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Medicinal Cannabis (THC vs. CBD): Effects on Anxiety, PTSD, and Epilepsy

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ABSTRACT

As of November 4th, 2020, thirty-six states and four territories (District of Columbia, Guam, Puerto Rico, and U.S. Virgin Islands) have approved a measure that regulates cannabis for medicinal use (Markle & Nativio, 2019). In particular, Pennsylvania law allows residents with twenty-three different medical conditions to apply for an ID card that will enable them to purchase medical marijuana from dispensaries. Some of the medical conditions included are anxiety disorders, autism, epilepsy, and post-traumatic stress disorder (PTSD). As more states approve marijuana for medicinal use, researchers continue to investigate the interaction between medicinal cannabis and the endocannabinoid system.

The cannabis plant consists of about 100 molecules called phytocannabinoids, with the two most studied as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is responsible for the intoxicating effects of cannabis due to its action on CB1 cannabinoid receptors (Arnold, 2020). Clinical trial results have shown that THC is efficacious in chronic pain and spasticity in multiple sclerosis, among other symptoms. Other research studies have shown CBD to be effective in treating epilepsy and anxiety. However, CBD has a wide range of pharmacological actions without any euphoric effects. Although CBD and THC produce different results, both molecules enter the brain through the endocannabinoid system. This system is essential for modulating many organ systems, including the central and peripheral nervous systems. Within this system, there are two receptors that THC and CBD can bind to, cannabinoid 1 and 2 (CB1 and CB2) receptors (Arnold, 2020). Through this interaction, researchers have conducted clinical

trials where altered doses of cannabis showed a reduction in pain intensity for patients with neuropathic pain.

Previous clinical findings, case studies, and focus group research have shown that consistent use of CBD in the endocannabinoid system effectively reduces seizures in epileptic patients and reduces nightmares and irritability of PTSD patients (Krediet et al., 2020). As research continues to look into the endocannabinoid systems', painstaking efforts are underway to analyze the proper THC and CBD ratio in medicinal cannabis patients. This paper investigates the effects of medicinal cannabis on patients with anxiety, PTSD, and epilepsy.

BACKGROUND

Introduction

In Pennsylvania, residents can apply for a special ID card that permits them to purchase medical marijuana for twenty-three different medical conditions, including anxiety disorders, autism, and neurodegenerative diseases. As more states legalize medicinal cannabis, researchers continue to investigate the relationship between this scheduled one controlled substance and the endocannabinoid system. This paper examines medicinal cannabis's effects on patients with anxiety, PTSD, and epilepsy. The goal is that through a detailed understanding of medicinal cannabis's effects, patients will have an alternative treatment for their symptoms.

Anxiety Disorder

Anxiety disorders are the most prevalent mental disorder, with about thirty percent of individuals affected throughout the world (Turna et al., 2019). This general term includes generalized anxiety disorder, panic disorder, agoraphobia, social anxiety disorder, and specific phobias. Overall, anxiety is an incapacitating signal that warns an individual of imminent danger (Premoli et al., 2019). A distinguishing feature of anxiety disorders is an individual's inability to establish signs to differentiate between safety and hazard feelings. This disorder has multiple comorbidities, including personality disorders, substance use disorders, depression, and medical conditions such as asthma and hyperthyroidism (Bahji et al., 2020).

When someone is frightened or nervous, a stimulus activates certain brain areas, which can be detected with a PET scan (Martin et al., 2009). For example, in individuals with panic disorder, scientists have found an overall decrease in cerebral blood flow and an elevated metabolism of glucose in the amygdala and hippocampus (Martin et al., 2009). Conversely, patients with a social anxiety disorder/social phobia had a hyperactivation of the amygdala supplemented with increased activity in the left postcentral gyrus and the middle temporal and right inferior frontal gyrus (Martin et al., 2009). Martin et al. 2009 realized and observed in generalized anxiety disorder an elevated ratio of grey matter to white matter in superior portions of the temporal lobe, resulting in high activation of the insular cortex and amygdala (Martin et al., 2009).

There are various treatments for anxiety disorder, but first-line treatments include psychotherapy such as Cognitive Behavioral Therapy (CBT) and pharmacotherapy. CBT addresses negative cognitions to produce a positive behavior and affect. This type of psychotherapy is evidence-based that includes homework between counseling sessions, and has helped treat social and specific phobias, generalized anxiety, and panic disorders. Additionally, exposure therapy, which is a part of CBT, has benefited particular phobias. Specifically, clients will expose themselves to anxiety-provoking stimuli in a gradual list from least to most anxious. Through breathing and relaxation, the goal of CBT is for patients to hopefully become desensitized to the most painful and tense experiences (Corey, 2018).

Nonetheless, medications such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline-reuptake inhibitors (SNRIs) help respond to aversive stimuli

with psychotherapy. Although about 50% of patients benefit from these treatments, Turna et al. 2017 commented that the remaining half continue to have lingering symptoms or non-compliant due to the inability to afford medication (Turna et al., 2017). Research into the cannabis plant has found that psychoactive ingredients such as cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) produce anxiolytic effects. Thus, cannabis can be used as an alternative to traditional treatments.

