study. Individuals with psychosis and sensitivity to cannabinoids were excluded from the study. Dosage of nabilone started at 0.5 mg 1 hour before sleeping. Patients were seen within 7 days of starting nabilone treatment to monitor side effects and to increase dose if the nabilone was tolerated and nightmare symptoms were not decreasing. The participants were seen weekly for monitoring and adjustments, and the participant's dosage after adjustment ranged from 0.2 mg to 4.0 mg. Of the participants, 72% reported a significant decrease in the severity of nightmare symptoms or a complete remission of nightmares. Four participants experienced sustained reduction or reduced intensity in nightmares 4 to 12 months after the discontinuation of nabilone use compared to the 43 participants who had a resurgence of

nightmares. Thirteen participants experienced side effects such as headache, lightheadedness, forgetfulness, and dizziness that lead to discontinuation of nabilone (Fraser, 2009).

Fraser (2009) identified that a major limitation of the study was there was no control group to measure effectiveness. Similarly, to Cameron et al. (2014), the study lacked a double-blind placebo control design and instead incorporated a within-subject open labeled design that cannot enhance the current knowledge to determine nabilone's effectiveness for reducing and eliminating nightmares. Fraser also indicated that the subjective reports of nightmare change and the small number of patients was a disadvantage to the study due to a lack of objective measures to track changes and reduced ability to generalize to larger groups. The last major limitation Fraser discussed was selection bias because all of the patients who were referred had a diagnosis of PTSD and experienced treatment resistant nightmares. On the one hand, this participant selection method may potentially increase the understanding of nabilone's effect on treatment resistant nightmares. However, selecting a subgroup of individuals with PTSD may ignore the effect nabilone may have on individuals with PTSD that do not experience treatment resistant nightmares. Fraser's results are consistent with Jetly et al. (2015) and Cameron et al. (2014) in demonstrating PTSD related nightmare reduction with nabilone treatment. However, further studies are necessary to determine the effectiveness of nabilone for other groups with symptoms of PTSD or other individuals who experience nightmares.

Nabilone has been shown to have low indicators of abuse potential. Ware and St. Arnaud-Trempe (2010) conducted a literature review of scientific literature, popular press, and internet databases to investigate the abuse potential for nabilone from 2002 to 2006. Ware and St. Arnaud-Trempe reported there has been little evidence for recreational use and abuse of nabilone (Clark et al., 2005; Gourlay, 2005). Two studies that tested subjective effects in humans showed

that a single dose of 1 to 5 mg of nabilone does not significantly alter mood state (Glass et al., 1980) or serve as a reinforcer (Mendelson & Mello, 1984; Ware & St. Arnaud-Trempe, 2010).

Treatment for PTSD with CBD

CBD treatment has not been extensively researched for various mental health concerns, including PTSD. However, in a related study, Das et al. (2013) attempted to evaluate CBD's effect on fear extinction in humans, using a "Pavlovian fear-conditioning paradigm." Das et al. examined whether CBD could aid in the treatment of fear memories. Das et al. utilized a double-blind, placebo-controlled between-subjects design. Participants were recruited by community advertisements and word of mouth. The inclusion criteria required an age of 18-35 years old, fluency in English, no history of serious mental or physical health problems, no substance abuse, normal color vision, no learning impairment or neurological impairment history, and the participant could not be pregnant. Forty-eight participants were randomly assigned to three groups: 32 mg of inhaled CBD prior to extinction (pre-extinction group), 32 mg of inhaled CBD following extinction (post-extinction group), and inhaled placebo ethanol, which were all vaporized at 210 degrees C. (Das et al., 2013).

The pre-extinction group received 32 mg of inhaled CBD and each member of the other two groups received a placebo 5 minutes prior to the fear extinction task (Das et al., 2013). The post-extinction group received 32 mg of inhaled CBD and the other two groups inhaled a placebo after the fear extinction task. The fear conditioning included a computer monitor called "Room A," which incorporated an image of a white wall. The unconditioned stimulus (UCS) was an electric shock (250-ms; 4-mA electric shock). The conditioned stimuli (CS) were red and yellow boxes that would appear in the background. One box (CS+) was paired with the shock, and the other box (CS-) was never paired with the shock. Thirty-two conditioning trials either

elicited a shock (CS+) or no shock (CS-), and skin conductance response was measured through silver chloride electrodes attached to the middle finger of the participants. Explicit learning was measured by shock expectancy ratings from 0 to 5; the higher the number, the more certain there would be a shock (Das et al., 2013).

In "Room B" the fear extinction consisted of the same process as Room A but with no shocks. The fear recall task was administered 34 hours later and had 2 phases (recall and reinstatement). Recall consisted of presenting the CSs from the conditioning and extinction trials. The recall contexts were presented in an alternating fashion, with each CS appearing in each context before context change. The reinstatement phase was almost exactly like the recall phase but was preceded by a single UCS presentation in each context to reactivate contextual fear memory. The results showed a significant conditioning effect of the CS in the second and first block based on the measurements from the skin conductive response. Decrease in skin conductive responses happened during the course the trials was believed to be due to habituation of the UCS. Extinction was reportedly evidenced by a significant decrease in skin conductive responses between the last block of conditioning and all extinction blocks, and between the first and later blocks of extinction trials. Das et al. found that CBD administered after extinction learning led to a reduced impact of explicit fearful responding during recall and reinstatement. Das et al. concluded that CBD could increase consolidation of extinction learning (Das et al., 2013). Specifically, Das et al. proposed that their findings suggest sub-anxiolytic dose of CBD given post-extinction increased the consolidation of extinction learned by reducing the UCS expectancy, which may have implications of reducing fear for individuals who have a fear response to an item, situation, or person.

However, the applicability to PTSD and reducing the association of a trauma response towards a conditioned stimulus created through trauma is not directly evidenced in this study. The double-blind, placebo-controlled between-subjects design study provided control to examine the effects of CBD administered before and after electric shocks to determine whether fear expectancy has changed in individuals without PTSD. However, the same claims cannot be generalized to individuals with PTSD due to the nature of the disorder and the design of the study. It is not clear who will develop PTSD following a traumatic event or repeated exposure to trauma. The expectancy of a low-level electric shock can cause an association of fear through conditioning. However, it is not entirely comparable to the association between the strength of association between trauma and fears associated responses for individuals with PTSD. The study may provide insight on how CBD use effects conditioning, extinction, and recall in a controlled environment but does not provide evidence to support the conclusion that same effect may take place in extinction of PTSD related memories and associations.

Additional research has also supported the idea that CBD may be effective in treating PTSD by reducing nightmares and other associated symptoms. Elms et al. (2019) conducted a retrospective case study to determine CBD effectiveness as a treatment for PTSD with participants from a mental health clinic. CBD (in capsule and liquid spray form) was administered to 11 adult patients diagnosed with PTSD. Eight patients were female and three were males. Eight patients were receiving psychotherapy, and each patient was taking at least one medication, which included antidepressants, mood stabilizers, anxiolytics, and stimulants. Comorbid mental disorders and cannabis use were not exclusion criteria. The patients also received various treatments such as medications and psychotherapy. Four patients received oral CBD, one patient received oral liquid spray CBD, and six patients received both liquid spray

CBD and oral CBD. The oral CBD capsules contained 22-28 mg of CBD. The liquid spray CBD contained 1.5 mg per spray, with the average dose per day being 9 mg. Each participant took CBD twice per day. Each patient's symptoms were measured once at 4 weeks and after 8 weeks by patient completed PTSD Checklist for the DSM-5 (PCL-5; Weathers et al., 2013). The average starting dose for either the liquid spray or the capsule was 33.18 mg. At the conclusion of the study, the average dose was 48.64 mg. Increase in CBD dosage appeared to have the most impact on the reduction of PTSD symptoms. At week 4, 10 of the 11 patients reported a decrease in the symptoms of PTSD according to their PCL-5, with 1 patient experiencing an increase in PTSD symptoms. After 8 weeks, eight patients reported a decrease in PTSD symptoms from their results at 4 weeks. Three patients reported an increase in PTSD symptoms at eight weeks compared to their results at four weeks. CBD use was shown to decrease both frequency and intensity appeared to have the largest decrease in PTSD symptoms (Elms et al., 2019).

Elms et al.'s (2019) conducted a retrospective case study, which has similar concerns to Cameron et al. (2014) and Fraser (2009) studies in that it did not incorporate a double-blind placebo control design and instead utilized a within-subject open labeled design that can only provide correlational data that cannot determine causation. Therefore, the study does not provide data that CBD is the reason for the reduction in PTSD related symptoms. CBD was also administered in oral and liquid spray, and the impact of different routes of administration was unknown. The study does suggest decreased PTSD symptoms when considering the decrease in PCL-5 scores, but future controlled studies are needed to confirm whether CBD truly reduces PTSD symptoms.

Inconclusive or Unsupportive Research for use of Medical Marijuana for PTSD Treatment

Johnson et al. (2016) conducted a matched case-control cross-sectional study with veterans to understand the association between cannabis use and PTSD symptoms from January 2011 to December 2014. The veterans in the study were classified as veterans with probable PTSD. Seven hundred patients were classified in two groups, "cannabis users" ($N = 350$) or "non-users" ($N = 350$), and the non-users were used as a control group. The PTSD Checklist-Civilian version (PCL-C; Weathers et al., 1994) was utilized to measure the impact of cannabis on PTSD symptoms. The participants were also administered two questions related to alcohol from the Substance Involvement Screening Test (ASSIST; Ali et al., 2002), and the Patient Health Questionnaire (PHQ-9; Kroenke & Spitzer, 2001) was used to assess for depression, and Paykel Questionnaire (PQ; Paykel et al., 1974) was used to assess for suicidal ideation. Johnson et al. did not find significant difference in PCL-C scores between cannabis users and non-users. Frequency of cannabis use in the cannabis use group did not appear to have an impact on PCL-C scores. Cannabis users appeared to have greater levels of alcohol consumption and suicidal ideation compared to non-users (Johnson et al., 2016).