Post-Traumatic Stress Disorder

Post-Traumatic Stress Disorder (PTSD) is a stress-related and trauma disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V). This disorder's diagnosis includes exposure to a traumatic event, disturbing memories, adverse changes in mood and cognition, avoidance, hyperarousal, and increased reactivity to cues from a traumatic event (Shishko et al., 2018).

Brain imaging studies of PTSD patients show that hyperactivation of the amygdala with decreased prefrontal functioning and decreased activation of the hippocampus (Shishko et al., 2018). These differences lead to increased arousal, impulsivity, and flashbacks, among other symptoms associated with PTSD. Additionally, functional MRIs have shown that there is also a hyperactivation of the anterior cingulate cortex, which is responsible for emotional and impulsive behavior (Martin et al., 2009). Also, there are neurotransmitter imbalances due to the lack of a response to external stressors that result in a decreased serotonin and an increase in norepinephrine and glutamate (Shishko et al., 2018).

Treatments for PTSD are similar to anxiety disorder. First-line therapies are SSRIs, which modulate neurotransmitter imbalance and the hyperactivation of the amygdala. Additionally, a specific type of exposure therapy called eye movement desensitization and reprocessing (EMDR) combines with SSRIs to reduce arousal. EMDR is a specific therapeutic technique that allows the patient to envision their traumatic experience while focusing on a therapist's finger or hand (Corey, 2018). This approach also encompasses relaxation and breathing techniques. Despite the treatments used, about 20-30% of patients report a remission of symptoms (Shishko et al., 2018). This finding has led to an increased interest in cannabis and the endocannabinoid system.

Epilepsy

Epilepsy is a prevalent neurological disorder characterized by transient disruptions in the brain (Leo et al., 2016). Typically, it is a condition that causes spontaneous yet frequent seizures due to glutamate hyperexcitability (Leo et al., 2016). Due to the number and severity of seizures, many patients will suffer from cognitive and behavioral abnormalities.

Epilepsy affects about 65 million people worldwide (Ong et al., 2020). This approximation includes 0.6% of children under 18, and 82% of those children will be under age 10. The most deleterious childhood epilepsies are called developmental and epileptic encephalopathies (DEEs) (Ali et al., 2019). One specific type of DEE is Dravet Syndrome. Mutations of the SCN1A gene responsible for creating sodium channels in the brain are the primary cause of this syndrome (Ali et al., 2019). This condition usually affects children between the ages of three and fifteen months. Commonly, it manifests

itself as a generalized tonic-clonic seizure, a type of seizure that affects both sides of the brain and correlates with a fever (Ali et al., 2019). Additionally, patients by the age of five may suffer from focal seizures and status epileptics, which can cause intellectual and developmental incapacities (Ali et al., 2019). However, this syndrome has a high mortality risk due to persistent seizures leading to the status epilepticus (Miller et al., 2020).

Although some antiepileptic drugs and surgeries can reduce seizures, many patients have treatment-resistant epilepsy (TRE). Park & Linder 2020 expressed TRE as a patient having ≥ 4 countable seizures per month (28 days) for at least two consecutive months and a history of trying at least four different antiepileptic therapies to get their epilepsy in control (Park et al., 2020). TRE affects nearly 30% of epileptic patients (Mitelpunkt et al., 2019). Typical antiepileptic treatments (AEDs) include valproate and carbamazepine, a ketogenic diet, and vagal nerve stimulation (Park & Linder Article). Leo et al. 2016 noted that the old and new AEDs were only present with side effects and negatively influenced a patient's quality of life (Leo et al., 2016). Thus, scientists and researchers have taken great interest in the possible therapeutic effects of cannabis.

Cannabis may be helpful in the reduction of seizures due to its anticonvulsant activity. Leo et al. 2016 explained that cannabidiol might impact neuronal hyperexcitability by multiple mechanisms (Leo et al., 2016). These mechanisms include reducing the synaptic release of glutamate, activating serotonin receptors, and inhibiting the synaptic reuptake of norepinephrine, GABA, and dopamine. CBD directly affects the

seizure threshold by reducing seizure severity and frequency for more extended periods than typical AEDs (Dor & Ben-Zeev, 2020).

Cannabis

Cannabis is a derivative of the Cannabis sativa plant and is the most commonly used drug worldwide (Turna et al., 2017). Although many consumers use cannabis for its euphoric and relaxing effects, this schedule one controlled substance has many therapeutic potentials. These effects are a result of the hundreds of phytocannabinoids that have been isolated in this plant, with the primary two being delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the primary phytocannabinoid responsible for varied sensory reactions and euphoria (Rong et al., 2017). Researchers have also found that THC has anxiolytic and hypnotic effects that may help individuals with anxiety and anxiety-related disorders.

However, CBD is another psychoactive ingredient that differs in effects from THC. Anxiety disorders, chronic pain, and sleep disorders are among 4000 medical conditions that use cannabidiol (Bonaccorso et al., 2019). It differs in the psychoactive effects of THC, and many scientists have concluded that it can offset some neurobehavioral and cognitive effects of THC when both phytocannabinoids are administered together (Steenson & Chambers, 2019). Despite the differences between these phytocannabinoids, both of these ingredients act on the endocannabinoid system to exert their effects.