Johnson et al. (2016) proposed that their results suggest cannabis use is not associated with PTSD symptom reduction. A major concern with that conclusion is that they are assuming that PTSD severity did not differ between users and non-users. However, the veterans did not appear to have a definite diagnosis of PTSD and were considered to have "probable PTSD". Therefore, conclusions on whether cannabis has an impact on PTSD can only be generalized to PCL-5 score consistency within a case-match design. Johnson et al. stated that a limitation to their study was the sample is a convenience sample of veterans being referred for clinical assessments and thus sampling bias may limit generalizability to veterans who are not seeking

treatment. Another limitation was the data available for the cannabis that is being used. The cannabis was not designated as medical or recreational, dosage was not included, nor was the route of administration. The study also did not control for prior or current treatment with therapeutic interventions or psychotropic medication. Finally, the conclusions from this study are correlational, which makes it difficult to determine how applicable their results are to cannabis use and the impact it has on PTSD symptoms, particularly due to the design that compares users and non-users without within-subject repeated measures over time.

Brown University (2017) conducted a systematic review of cannabis treatment for PTSD and chronic pain, which was inconclusive due to the lack of well-designed studies on cannabis' effects and insufficient evidence presented within the available studies. The review included a "comprehensive search" of data published to March 2017 that included use of cannabis treatment for PTSD, which included plant-based cannabis preparations or whole-plant extracts but synthetic cannabinoids were not included. The review yielded two systematic reviews. One of the systematic reviews focused on six studies. Of those six studies, two were prospective, open label trails with no control group and one was a case study. The other systematic review included four observational studies. Three of the studies reported that cannabis was associated with reduction in PTSD symptoms and the remaining fourth observational study stated that cannabis was associated with increase in PTSD symptoms (Brown University, 2017). There are several limitations to the conclusions of this review. The review focused on general cannabis use and not medical cannabis and also excluded synthetic cannabinoids, which have shown promise in PTSD symptom reduction. The focus on cannabis in general as opposed to focusing on medical marijuana may explain the inconclusive results. The review also stated that there are a lack of

well-designed studies and that the evidence is too limited to determine if cannabis can be a treatment for PTSD or potentially cause more harm.

Metrik et al. (2018) conducted a study to compare medical cannabis users with recreational cannabis users. Researchers utilized data from an ongoing prospective study on cannabis use and affective disorders in returning veterans deployed post 9/11. The study identified 143 participants who endorsed cannabis use in the past year, and 93% of the participants were male. The participants were administered the Medical Marijuana Patient Questionnaire (MMPQ; Cohen, Heinz, Ilgen, & Bonn-Miller, 2016) and were classified as "medicinal cannabis" users if they reported ever using cannabis for medical purposes on the MMPQ. Sixty-six participants were identified as medical cannabis users if they endorsed ever using cannabis for medical purposes and 25% of these participants reported having a state-issued medical marijuana card. The medicinal cannabis users were then administered the Reasons for Medical Marijuana Questionnaire (RFUMM; Reinarman, Nunberg, Lanthier, & Heddleston, 2011) to determine how often they used medical marijuana and the reason why. Seventy-seven participants were identified as recreational users if they did not endorse using marijuana for medicinal purposes on the MMPQ. The Clinician-Administered PTSD Scale for *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; CAPS; Blake et al., 1995) was administered to both medicinal users and recreational users to assess for PTSD symptoms. Structured Clinical Interview for *DSM* nonpatient edition (SCID-NP; First, Spitzer, Gibbon, & Williams, 2002) was used to determine the past-month and lifetime diagnosis. The Time-Line Follow-Back (TLFB; Dennis et al., 2004; Sobell & Sobell, 1992) is a structured interview that was used to determine the frequency and quantity of cannabis consumed within the past 6 months. The TLFB also assessed the frequency and quantity of alcohol consumption and other drug use. Marijuana

Problems Scale (MPS; Stephens, Roffman, & Curtin, 2000) was administered to assess cannabis related problems in the past 90 days. The Comprehensive Marijuana Motives Questionnaire (CMMQ; Lee, Neighbors, Hendershot, & Grossbard, 2009) was administered to evaluate how often the participants used cannabis and the reason for cannabis use. The Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) was also utilized to assess for sleep quality and sleep disturbances over a 1-month period. The RAND (SF-36; Hays & Morales, 2001) was utilized as a health-related quality of life measure of physical and mental health. The Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983) was used to measure the participant's perception of life stress and the Satisfaction with Life Scale (SWLS; Diener, Emmons, Larsen, & Griffin, 1985) was also used to measure the participants' judgments of their life satisfaction (Metrik et al., 2018).

Metrik et al. (2018) found that medicinal cannabis users reported using marijuana for anxiety, stress, PTSD, pain, depression, and insomnia. The RFUMM results indicated that medicinal users' most frequent reason for use was to improve sleep and relaxation, with the second most frequent reason for use to relieve PTSD. Metrik et al. also found that medicinal users were five times more likely than recreational users to have a current diagnosis of PTSD and four times more likely to have a current diagnosis of major depressive disorder. The results for cannabis use motives indicated that medicinal users reported using cannabis more frequently than recreational users for enjoyment, coping, social anxiety, and sleep. Medicinal users also had indicators of worse sleep qualities compared to recreational use on their PSQI scores and also had lower scores on their SF-36 (Metrik et al., 2018).

Metrik et al.'s (2018) strengths of the study are that it was a cross-sectional between group quantitative research design that utilized several objective measures to make comparisons

between recreational cannabis users and medicinal cannabis users. The results indicated that medicinal users were more likely to have a current diagnosis of PTSD and MDD. These mental health concerns may explain the reason medicinal users consume cannabis and the increased frequency and quantity of cannabis used compared to recreational users. The study did not provide information whether cannabis use is benefitting the medicinal or recreational user, which would require more data and measures over time. Metrik et al. also identified the limitation that their findings cannot be generalized to women due to the low number of women involved in the study. Another limitation that was endorsed was the inability of the study to determine a relationship between cannabis use and increase or decrease in symptoms regardless of whether participants were a medicinal user or recreational user. Metrik et al. proposed that planned longitudinal analysis is needed to determine the relationship between the variables in question.

Supportive Research on Medical Cannabis for Anxiety Disorders

There are indicators that suggest medical cannabis use can reduce symptoms in anxiety disorders. The *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; American Psychiatric Association, 2013) has several disorders in the anxiety category. Common symptoms of these disorders include feelings of nervousness and/or excessive fear, restlessness, fatigued, difficulty with concentration, and irritability. Anxiety disorders can also be accompanied by physiological systems such as palpitations, sweating, chest pain, feeling dizzy, numbness, and heat sensations. The endocannabinoid system has been shown to have an interaction with anxiety. Alger (2014) wrote about how the endocannabinoid system plays a role in cell signaling and is involved in regulating mood, appetite, learning, memory, reproduction, and fertility. The central nervous system (CNS) contains the bulk of cannabinoid receptors (CB1), and CB2 receptors are predominately found outside of the CNS and play a role in the immune system.

CB1 is located in the neocortex, hippocampus, basal ganglia, amygdala, striatum, cerebellum, and hypothalamus. Activation of the CB1 receptors has been shown to assist in fear extinction (Alger, 2014). Rey et al. (2012) conducted a study to investigate the effect of cannabinoids on anxiety responses for CB1 receptors, GABA receptors, and glutamate neurons on genetically modified mice and wild mice. Rey et al. measured anxiety symptoms in mice when given two different types of cannabinoids: cannabinoids that targeted GABA-sensitive neurons and cannabinoids targeting glutamate. The genetically altered mice were divided in two categories: mice with no cannabinoid receptors on glutamate-sensitive neurons and mice with no cannabinoid receptors on GABA-sensitive neurons. The cannabinoids targeting glutamate-sensitive neurons both increased and decreased the anxiety of the wild mice, depending on the dose. The genetically altered mice without cannabinoid receptors on GABA-sensitive neurons experienced less anxiety regardless of the dosage. This experiment provided preliminary support for the idea that dosage and cannabinoids could be altered to enhance anxiety treatment (Rey et al., 2012). Rey et al. stated that the biphasic effects (low and high doses can produce opposite effects) of cannabinoids in anxiety behavior is explained through anxiogenic-like behavior through activation of CB1 receptors on GABAergic neurons from a high dose of cannabinoids. The high dose of cannabinoids appears to partially reduce GABAergic signaling on $GABA_B$ receptors. Rey et al.'s finding appeared to be the first neurobiological explanation of a differential regulation of anxiety processing by cannabinoids and the interaction of the endocannabinoid system with GABAergic and glutamatergic systems. Understanding how the endocannabinoid system interacts with anxiety disorders shows validity for cannabinoid-based treatments. Human trials are needed to determine if the results are applicable to humans.

Crippa et al. (2011) conducted a study on the anxiolytic effects of CBD in social anxiety disorder (SAD). Crippa et al. used a double-blind study with 10 male participants with a prior diagnosis of SAD who were recruited from an epidemiological sample of 2320 university students. The SAD diagnosis was confirmed by the Structured Clinical Interview for *DSM-IV* (SCID). The severity of SAD was assessed with the Portuguese version (Osório et al., 2006, 2010) of the Brief Social Phobia Scale (BSPS; Davidson, et al., 1991). Social phobia was further assessed using the Portuguese version (Osório et al., 2009) of the Social Phobia Inventory (SPIN; Connor et al., 2000). Participants were considered "treatment naïve" with no comorbid mental health disorders. All 10 participants were classified to have severe social phobia. Participants were administered 400 mg of CBD dissolved in corn oil and packaged in a gelatin capsule or a placebo gelatin capsule with just corn oil. The Visual Analogue Mood Scale (VAMS; Norris, 1971), translated into Portuguese (Zuardi & Karniol, 1981) was utilized to evaluate subjective states such as calm and agitated. The participants were told to mark a point that identified their present state on a 10cm line placed between two words that describe opposite moods. Crippa et al. used the SPECT technique of neural imaging to compare the effects of CBD and placebo on resting regional cerebral blood flow (rCBF) in the SAD participants, and the participants were measured twice, one week apart. The participants reported subjective ratings on the VAMS at five different time-points, which were 30 minutes prior to ingestion of CBD or placebo, at the time of drug administration, at 60 minutes, at 75 minutes, and after SPECT scanning 140 min after drug intake. The anxiety-evoking procedure consisted of the whole SPECT procedure itself, which involves the insertion of an intravenous cannula and the exposure to a totally uncommon situation (i.e., medical environment, large examination apparatus). The terms 'pre-stress', 'adaptation' and 'post-stress', refer to the moments of the scanning session in which the VAMS

was completed. The researchers took images of each subject's brain to monitor the activity of the brain during a stressful event. When comparing the CBD group to the placebo group, the CBD group had significant decreases in subjective reports of anxiety on the VAMS (VAMS; Crippa et al., 2011).

Strengths of the Crippa et al. (2011) study included the use of a double-blind, randomized, repeated measures, within-subject cross-over design and the study concluded that CBD can reduce subjective anxiety in patients diagnosed with social anxiety disorder. However, Crippa et al. conveyed that additional longitudinal research with a larger sample size and gender diversity is necessary to confirm their findings. In addition, the fear inducing condition of the study was the SPECT scanning, which appeared to elicit anxiety in the participants, although the generalizability to SAD is unclear. SAD is characterized by anxiety experienced in social situations. A naturalistic observational study that incorporated administering CBD prior to a social event that would evoke SAD related anxiety may be needed to have a clearer understanding of whether CBD will reduce SAD.

Linares et al. (2019) researched whether increasing doses of CBD would produce bell-shaped dose-responsive curves in humans. Linares et al. reported that the study was a double-blind placebo-controlled experiment. There was a total of fifty-seven healthy male volunteers who participated. The setting of participant recruitment was not specified. The participants were randomly assigned to four different groups, in which three groups were given CBD and one was a placebo group. The four groups were given either a varying dose of CBD: 150 mg (n = 15), 300 mg (n = 15), 600 mg (n = 12), or a placebo (n = 15). The participants were administered the Visual Analogue Mood Scale (VAMS; Norris, 1971), and physiological measures (e.g., systolic and diastolic blood pressure, heart rate) were used to measure anxiety. Groups were matched by

age. The average age of the placebo group was 24.5 years old, the CBD 150 mg group was 24.2 years old, CBD 300 mg group was 24.6 years old, and the CBD 600 mg group was 22.6 years old. Groups were also matched by their years of education and socioeconomic status. Each participant was assessed for psychiatric disorders with the Portuguese version of the Structured Clinical Interview for the *DSM-IV*, clinical version (SCID-CV; First et al., 1997). Each participant did not have a substance abuse history and did not use marijuana more than five times in their lifetime. Baseline measurements were taken after a 15-minute adaptation period and then was administered either a varying dose of CBD or placebo. CBD or placebo was administered 1 hour and 30 minutes prior to a simulated public speaking test (SPST; Lipper & McNair, 1972) and another "pre-test" measurement of VAMS, heart rate, and blood pressure were taken prior to the SPST. For the SPSR, participants were instructed that they had 2 minutes to prepare a 4-minute speech about public transportation system in their city. The speech was interrupted in the middle and VAMS, heart rate, and blood pressure measurements were taken again. After the speech, the same measurements were taken immediately after the SPST and again after 30 minutes of the SPST. The results showed that pretreatment with 300 mg of CBD significantly reduced anxiety during the speech compared to the placebo group according to VAMS scores. No significant differences in VAMS scores were indicated between groups receiving CBD 150 mg, 600 mg, and placebo, which is indicative of a U-shaped dose-response curve. The U-shape indicated that 300 mg was shown to reduce anxiety compared to the lower or higher amounts of CBD, which did not appear to have an impact on anxiety compared to placebo. Linares et al. indicated that a limitation to the study only showed significant results in the subjective reporting of anxiety reduction (VAMS) and did not yield significant results for physiological effects. (Linares et al., 2019). The study focused on healthy individuals, which makes generalizing CBD

reduction to individuals with anxiety disorders difficult based on this study alone. The design of the study was a double-blind placebo-controlled experiment, and each participant was matched based on demographics, which randomizing the groups can reduce selection bias. However, the sample size was small and the number of individuals within the conditions was also small, which may limit power for finding robust results, and also limit generalizability. All participants were men and generally around the age of 24, which also limits the generalizability to women and to individuals of various ages.

Bergamaschi et al. (2011) conducted a double-blind, randomized design study to investigate CBD's therapeutic effect on individuals with social anxiety disorder (SAD). Bergamaschi et al. were interested in the effects of a simulation public speaking test (SPST; Lipper & McNair, 1972) on healthy control (HC) participants and treatment-naive SAD participants. They recruited 2,319 undergraduate students, who were screened with the short version of the Social Phobia Inventory (MINI-SPIN; Osório et al., 2010; Connor et al., 2001) to identify participants with "SAD". The participants were narrowed down to 237 male and female participants with probable SAD based on their MINI-SPIN scores. The 237 participants were then given a Structured Clinical Interview for the *DSM-IV*, clinical version (SCID-CV; First et al, 1997), translated into Portuguese (Del-Ben et al., 2001). Twenty-four subjects were identified to meet the criteria for SAD based on the results of their SCID-CV and MINI-SPIN and 12 individuals were selected as healthy control group (HC). The SAD patients were randomly assigned to either the CBD group (600 mg SAD-CBD; $n = 12$) or the placebo group (SAD-PLAC; $n = 12$). The SAD-CBD group and SAD-PLAC group were administered either 600 mg of CBD or a placebo 1.5 hours before the SPST. The 12 healthy controls were not given any medication before the SPST. The Self-Statements during Public Speaking Scale (SPSS;

Hoffmann and Di Bartolo, 2000) translated into Portuguese (de Lima Osório et al., 2008) was administered, which is a self-report instrument that measures self-perception of performance in a specific situation of public speaking, one subscale was used for negative self-evaluation (SSPS-N). All participants were administered the Visual Analogue Mood Scale (VAMS; Norris, 1971) to measure state anxiety levels, the Negative Self-Statement Scale (SSPS-N), and physiological measures (i.e., blood pressure, heart rate, and skin conductance). All participants had a 15-min adaptation period following a baseline measurement, which was followed by a single dose of oral CBD, placebo, or no medication. Pretest measurements were made 80 minutes after the drug ingestion. The participants received the instructions and had 2 min to prepare a 4-min speech about the public transportation system of their city. Anticipatory speech measurements were taken before the subject started. The speech was interrupted in the middle of their speech and additional measurements were taken. Post-test measurements were made 15 and 35 min after the end of the SPSS. The SAD placebo (SAD-PLAC) group presented higher anxiety, cognitive impairment, discomfort, and alert levels when compared with the control group as assessed with the VAMS. Pretreatment with CBD in the SAD-CBD group significantly reduced anxiety, cognitive impairment, discomfort in speech performance, and significantly decreased alertness in their anticipatory speech compared to the SAD-PLAC group. The SSPS-N scores showed significant increases during the testing of the SAD-PLAC group. The SAD-CBD group showed significant decreases in SSPS-N scores. No significant differences were observed between SAD-CBD and healthy control groups in SSPS-N scores or in the cognitive impairment, discomfort, and alert factors of VAMS. Thus reveal, increases in anxiety induced by the SPST on participants with overall SAD were reduced with the use of CBD, resulting in a similar response as the healthy controls (Bergamaschi et al., 2011). The results of the study are similar to Linares

et al. (2019) in that CBD use produced reduction in subjective self-report but not in physiological measures during the SPST. Bergamaschi et al. utilized the randomized double-blind placebo-controlled design, which allowed a higher probability that their study exhibited significant results and that CBD was the factor that reduced anxiety during the SPST. Bergamaschi et al. acknowledged that their sample size is small, which reduces statistical power for the VAMS and SPSS and stated that there is a need for additional randomized double-blind placebo-controlled studies with a larger sample size and more gender diversity to confirm their findings. The use of the SPST appeared to simulate a real-life event that can evoke anxiety, which appeared to be a strength of the study.

Research on Medical Cannabis for Treating Depressive Disorders

Medical cannabis has shown inconsistent results for treating depressive disorders. The *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; American Psychiatric Association, 2013) has several disorders in the depressive category. Common symptoms of these disorders indicate: depressed mood ; feeling of sadness, emptiness, or hopelessness; loss of interest or pleasure in all or almost all activities; significant weight loss when not dieting or weight gain; inability to sleep or oversleeping; psychomotor agitation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate, or indecisiveness, and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt, or a specific plan for committing suicide.

Some research has shown exacerbation of depressive symptoms or little impact on treatment effects with medical cannabis use. Conversely, additional research suggests medical cannabis, as well as recreational use of cannabis, has resulted in improved symptoms of depressive disorders. Zanelati et al. (2010) conducted a study to explore whether CBD has an

antidepressant activity in mice in a forced swimming test. They also researched whether antidepressant activity was contingent on 5-HT1A receptor activation and hippocampal expression of brain-derived neurotropic factors. Male mice were dispensed CBD (extracts of *cannabis sativa* plant) in 3 mg, 10 mg, 30 mg, 100 mg, or the prototype antidepressant imipramine. The mice were forced into a swimming test or an open field arena 30 minutes after the administration of CBD or prototype antidepressant imipramine. Another mouse group received WAY100635 (0.1 mg·kg−1, i.p.), a 5-HT1A receptor antagonist before CBD (30 mg) and assessment prior to the forced swimming test. CBD was shown to increase mobility in forced swimming, which the antidepressant has a similar effect (Zanelati et al., 2010). Activation of 5-HT1A receptors has been consistently related to the therapeutic effect of antidepressant drugs in humans (Savitz et al., 2009), however a connection between these receptors and antidepressant-like effect of CBD was not investigated at that point. CBD appeared to be an agonist to the 5-HT1A receptor, which has shown antidepressant-like effects that are comparable to imipramine (anti-depressant). Additional human trials are necessary to understand if CBD would provide an anti-depressant like effect in humans.

Khadrawy et al. (2017) conducted a study to investigate the effect of cannabis extract on "depressive-like" rats. Twenty-four rats were placed into three groups: control, rat model of depression induced by reserpine, and depressive-like rats treated with cannabis sativa extract (10 mg/kg expressed as Δ9-tetrahydrocannabinol). The rat model of depression was induced by olfactory bulbectomy, which was identified as an alteration in brain rewards function produced in by the cannabinoid CB1 receptor agonist WIN%%-212,2, and a dopaminergic receptor. The rats were measured in an open field test. No significant differences were noted in open field test results between depressive-like rats treated with cannabis and other rat groups. Significant

differences in open field tests were found between the rat model of depression induced by reserpine rats and control rats. The depressive-like rats had a significant decrease in motor activity that was assessed by the open field test compared to control rats and rat model of depression rats. The results suggest that cannabis sativa may increase motor deficits, increasing depressive symptoms and memory impairment (Khadrawy et al., 2017).

Round et al. (2020) conducted an observational cohort study of 37,338 patients receiving medical cannabis between 2014 and 2019. The patients were administered the Patient Health Questionnaire (PHQ-9; Kroenke & Spitzer, 2001), a self-report measure to assess for depression. Adults of any race, SES, or gender seeking medical cannabis from authorized cannabis clinics were included in the study. Any individual who did not complete in the PHQ-9 on the follow-up questionnaire at baseline were excluded, which resulted in a total of 5,103 patients of various ages, SES, and genders. Participants used various routes of administration, which included ingesting, smoking, vaping, or topical use. A subcategory of participants also endorsed antidepressant usage that included selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), and other antidepressants. Other antidepressants included norepinephrine-dopamine reuptake inhibitors, noradrenergic and specific serotonergic antidepressants, and monoamine oxidase inhibitors (MAOI). The PHQ-9 was administered at baseline and follow-up scores for the PHDQ9 were obtained after at least 6 months of medical cannabis use. Of 5103 participants who had baseline and follow-up scores for the PHQ-9, 50% met the criteria for depression at baseline. After 6 months of medical cannabis use, 4855 participants reported no clinically significant changes in their PHQ-9 scores, 172 participants reported clinically significant improvements in depressive symptoms, and 76 participants reported an increase in depressive symptoms (Round et al., 2020).

Based on these results Round et al. (2020) concluded there was no major impact of medical cannabis as a treatment for depressive symptoms. Major limitations in the study were the variations in the types of medical cannabis used and in the dosage consumed by the participants. Therefore, it is difficult to formulate the treatment impact on depressive symptoms without knowing which medical marijuana product is being utilized and at what doses, frequency, and amount. Also, a majority of participants did not have follow up PHQ-9 scores and therefore were not included or assessed. Finally, use of the one short self-report measure at one point in time is likely to miss changed in depression and cannot assess at what points following medical cannabis use changes might occur.

CHAPTER III. RECREATIONAL USE AND MISUSE OF MEDICAL MARIJUANA

Abizaid et al. (2019) conducted a review of available research and studies from 2003 to 2018 on treating PTSD and other mental health disorders with cannabis from. Abizaid et al. conveyed that there are both positive and negative outcomes repeated in the literature for treating mental health with cannabis that has a limited number of clinical trials conducted, the true benefit or adverse effects of cannabis is difficult to assess currently. The available research suggests that the use of cannabis could have potentially harmful effects such as cognitive disturbance and impaired neuronal plasticity and organization in the adolescent brain. Medical marijuana may create functional brain changes, be a risk factor for marijuana abuse, and may increase the symptoms of schizophrenia. Abizaid et al. indicated that the neurobiological mechanisms involved in PTSD are not yet completely understood studies how typically used animal models in an attempt to gain understanding of associated areas in the brain, and these models may not generalize to humans. Additional research needs to be conducted to have a better conceptualization of all the associated brain areas involved (Abizaid et al., 2019).

Impact of Recreational Use or Misuse of Cannabis on PTSD

Wilkinson et al. (2015) investigated the effects of marijuana use and PTSD symptom severity in a longitudinal observational study from 1992 to 2011. There were 2,276 participants who were veterans diagnosed with PTSD based on *DSM-III* criteria (until 1994) and then *DSM-IV* criteria subsequently. The participants were admitted to a specialized intensive VA treatment program for PTSD with assessments conducted at intake and 4 months after discharge. PTSD symptom severity was also measured using the Short Form of the Mississippi Scale (MISS; Fontana, 1994). No participants had been prescribed medical marijuana in the past, and their drug and alcohol use was assessed with the Addiction Severity Index (ASI; McLellan et al.,

1985). Violent behavior was assessed using a four-item self-report questionnaire from the National Vietnam Veterans Readjustment Study (Kulka et al., 1990). Community adjustment was measured by several factors which included: employment status, violent behavior, history of incarceration, and whether the veteran was planning on attending military reunions after discharge. The average age of the participants was 51.7 years old with 96.7% being male. The average length of stay in the program was 42.5 days. The participants were classified into four groups: no use at admission "never-users"; used at admission but not after discharge "stoppers"; used at admission and after discharge "continuing users"; and use after discharge but not at admission "starters". The analysis of covariance compared groups on follow-up for PTSD symptoms, drug and alcohol use, violent behavior, and employment. The results at baseline were the following: continued marijuana use was significantly associated with worse outcomes in PTSD symptom severity (MISS scores), violent behavior, and measures of alcohol and drug use (ASI) compared to stoppers and never-users. The follow-up results: Stoppers and never-users had the lowest levels of PTSD symptoms (MISS), and starters had the highest level of violent behavior. Wilkinson et al. concluded that starting marijuana use after psychological treatment may worsen PTSD symptoms, increase violent behaviors, and increase alcohol use. Also, they concluded marijuana may decrease the effectiveness of PTSD treatment (Wilkinson et al., 2015). However, the longitudinal observational study incorporated within subject repeated measurements and between subject design that provided correlational data. The study does not provide insight on types of marijuana used, frequency, dosage, and amounts consumed per use, which affects the ability to control for those and other factors that can potentially have an impact on the results. Wilkinson et al. conveyed that another limitation of the study was the fact it was not randomized, and the groups could not be considered to have equal time in the program.

Therefore, on the basis of this study, casual relationships cannot be made between marijuana use and PTSD severity, drug and alcohol use, and violent behavior. The information in the study does not correlate with a past studies (Elms et al., 2019 & Roitman et al., 2014) that suggest marijuana can potentially improve PTSD symptoms. While this study suggests that marijuana use may worsen PTSD symptoms, additional clinical trials are necessary to either support or contrast with these findings.

Bonn-Miller et al. (2013) conducted a study to investigate the association between current cannabis use disorder and changes in PTSD symptoms over time after discontinuation of cannabis use. The study was longitudinal and consisted of 260 male combat-exposed military veteran patients diagnosed with PTSD and admitted to a VA residential rehabilitation program for PTSD between 2000 and 2008. The average length of stay for the participants was 78.07 days but any veteran who completed any amount of treatment was included in the study. Eighty-one of the participants met the criteria for cannabis use disorder. PTSD symptoms were measured by the Structured Clinical Interview for *DSM–IV* - Clinician Version (SCID-CV; First et al., 1997) and the PTSD Checklist - Military Version (PCL–M; Weathers, et al., 1993). Psychological distress was measured using the Beck Depression Inventory (BDI; Beck, Steer, & Garbin, 1988). Trauma severity was also measured by using the Combat Exposure Scale (CES; Keane et al., 1989). All the participants were measured at two time periods, which were within the first week of intake and during the final week during discharge. SCID–CV, BDI, PCL-M, and CES information was gathered at intake and the PCL-M was administered at discharge. The results indicated that participants reported high PCL-M scores at treatment intake ($M = 66.25$) and the PCL-M scores were reduced at the time of discharge ($M = 62.37$). Participants with cannabis use disorder results did not report higher PCL-M scores at intake, but participants with cannabis use

disorder reported lower levels of improvement in the PCL-M at discharge (Bon-Miller et al., 2013).

Bon-Miller et al. (2013) indicated that their results do suggest that marijuana may worsen PTSD symptoms. However, their results can only be generalized to men. In addition, the longitudinal design only provides correlational data, so no causality can be obtained from their results. Another concern is that the claim that marijuana may worsen PTSD symptoms is based on the notion that individuals with cannabis use disorder showed less improvement in their PTSD symptoms in the absence of the drug. However, the results are more suggestive of the idea that individuals with cannabis use disorder recover at a reduced rate compared to other individuals with PTSD without cannabis use disorder.

Tull et al. (2016) designed a study to investigate the role of marijuana dependence on PTSD and subjective and biological emotional reactivity in response to a trauma cue. Participants consisted of 202 male and females with or without current PTSD admitted to a substance use disorder treatment facility with at least one potentially traumatic event experienced. The participants were administered diagnostic interviews and asked for subjective emotional reactivity to experienced traumatic events, and their biological reactivity was measured with saliva samples. Substance use was measured by the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I; First et al., 1996). PTSD was diagnosed during an interview using the *DSM-IV* version of the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1990). The participants also were administered the Mini International Neuropsychiatric Interview, Version 6.0 (MINI; Sheehan et al., 2009) to assess for current *DSM-IV* Axis I disorders with the exception of PTSD and SUD. Borderline personality disorder module of the Diagnostic Interview for *DSM-IV* Personality Disorders (DIPD-IV; Zanarini et al., 1996) was

utilized to identify borderline personality disorder. The participants were split into two groups: substance abuse disorder (SUD) with PTSD and SUD without PTSD. Both groups were asked to describe their traumatic events and an associated distress while being video recorded. To assess for subjective emotional reactivity to the traumatic events, the participants were administered the negative affect (NA) subscale in the Positive and Negative Affect Scales (PANAS; Watson et al., 1988). Saliva samples were taken at two different time periods, which were before talking about the trauma and 20 minutes after talking about the trauma. Marijuana frequency of use was assessed using the Drug Use Questionnaire (DUQ; Hien and First, 1991). The study involved two sessions on separate days with an average time between sessions of 6.23 days. The initial session consisted of completion of the above assessments, and participants were recorded during their time describing their traumatic experience. In the second session the participants listened to their recording from the previous session and were instructed to close their eyes and imagine the event and then were administered the PANAS-NA and given saliva samples 20 minutes after the task. The results suggested that PTSD was associated with greater subjective emotional reactivity (PANAS-NA) to the trauma script only among participants without marijuana dependence. Also, marijuana dependent participants with or without PTSD reported less subjective emotional reactivity (PANAS-NA) compared to the participants with PTSD but without marijuana dependence (Tull et al., 2016).

Tull et al.'s (2016) study had a design that focused on between-subject and within-subject comparisons that provided correlational results. Their results found that individuals with marijuana dependence had less subjective emotional reactivity towards their trauma scripts compared to individuals with PTSD without marijuana dependence. The authors speculate that these results may be due to the high density CB1 cannabinoid receptors in the amygdala, which

with intake of THC (CB1 agonist), can lead to reduced activation in the amygdala, therefore resulting in reduced emotional reactivity. Tull et al. also postulated that their results may suggest that participants with marijuana dependence and PTSD may have a greater tendency to avoid negative emotions, but this claim appeared to be speculation and is not supported by data. Alternatively, the scores may be interpreted as marijuana dependent participants with PTSD may improve their emotional reactivity and thus yielding lower subjective reporting. Without the use of clinical trials that involve randomized double blind placebo control designs, the impact of marijuana dependence on PTSD is unclear, and causality cannot be assessed. Other limitations were that variations in the extent to which participants were able to successfully reimagine the trauma script were not measured or accounted for.

Impact of Recreational Use or Misuse on Anxiety

Rusby et al. (2019) conducted a review of an ecological momentary assessment (EMA) study of social influences of risky behavior in adolescence in order to understand the relationship between marijuana use and anxious mood lability during early to mid-adolescence. The EMA study was extrapolated from a larger study that focused on investigating social influences of risky behaviors during adolescence and consisted of 1,188 students. The EMA study occurred from 2014 to 2017 and male and female students completed brief random surveys over a 4-day period beginning in eighth grade and ending when they were in 10^{th} grade. The survey consisted of 10 quarterly assessment waves and was administered at 18 random times per assessment wave, which resulted in a total of 180 possible EMAs per participant. The EMA asked questions about mood, current activities, and social context during non-school hours. Mood lability was extrapolated out of the EMA and used to assess for an average anxious mood lability score (MSSD). The participants also completed brief surveys in the spring of eighth grade, and fall,

winter, and spring of ninth and 10th grade. These surveys assessed for adolescent substance use in their lifetime and within the past 30 days and asked about marijuana use for an overall of seven different time periods. Marijuana use was assessed with the Oregon Healthy Teens Survey (Boles, Biglan, & Smolkowski, 2006). A total of 466 eighth grade participants were included in the study. The results showed that 8% to 13% endorsed using marijuana recently across the assessment waves. Participants had higher reported scores on MSSD (anxious mood lability) when reporting recent marijuana use compared to the MSSD scores without recent marijuana use (Rusby et al., 2019).

Although, Rusby et al. (2019) utilized quantitative survey information from a longitudinal study and found that recent marijuana use was associated with higher anxious mood lability, these findings have several areas of weakness. The research does show a correlation between the two variables. However, the sample size of individuals who used marijuana recently was rather small, which affects the power of the results. Also, recent marijuana use is considered in the last 30 days but there can be significant variability in the impact from marijuana in a person who used marijuana 30 days ago opposed to the day before being surveyed. Also, Rusby et al. reported that their results can only apply to youth who live in rural and suburban communities, and the MSSD scores of anxious mood lability do not indicate that anxiety was interfering with the participants' lives. Finally, the MSSD is not validated, and therefore the results should be viewed with caution due to use of a measure that is not validated as a primary outcome measure.

Impact of Recreational use or Misuse on Symptoms of Depression

Bahorik et al. (2018) conducted research concerning medical versus nonmedical marijuana use as a treatment for depression. There hundred and seven psychiatry outpatients

were the participants in a trial of medical marijuana use treatment for individuals with depression. The Patient Health Questionnaire (PHQ-9; Kroenke & Spitzer, 2001) was used to determine depression severity and suicidal ideation. Functional outcomes were measured with the Short Form 12 Health Survey (SF-12; Turner-Bowker & Hogue, 2014), which is a self-report questionnaire and consists of physical and mental health subscales. Marijuana use in the past 30 days was assessed during interviews at baseline, 3, 6, and 12 months. The data was collected from participants in a randomized controlled trial with the use of motivational interviewing for medical marijuana use treatment in depressed individuals. The participants were randomized into one of two studies after they completed screen procedures, which were motivational interviewing (MI) or treatment control. Results at baseline were that 40.0% of the sample used marijuana. The MI group had a 45-minute motivational interview session followed by two 15-minute telephone booster sessions that were about 2 weeks apart. The control group were given two brochures on the risks specific to the substances they had reported at baseline and received "usual depression care", which consisted of medication management and individual psychotherapy. Of the 40.0% of participants who used marijuana at baseline, 28.2% used marijuana for medicinal purposes. Participants who used non-medicinal marijuana showed a higher level of depression severity (PHQ-9), suicidal ideation, poorer mental health functioning (SF-12), and fewer psychiatry visits compared to participants who did not use marijuana. Participants using medicinal marijuana had significantly worse mental health and physical health functioning, a higher level of depression severity, and poorer everyday functioning compared to non-users. After 1 year, non-medicinal marijuana users were less likely to have psychiatry visits and had poorer mental health functioning compared to non-users. Patients using non-medical marijuana for over 1 year had

significantly less improvement in depression symptoms and suicidal ideation compared to non-users (Bahorik et al., 2018).

Bahorik et al.'s (2018) study was longitudinal and focused on between subject and within subject results. The researchers specified that their results are only generalizable to an outpatient psychiatry setting of insured patients in San Francisco area. The PHQ-9 scores that were included into the study may not reach the threshold for a diagnosis of major depressive disorder (MDD) through the *DSM*, which indicates that many of the participants may not have met the criteria for MDD. The results tended to focus on cross sectional data between medicinal users, non-medicinal users, and non-users, without highlighting the differences of treatment (MI versus control) in their results.

In contrast, Denson and Earleywine (2006) conducted a study to investigate the relationship between depression and marijuana use. They hypothesized that marijuana use might inhibit the likelihood of depressive symptoms improving, especially in nonmedical marijuana use. The goal was to find participants who were significantly depressed and used marijuana to include in the study. Denson and Earleywine used an internet survey for 4,494 male and females who endorsed using cannabis either daily (n = 3323), once a week or less (n = 861), or never (n = 310). Medical use of cannabis was identified by the participants during the survey, and the common conditions for use were nausea, vomiting, cancer, attention deficit, and poor appetite. The Center for Epidemiologic Studies Depression scale (CES-D; Radloff, 1977) was administered to identify depressed affect, positive affect, somatic and psychomotor retardation activity, and interpersonal symptoms. The results revealed that medical cannabis users reported more depression than recreational users. However, non-users reported more depression than recreational users. Medical users also reported more somatic complaints than recreational users.

However, weekly users had less depressed mood, more positive affect, and fewer somatic complaints than non-users (Denson & Earleywine, 2006).

Denson and Earleywine's (2006) research appeared to be the first research that compared recreational users of cannabis, medical users of cannabis, and non-users. The study results may be skewed from those that would be seen in the general population due to selecting participants who were the "most depressed" of all the individuals they surveyed. The design of the study focused on cross sectional between subject measurements, so no causality can be ascertained from their results. Also, medical users had aliments like cancer, nausea, and vomiting, which also may impact depressive symptoms. Overall, studies that survey community samples but leave no way of verifying medicinal (i.e., prescription) versus recreational users are based on self-report, which is less reliable than verified data.

CHAPTER IV: INTEGRATION OF MEDICAL MARIJUANA USE VERSUS RECREATIONAL MARIJUANA USE OR MISUSE

Synthesis of the Data on PTSD

When examining the treatment of PTSD with marijuana, it is important to distinguish between medical marijuana and recreational use or misuse. Focusing on medical marijuana first, it can come in several forms, with the two major categories being THC and CBD. Both CBD and THC come in various administration routes (i.e., smoked, vaped, and ingested). The dosage of medical marijuana is important for treatment implications and is rarely consistent across available research. Another consideration is viewing how treatment effects are being measured, whether self-report, clinical interpretation, or biological measures (e.g., vitals, MRIs, CTs). When discussing symptom reduction, what symptoms are being reduced and to what extent? The challenge is to compare effective treatment across various research studies with a lack of consistency in these factors. Available research that compared THC and CBD has been extremely limited. LaFrance et al. (2020) found that individuals with PTSD reported a 62% reduction in intrusive thoughts, 51% reduction in flashbacks, 67% reduction in irritability, and 57% reduction in anxiety when measuring before and after inhaling cannabis. Higher doses were used to manage anxiety. Individuals with higher severity in symptoms showed a larger reduction in symptom severity. There was no significant difference in symptom changes when comparing THC to CBD. Overall, cannabis intoxication appeared to assist in temporary relief from PTSD symptoms. However, the results indicated that individuals' baseline PTSD symptom ratings showed no change over time. (LaFrance et al., 2020).

THC

PTSD symptom reduction has been shown when using medical THC. In a 3-week trial, synthetic oral extracts such as nabilone have shown a reduction in hyperarousal symptoms, reduced nightmares, and improved sleep quality with a dosage range from 2.5 mg to 5 mg administered below the tongue (Roitman et al., 2014). Cameron et al., (2014) indicated that nabilone use with a dosage from 1.4 mg to 4.0 mg for an average of an 11.2 weeks showed a reduction in nightmares and sleep quality/time improvement were reported. Nabilone is a C1 receptor agonist, which is spread throughout the brain and has limited interaction with cardiorespiratory areas in the brain stem (Cameron et al., 2014). Frazer (2009) conducted the research on "treatment-resistant" individuals who have tried medication interventions to treat their PTSD symptoms. Frazer found that participants reported a clinically significant reduction in the severity of trauma-related nightmares (Fraser, 2009). Nabilone has been shown to have low indicators of abuse potential (Ware & St. Arnaud-Trempe, 2010). However, Fugh-Berman et al. (2020) suggest that nabilone use has potential abuse for individuals with substance abuse history due to the potential to experience euphoria.

Nabilone appeared to have the highest therapeutic advantages for the treatment of PTSD symptoms. Research has consistently found a reduction in nightmares and improvement in sleep quality. Effective dosage appeared to range from 0.2 mg to 4.0 mg, with a trend towards the higher end of dosage (Frazer, 2009). Individuals who reported psychosis were typically excluded from these trials due to the potential to exacerbate their symptomology, but this claim had not clearly been documented. No gender differences have been noted, but gender differences have rarely been studied.

CBD

CBD has been shown to be effective in treating symptoms of PTSD. CBD is theorized to increase the consolidation of extinction learning (Das et al. 2013), which may potentially aid in the extinction of traumatic memories using 32 mg of inhaled CBD. Similar to nabilone, CBD has been shown to reduce PTSD-related nightmares. Additional support for CBD treatment of PTSD examined the impact of either oral CBD capsules or liquid spray CBD with an average dose between 33.18 mg to 48.64 mg over eight weeks. Overall, a reduction in frequency and intensity of PTSD symptoms was noted (Elms et al., 2019).

It is challenging to draw conclusions and commonality on limited research for the therapeutic effectiveness of CBD. With the available research, it appeared that the "effective dosage" can range from around 30 mg to 50 mg of CBD administered daily (Das et al., 2013; Elms et al., 2019). Best route of administration cannot be determined based on the available research. While studies have shown that CBD may increase the consolidation of extinction learning, the theory has not been extensively studied on individuals with PTSD. In current studies, CBD is typically administered following an induced fear response, which may or may not mimic PTSD symptoms. Medical marijuana may also create functional brain changes, which may increase symptoms of schizophrenia and may be a risk factor for marijuana abuse (Abizaid et al., 2019).

Marijuana Use and Misuse

Nonmedical cannabis use has been shown to be related to cognitive disturbances and impaired neuronal plasticity and organization in an adolescent brain (Abizaid et al., 2019). Marijuana use was associated with increased PTSD symptom severity, violent behavior, and higher rates of alcohol and drug use in veterans diagnosed with PTSD and admitted to a

specialized intensive VA treatment program for PTSD. Also, starting marijuana use after psychological treatment for PTSD may contribute to worsening of PTSD symptoms and may decrease the effectiveness of PTSD treatment compared to individuals who stopped or never used marijuana (Wilkinson et al., 2015). Marijuana use has also been shown to increase PTSD symptoms. A positive correlation was noted between higher amounts of marijuana use, and increases PTSD symptoms (Bonn-Miller et al., 2010). In terms of marijuana misuse, Individuals with cannabis use disorder were likely to experience lower levels of PTSD symptom changes (Bonn-Miller et al., 2013). Additional research found no more significant differences in subjective reactivity for individuals with PTSD and marijuana dependence than individuals with PTSD without marijuana dependence, although this may be due to the idea that marijuana-dependent individuals may have alterations in their emotional processing in response to a trauma cue and thus may generally show lower emotional reactivity (Tull et al., 2016).

Synthesis of the Data on Anxiety

The limited research on medical marijuana treatment for anxiety disorders has examined use of CBD. Studies that focused on THC were limited. Two studies identified that THC use has shown reduction in self-reported anxiety (Feingold et al., 2017; LaFrance et al., 2020). The factors of administration routes (i.e., smoked, vaped, and ingested), how treatment effects are being measured (i.e., using self-report, clinical interpretation, or biological measures), and dosage was considered. The challenge was to compare effective treatment across various research with limited consistency in these factors. Another challenge was comparing various anxiety disorders with medical marijuana treatment, considering that there was no universality with types of medical marijuana used for treatment, and there were a lack of double-blind studies.

CBD

Individuals with SAD were shown to have significant decreases in subjective reports of anxiety compared to placebo. The participants with SAD were administered 400 mg of CBD, which appeared to be an effective dose to reduce anxiety (Crippa et al., 2011). Additional research on SAD and CBD treatment concluded that pretreatment with 600 mg of CBD showed significant reductions in anxiety, cognitive impairment, discomfort in speech performance, and significantly decreased alertness in anticipatory speech compared to SAD placebo groups (Bergamaschi et al., 2011). Regarding performance anxiety, "healthy individuals" administered 300 mg of CBD as a pretreatment have shown significant reductions in the Visual Analogue Mood Scale (VAMS) compared to placebo. VAMs was used to evaluate subjective states such as calm and agitated. However, in this study, individuals receiving 150 mg of CBD, 600 mg of CBD, or placebo did not yield significant differences in VAMS scores (Linares et al., 2019). The differences between the studies regarding optimal dose may be due to the differences within the design and participant selection. Two studies (Crippa et al., 2011; Bergamaschi et al., 2011) included participants with social anxiety disorder (SAD), whereas the other study (Linares et al., 2019) exclusively included participants without significant levels of anxiety. Individuals with anxiety may require a higher dose of CBD to reduce anxious symptomology. Crippa et al. indicated that the effective dose of CBD to reduce SAD symptoms was 400 mg. However, Bergamaschi et al. reported that 600 mg of CBD was found to be an effective dose to reduce SAD symptoms. Both Crippa et al. and Bergamaschi et al. only used one dose of CBD to compare to placebo groups and control groups. Thus, future research on various dosages of CBD use is needed to determine its effectiveness in reducing SAD symptoms.

Marijuana Use and Misuse

There has been limited research conducted on marijuana use and misuse and anxiety disorders. Some research has focused on rats exposed to cannabis smoke or various doses of THC. Results were inconclusive and non-significant.

Synthesis of the Data for Depression

The research has been inconsistent in the effectiveness and benefits of medical marijuana treatment for depression. Research has provided contradicting results regarding reducing symptomology or exacerbating depressive symptomology. Due to the lack of research, treatment effectiveness determination is difficult to discern with certainty.

Medical Marijuana Treatment

CBD was utilized as an antidepressant on male mice with doses of from 3 to 100 mg. The mice given CBD were shown to increase mobility in forced swimming activities; mice administered antidepressants had similar effects (Zanelati et al., 2010). However, dosage and depressive symptom reduction cannot be compared to human subjects due to CBD being tested on mice. The research implications are that CBD may combat motor deficit effects of depression, although the claim cannot be substantiated from the research available. Results of additional research on “depressive-like” rats administered a cannabis sativa extract (10 mg/kg expressed as Δ9-tetrahydrocannabinol) suggest an increase in motor deficits, depressive symptoms, and memory impairment (Khadrawy et al., 2017). The major difference in these two studies is the rodents being administered CBD or THC forms of marijuana. CBD appeared to reduce the impact of motor deficits caused by depression, and conversely, THC appeared to worsen motor deficits and depressive symptomology.

In the study of human participants, medical cannabis was utilized as a treatment for depression using various administration routes, which included ingesting, smoking, vaping, or topical use. Depressive symptoms were assessed and measured by the PHQ-9. Of 5103 participants, 172 reported significant improvements in depressive symptoms, 76 reported an increase in depressive symptoms, and 4855 reported no clinically significant changes, based on PHQ-9 scores (Round et al., 2020). A major limitation in the study was the types of medical cannabis used and the participants' dosage, as well as limited data on changes in depression over time. Therefore, it is difficult to formulate the treatment impact on depressive symptoms without knowing which medical marijuana product is being utilized, and without studies with more robust assessments of symptom change.

Marijuana Use and Misuse

One study examined medical marijuana users with depression versus nonmedical marijuana users with depression. The research highlighted that both nonmedical marijuana users and medical marijuana users had worse mental health functioning than individuals with depression who did not use any form of marijuana. Nonmedical marijuana users had higher rates of suicidal ideation compared with non-users. Medical marijuana users had worse mental and physical health functioning when compared to non-users (Bahorik et al., 2018). This study suggests that either medical or nonmedical use of marijuana can worsen depressive symptoms and negatively impact psychological and physical health functioning. Conversely, in another study individuals using nonmedical marijuana once per week and daily users reported less depressed mood, more positive affect, and fewer somatic complaints than non-users. When comparing medical versus recreational use, medical users indicated more depressed mood and

somatic complaints than recreational users. However, a confounding variable may be medical conditions impacting depressive symptoms (Denson & Earleywine, 2006).

Who Should Be Prescribed Medical Marijuana?

Based on the available research, several studies have shown both positive and negative indicators for prescribing medical marijuana for PTSD, anxiety disorder, and depressive disorders. The goal was to find the best practices and considerations that should be considered when using medical marijuana as a treatment modality for these mental health disorders. The following conclusions were not approved by any medical committee and should be taken as considerations and not medical guidelines to prescribing medical marijuana. Medical marijuana appeared to have benefits for reducing and managing symptoms of PTSD and anxiety disorders. Depressive disorders do not have clear indicators of treatment success or symptom reduction based on available research.

PTSD

There are indicators that both THC and CBD have shown symptom reduction for PTSD. No significant differences were found in symptom reduction for PTSD when comparing THC to CBD (LaFrance et al., 2020). THC has been shown to reduce hyperarousal, reduction in nightmares, and improve sleep quality. Many of the THC studies involved nabilone, a synthetic extract from the medical cannabis flower. The “effective dose” appeared to range between 0.2 mg to 4.0 mg (Frazer, 2009); height and weight should be considered for dosage. THC may be beneficial to prescribe to PTSD patients with predominant concerns related to nightmares and sleep quality. However, nabilone may cause dizziness, drowsiness, dry mouth, and euphoria. Nabilone has also been associated with hypotension and hypertension; individuals with cardiovascular disease may be at higher risk for health complications. Individuals with PTSD

and substance abuse history may not be a suitable fit due to the experience of euphoria while on nabilone and the potential for abuse. Individuals who also experience psychosis and/or depression may be at risk of exacerbating depressive symptoms, hallucinations, or psychosis using nabilone. Nabilone has not been studied on women during pregnancy and has only been studied on pregnant animals, which have been shown to have increased embryo lethality, fetal resorptions, decreased fetal weight, and pregnancy disruptions. The FDA does not recommend breastfeeding while on nabilone because some cannabinoids are excreted in breast milk (Fugh-Berman et al., 2020).

CBD has also been shown to improve symptoms of PTSD. CBD has been correlated with the consolidation of extinction learning, potentially helping to promote extinction in traumatic memories. CBD has also been shown to reduce PTSD-related nightmares. With the available research, it appeared that the "effective dosage" can range from around 30 mg to 50 mg of CBD administered daily. CBD has been shown to have an anxiolytic effect to help reduce anxiety-related symptoms synonymous with PTSD. CBD also does not lead to euphoria in contrast with flower cannabis that contains THC. However, CBD can cause dry mouth, diarrhea, reduced appetite, and fatigue. CBD also has interactions with other medications such as blood thinners, heart rhythm medication, thyroid medication, and seizure medications, and thus it is important to consult a doctor prior to CBD use (Bykov, 2021). Therefore, CBD may be an appropriate fit for individuals with PTSD who have related nightmares and experience high anxiety levels. CBD may provide extinction learning of traumatic memories, but more research is needed to replicate these findings. Individuals with substance use may be an appropriate fit to use CBD due to the absence of THC, which may reduce abuse potential.

Medical cannabis flower has not been extensively researched. Many studies are based on self-report, case reports, and observational studies and include both medical cannabis use and nonmedical cannabis use. Research has suggested that cannabis (medical or non) can create cognitive disturbances and may create other functional brain changes such as impaired neuronal plasticity and organization in adolescents (Abizaid et al., 2019). Additional research suggests that marijuana use was associated with worse PTSD symptom severity, violent behavior, decreased effectiveness of other PTSD treatments, and increased drug and alcohol use compared to individuals who never used marijuana or stopped using marijuana (Wilkinson et al., 2015). This research implies that marijuana use after the start of treatments can decrease the effectiveness and worsen PTSD symptoms overall. Therefore, using flower medical cannabis or nonmedical cannabis as a treatment for PTSD may be associated with increased symptomology and worse outcomes. However, flower medical cannabis or nonmedical cannabis efficacy is difficult to measure, and additional research is required to help substantiate any claims that there is a therapeutic benefit or significant harm.

Focusing primarily on flower cannabis abuse, individuals with cannabis abuse experienced lower levels of PTSD symptom change over time. Marijuana abuse appeared to adversely impact PTSD symptoms (Bonn-Miller et al., 2013). In addition, research also supports that marijuana utilized for coping can exacerbate PTSD symptoms; higher levels of PTSD symptoms were associated with higher levels of marijuana use for coping in contrast to recreational use of cannabis (Bonn-Miller et al., 2010). Individuals with marijuana dependence may experience alternations in their emotional processing in response to a trauma cue (Tull et al., 2016). In conclusion, marijuana abuse may worsen PTSD symptomology. Prescribing medical

marijuana to an individual with cannabis use disorder may have more potential risks than benefits, but additional research is needed.

Anxiety

Research on medical marijuana and nonmedical marijuana as a treatment for various anxiety disorders is limited. The available research consists of examining anxiety in general and does not always designate which anxiety disorder is the focus. CBD appeared to have anxiolytic effects to help reduce anxiety. Individuals with SAD have shown a reduction in self-reported anxiety when administered 400 mg of CBD (Crippa et al., 2011). Additional research suggests that CBD reduced anxiety for public speaking with a dosage of 300 mg. However, in this study, 150 mg of CBD and 600 mg of CBD did not yield any differences in anxiety reduction (Linares et al., 2019).

Conversely in other research, 600 mg CBD was shown to reduce anxiety if used prior to an anxiety-provoking event such as a speech performance. CBD can also reduce cognitive impairment, discomfort in performance, and decreased alertness (Bergamaschi et al., 2011). Therefore, based on available research, conclusions on the effectiveness of CBD are applied to social anxiety and social performance. Also, the dose of CBD effectiveness may vary among individuals, and additional research is needed to understand the effective dosage. Additional research is also needed for other various anxiety disorders to determine if CBD is an adequate treatment. Individuals with substance use or abuse and SAD may benefit from symptom reduction with the added benefit of reduced abuse potential. CBD side effects should also be taken into consideration when prescribed. CBD can cause dry mouth, diarrhea, reduced appetite, and fatigue. Again, CBD does have interactions with other medications such as blood thinners,

heart rhythm medication, thyroid medication, and seizure medications; it is important to consult a doctor prior to CBD use (Bykov, 2021).

Medical marijuana has been shown to reduce anxiety and depression for patients with chronic pain compared to patients utilizing prescription opioids. (Feingold et al., 2017). Among mental health disorders, anxiety is among the highest reasons for prescribing medical marijuana (Kosiba et al., 2019). Research also reports that individuals prescribed medical marijuana for anxiety have shown a significant decrease in anti-anxiety medication use (Piper et al., 2017). However, benefits and risks have not been adequately studied despite the frequency with which medical marijuana is prescribed for anxiety.

In conclusion, medical marijuana may provide an anxiolytic effect in treating anxiety disorders, although dosage and type of medical marijuana are not clear to provide maximum benefit are not clear. Different strains of medical marijuana have various concentrations of THC, which adds additional confusion on what amount of medical marijuana is appropriate for the user. However, studies regarding THC as a treatment for anxiety in humans are absent. (Mayo Clinic, 2020).

Depression

Medical marijuana appeared to have the lowest therapeutic benefits for individuals with depressive disorders. However, there is limited research providing clarification on the therapeutic benefits of medical marijuana for depression. CBD has shown antidepressant qualities in mice (Zanelati et al., 2010), but humans may not necessarily have the same results. CBD may provide relief in depressive symptoms, although additional research on humans is needed to provide clarity. THC extract research has suggested that worsening depressive symptoms, motor deficits, and memory impairment were found for “depressive-like” rats

(Khadrawy et al., 2017). Again, it is difficult to conclude the efficacy of treatment with a THC extract as applied to humans. Limited available research suggests that medical cannabis does not have a major impact on depressive symptoms and may worsen depressive symptoms (Round et al., 2020). Due to the limited research and lack of consistency among types of medical marijuana, quantity and frequency used, and administration route, conclusions are difficult to derive.

Research that focused on medical vs. nonmedical marijuana use for depression is limited and inconsistent. Medical marijuana has been shown to worsen mental and physical health functioning. Also, nonmedical users showed an increase in suicidal ideation rates, worse mental health functioning, and less improvement over time than non-users (Bahorik et al., 2018). Conversely, nonmedical cannabis users had less depressed mood, more positive affect, and fewer somatic complaints than non-users. When comparing medical versus recreational use, medical users had more depressed mood and somatic complaints than recreational users. However, a confounding variable may be medical conditions impacting depressive symptoms (Denson & Earleywine, 2006). Due to inconsistencies and lack of research, conclusions cannot be made to determine whether medical or nonmedical cannabis use increases or reduces depressive symptoms. Individuals with depression may not be best suited for medical marijuana due to the potential risks. Individuals who are prescribed medical marijuana should be monitored for worsening symptoms and suicidal ideation.

Cannabis can have an impact on drug interactions. THC may decrease concentrations of clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine. CBD may increase concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil, antihistamines, haloperidol, and antiretrovirals. CBD may increase SSRI

concentrations, tricyclic antidepressants, antipsychotics, beta-blockers and opioids (Fugh-Berman et al., 2020). The implications of cannabis increasing or decreasing medication concentration can potentially disturb the effectiveness of the medication. In particular, individuals prescribed medical marijuana for depression should be screened for potential medication interactions to determine whether the benefits outweigh the risks.

CHAPTER V: DISCUSSION

The purpose of this review was to gain an understanding of the current research on medical marijuana use for PTSD, anxiety disorders, and depressive disorders in an attempt to determine best practices in prescribing medical marijuana. Medical marijuana continues to be a multilayered issue due to various legal implications from state to state, discrepancies in research on effectiveness, lack of clarity in types of medical marijuana best suited for mental health disorders, and health-related concerns. Marijuana is still considered a schedule I drug via the Controlled Substance Act (Hudak, 2016; Drug scheduling, 2019). Therefore, certain professions will not be able to obtain a medical marijuana card and remain employed. Marijuana laws vary from state to state, and several states have both medical and recreational marijuana still classified as illegal ("Map of marijuana legality by state," 2021). The implications are that even though medical marijuana can be an effective treatment, many Americans do not have the option to access marijuana treatment.

There are discrepancies in the research for the addiction potential when using nabilone due to some reported euphoric experiences due to consuming nabilone. There is considerably more research that indicated that nabilone has been considered low in abuse potential (Clark et al., 2005; Gourlay, 2005), and doses from the range of 1.0 mg to 5.0 mg do not have a significant impact on altering mood states (Glass et al., 1980). Conversely, nabilone has been suggestive of having abuse potential for individuals with substance abuse history (Fugh-Berman et al., 2020). Therefore, substance abuse history should be considered when prescribing medical marijuana in the THC form because the potential for cannabis abuse. Alternatively, CBD does not contain THC and does not possess any euphoric qualities. CBD use did not show any indictors for abuse

potential (Bykov, 2021). CBD may be a safer alternative for individuals with treatment abuse history and may decrease the chance of substance abuse or misuse.

Medical marijuana treatment for PTSD appeared to show promising results for the THC extract nabilone and CBD. Additionally, one of the defining characteristics for many individuals with PTSD is reexperiencing traumatic events. Current research suggests that CBD may increase the consolidation of extinction learning and could reduce the impact and intensity of reexperiencing traumatic events and potentially reduce the impact of associated stimuli that induce traumatic memories and flashbacks. Additional research is needed to understand whether CBD effectively increases the consolidation of extinction learning in PTSD specifically. CBD has also been shown to reduce PTSD-related nightmares. The effective dosage for CBD is still in question, but research has found a potential effective range. Although the dosage for effective symptom reduction for PTSD in both THC and CBD does not appear to be fully explored, there are general guidelines for the quantity and frequency with which these marijuana products should be used. Flower form of medical marijuana also has limited research. Although the current research did not include dosage (LaFrance et al., 2020), one study concluded that the higher number of puffs of marijuana yielded greater symptom relief for PTSD. However, it is unclear what the different potencies are between the various strains of marijuana used, and how much marijuana (puffs) provided the maximum benefit. Also, it is unclear at what number of puffs does the increase in symptom relief end and additional marijuana use stops providing additional symptom relief. LaFrance et al. (2020) also noted that there were no significant differences in PTSD symptom reduction when comparing CBD versus THC, but the dosage was not disclosed and therefore cannot be specified based on the current research. Nabilone use has shown improvement in PTSD symptoms including improved sleep quality and reduction in

nightmares and a range of effective doses has been determined in several research studies. (Cameron et al.; Roitman et al., 2014; Frazer, 2009). However, it is unclear if the dose and type of medical marijuana (CBD or THC) is being conveyed to the actual individuals being prescribed medical marijuana for PTSD. It may be important for medical marijuana prescribers and medical marijuana dispensaries to inform patients that nabilone in this dose range has been found to have an improvement on sleep related symptoms of PTSD. At the same time providing a dose range of nabilone as a treatment for PTSD may be inaccurate due to the limited research available and small sample sizes of participants used in research to confirm these findings.

The research for medical marijuana use to treat symptoms of anxiety disorders has shown reduction in anxiety symptoms. The research on CBD use for anxiety disorders also appeared to show indicators of effective symptoms reduction. However, the research does not have consistency in identifying the effective dose of CBD that reduces anxiety symptoms. It is also unclear of what the effective dose are for reducing anxiety symptoms in regard to individuals' gender, age, disorder, and physical characteristics. CBD has shown significant results in reducing social anxiety disorder (SAD) at two different doses: 400 mg (Crippa et al., 2011) and 600 mg (Bergamaschi et al., 2011). However, due to the limited research and small sample sizes within the research, it is difficult to confirm the effective dose for SAD symptom reduction. The research available on other anxiety disorders that are treated with CBD or medical marijuana is scarce. The generalizability of what the effective CBD dose is for treating various anxiety disorders is not well researched and remains uncertain. Research on THC has shown a reduction in self-reported anxiety symptoms (Feingold et al., 2017; LaFrance et al., 2020), but there is limited research available that focuses on THC based medical marijuana use as a treatment for anxiety disorders. Therefore, additional research is needed to understand what dose of THC

based medical marijuana is effective for decreasing anxiety symptoms. Nonmedical marijuana use in the flower form that is typically smoked appeared to have indicators of worsening PTSD symptoms. Starting marijuana use after psychological treatment for PTSD may also contribute to worsening of PTSD symptoms and may decrease the effectiveness of PTSD treatment. Marijuana use has also shown higher levels of PTSD symptoms and having a positive correlation with the higher amounts of marijuana use increases PTSD symptoms. The research suggests that non-medical use can exacerbate PTSD symptoms and appear to have worse outcomes for individuals with cannabis use disorder (Bon-Miller et al., 2013). Non-medical marijuana contains potential issues for physicians prescribing medical marijuana. Individuals who use non-medical marijuana not only may be worsening their symptoms, but they potentially increase the chances for cognitive disturbances and impaired neuronal placidity (Abizaid et al., 2019). Prior to prescribing medical marijuana, prescribers can utilize drug screenings to test for non-medical marijuana use. By testing for non-medical marijuana use, prescribers can limit the number of individuals with cannabis use disorder attempting to gain access to medical marijuana and provide education on the benefits of utilizing CBD over THC based medical marijuana treatments.

Research on THC is limited but has shown a reduction in acutely reducing anxiety. Indica strains of marijuana typically have higher CBD levels and lower THC levels and have been shown to have a calming effect, which may be of significant benefit for treating anxiety disorders. Until there is additional research, CBD or indica strains of marijuana is the most judicious recommendation to provide relief for anxiety in the absence of euphoria and with low abuse potential. Marijuana use has been shown to be associated with significant levels of anxiety in adolescents (Rusby et al., 2019) and may be a risk factor for prescribers and clinicians to

consider when treating an adolescent. For example, a question that has not been addressed is as follows: Is marijuana use increasing anxiety in adolescents or are adolescents who experience anxiety more likely to engage in marijuana use? The research does not answer this question and the results are correlational due to the research design. The legal and ethical issues may hinder medical marijuana research with minors.

Research on medical marijuana and marijuana use in depression has many discrepancies in the available research. Research utilizing mice and rats may help gain insight into medical marijuana's impact on depression, but the challenge is applying the research to humans. Medical marijuana has been shown to improve and worsen depressive symptoms (Round et al., 2020; Denson & Earleywine, 2006). The research that focuses on medical marijuana effective dosage for treating depression is non-existent. Medical marijuana prescribers cannot adequately inform their patients of the effective dose to treat depression because the information is not readily available. It raises the question whether medical marijuana should be prescribed for depression based on the limited data that supports its efficacy and the effective dose based on age, gender, weight, and height.

Limitations of Current Research

Because medical marijuana is still considered illegal at the federal level, and several states also deem medical marijuana use illegal. Researchers have additional barriers to overcome to get approved for research. The National Institute on Drug abuse controls marijuana utilized for research, which only allows federally authorized strains of marijuana. Researchers must gain approval from the FDA, apply to the National Institute of Drug Abuse, and obtain a license from the DEA to conduct the study (Anderson, 2017). The goal of these entities is to weigh the cost/benefit of conducting medical marijuana research. The limited amount of research is partly

due to these strict restrictions on marijuana use in studies. Researchers are at a disadvantage when trying to focus on medical marijuana as a treatment for mental health disorders. The alarming aspect is that medical marijuana is being prescribed for mental health disorders such as depression, and the available research and information conflicts and does not provide definitive answers concerning whether medical marijuana is an appropriate treatment. Other studies that utilize surveys or record reviews lack the ability to effectively study medical marijuana treatment or to confirm their research findings for several reasons including reliability of data and managing research design as stated below.

There is a major disparity in research designs in studies on medical marijuana. The research on medical marijuana lacks double-blind, randomized controlled studies. The research that does incorporate randomized controlled studies focuses primarily on CBD. While CBD has shown positive results in reducing PTSD, anxiety, and depressive symptoms, research is scarce. Other designs utilized in studies consist of open-label studies, prospective trials, case studies, retrospective chart reviews, and retrospective longitudinal observational studies. There is limited consistency among the available research in the designs, making conclusions difficult to confirm across the available research.

Another limitation of discussion is the wide inconsistency in how medical marijuana treatment efficacy is measured. Studies may include various self-report measures, clinical interpretations, and monitoring vitals, and imaging such as MRIs. Due to the lack of consistency in how medical marijuana's success in treating mental health disorders is measured, it is challenging to draw conclusions from standalone research. Research also lacked consistency between marijuana use, marijuana abuse, medical marijuana (flower form), medical THC extracts, and medical CBD extracts. Therefore, conclusions can only be considered

circumstantial and require additional uniform studies to help gain additional information on which form of marijuana is advantageous for various mental health disorders. Finally, studies suffer from a lack of generalizability due to small samples, predominately male participants, and other limited demographic information.

Recommendations for Future Research

The challenges of the legal process will continue to be a barrier for medical marijuana researchers unless federal laws change the schedule I narcotic status in the Controlled Substance Act. Recommendations for research are to increase the amount of randomized double-blind placebo-controlled studies to help reduce confounding variables and gain a clearer understanding of medical marijuana's impact on mental health treatment. Future studies should attempt to collect clearly defined demographics, increase sample sizes in research conducted on medical marijuana, attempt to find consistency in how mental health disorders are measured and diagnosed, and identify optimal medical marijuana dosage based on gender, height, weight, and age. Future research should focus on cannabis as a monotherapy compared to therapeutic and pharmacological treatment. Longitudinal research is recommended to investigate if continued medical marijuana use is needed to sustain symptom reduction or if medical marijuana use will be needed to achieve symptom relief from mental health disorders. Finally, incorporating research that focuses on improvement of quality of life and not only symptom reduction will be beneficial. There are limited studies that focus on the impact medical marijuana has on individuals treating their mental health disorders with medical marijuana.

Conclusion

Overall, medical marijuana appeared to have a therapeutic benefit for treating mental health disorders. CBD has shown to reduce PTSD related nightmares and hyperarousal while

also improving sleep quality. The research also suggested that CBD may promote the consolidation of extinction learning, which would be a major breakthrough discovery if confirmed. If CBD does assist in extinction learning, individuals who experience PTSD may have an additional tool to help disrupt the connection between the traumatic event and the lingering traumatic responses. Synthetic THC such as nabilone has also shown to reduce nightmares and improve sleep quality for individuals with PTSD. Anxiety disorders also have shown symptoms reduction with the use of both CBD and THC forms of medical marijuana. CBD appeared to have an anxiolytic effect that can be beneficial for individuals who struggle with managing their anxiety symptoms. As stated, THC has shown a reduction in hyperarousal, which may assist in the reduction of physiological symptoms association with anxiety. Medical marijuana has shown to have an acute reduction in PTSD and anxiety symptoms but does not appear to improve or eliminate these disorders over time. Medical marijuana users may develop a dependency on medical marijuana in order to manage their symptoms. If medical marijuana provides symptom relief for PTSD and anxiety disorder, but does not improve these disorders over time, does medical marijuana treatment potentially inhibit the improvement from psychotherapy or medication management? Due to limited research, it is not yet known if medical marijuana is more effective than psychotherapy and medication management. Additionally, THC forms of medical marijuana may increase the chances of abuse for individuals with a history of substance abuse. Based on the available research, treating depression with medical marijuana had inconsistent results. Medical marijuana may worsen depressive symptoms and may exacerbate psychosis.

Clinical psychologists, therapists, and social workers can assist in monitoring their clients who are treated with medical marijuana. Clinicians can assist their clients by tracking any

behavioral or emotional changes during the client's medical marijuana treatment. If the mental health symptoms worsen with the use of medical marijuana, clinicians can assist their clients in relaying this information to their medical marijuana prescribers to determine if a medication change is needed. Major warning signs include suicidal ideation, worsening depression, increase in anxiety or PTSD related symptoms, and reported or observed hallucinations or delusions. Marijuana has been illegal in the United States for many years and not every clinician may agree in medical marijuana treatment. It is important for clinicians to manage their own personal views on medical marijuana to not inhibit or promote the use of medical marijuana. Instead, clinicians can provide psychoeducation on the benefits and risks associated with treating mental health disorders with medical marijuana.

The question of who should be prescribed medical marijuana is not currently clear. Adult males with PTSD and no history of substance use appear to have PTSD symptoms reduction with medical marijuana use. Woman may also benefit from medical marijuana use, although, the majority of the research focuses on male participants. Anxiety disorder also appear to show reduction in symptoms when treated by medical marijuana. Research is promising in that there may be benefits for some individuals yet there also may be potential harm in others. Medical marijuana is likely here to stay and thus there is a strong need for continued and expanded studies to insure the greatest benefits for all.

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