Endocannabinoid System

The endocannabinoid system consists of cannabinoid receptors, enzymes, and endogenous ligands. The two central receptors that THC and CBD bind to are cannabinoid type receptor-1 and receptor-2 (CB1 and CB2) (Rong et al., 2017). The CB1 receptor is primarily in the central nervous system. In contrast, the CB2 receptor is in immune cells throughout the body, mainly in the tonsils and spleen (Premoli et al., 2019). Since the 1960s, researchers have investigated the relationship between the endocannabinoid system and anxiety disorders. Viana et al. 2019 has discovered that if a compound (e.g., THC or CBD) inhibited the endogenous endocannabinoids, anandamide (AEA), and 2-arachidonoyl glycerol (2-AG), it would help to reduce anxious symptoms (Viana et al., 2019).

Nonetheless, researchers have found more information regarding the endocannabinoid system's effects in individuals with Post-Traumatic Stress Disorder. Shishko et al. 2018 discovered that patients with this trauma and worry-related disorder have an increase in CB1 receptors that are not bound to a biological compound (Shishko et al., 2018). However, stimulation of CB1 receptors in the hippocampus, amygdala, and prefrontal cortex will relieve anxiety in these patients. For example, the amygdala has been the most promising since CB1 receptors can decrease stress, unpleasant memories, and fear. Furthermore, if a ligand or drug activates the CB1 receptors in the hippocampus, Shishko et al. 2018 explained that an individual would have a reduction in disturbing memories, hyperarousal, and hypervigilance (Shishko et al., 2018). The hippocampus will also affect the hypothalamic-pituitary-adrenal axis (HPA) by

normalizing cortisol levels, reducing arousal in PTSD individuals. Hence, researchers indicate that CBT and exposure therapy reduce symptoms in anxiety and post-traumatic stress disorders. However, researchers hypothesize that THC and CBD can produce a more prolonged, sustained effect.

Brain imagining studies have shown that the inhibition of AEA and 2-AG accompanies a reduction of aversive stimuli in the hippocampus and the ventromedial cortex. There is a hypothetical mechanism between the hypothalamus and the endocannabinoid system involved in alleviating panic symptoms. The primary target of investigation includes activation of CB1 and CB2 receptors at the hypothalamus, which prevents the hypothalamic-pituitary-adrenal axis (HPA) activation (Hillard et al., 2011). Viana et al. 2019 concluded from a study in mice that when CB1 and CB2 receptors activate 2-arachidonoyl glycerol, a subsequent decrease occurs in panic-like symptoms (Viana et al., 2019). Therefore, these findings substantiate the need to explore further the pharmaceutical potential of cannabis in reducing anxiety and panic symptoms.

RESEARCH STRATEGIES

For this review, online library databases through Philadelphia College of Osteopathic Medicine were used, such as Academic Search Premier, Medline/PubMed, and ScienceDirect Journals. Keyword searches used were “medicinal cannabis,” “medicinal CBD,” “anxiety,” “PTSD,” and “epilepsy” for papers published between 2009 to 2021. These articles were read for subject matter appropriateness and then evaluated for summary of the topics.

REVIEW OF STUDIES ON CBD VS. CANNABIS ON ANXIETY, PTSD, AND EPILEPSY

Cannabidiol in Anxiety and Sleep: A Large Case Series

Anxious symptoms are often associated with sleep concerns. Shannon, Lewis, Lee, & Hughes 2019 issued a retrospective study investigating whether CBD helped improve patients' anxiety or sleep (Shannon et al., 2019). This study focused on the safety, tolerability, and acceptability of cannabidiol. One hundred and three adult patients began the study, but only 72 completed the research of which (n =25) had confirmed sleep or (n =47) anxiety disorder diagnosis. Many participants continued using other psychiatric medication, and the study lasted for three months.

Patients started on a 25 mg/d capsule of CBD, but many had an increase in dosage of 50 or 75 mg/d (Shannon et al., 2019). This increase occurred because of a rise in anxious symptoms or sleep complaints. Monthly, patients attended a clinic that measured their anxiety and sleep quality through two assessments, and a physical examination.

The first test was the Pittsburgh Sleep Quality Index. This exam computed sleep concerns and was a self-report that comprised a 19-item list with scores ranging from 0 to 21. A higher score designated a decrease in sleep quality. An additional test, the Hamilton Anxiety Rating Scale measured anxious symptoms with fourteen questions. The assessment ranged in score from 0 to 56. A score of 17 or below suggested mild anxiety, and a score beyond 25 revealed severe anxiety (Shannon et al., 2019).

Additionally, patient self-evaluations indicated tolerability and side effects of cannabidiol.

Throughout the three-month study, not all patients completed the three follow-ups due to normal research attrition. At the first check-in, all 72 patients completed the treatment and assessments. By the second and third follow-up, 41 (56.9%) and 27 (37.5%) patients continued the treatment process.

The summary of the results showed that sleep and anxiety symptoms decreased for the majority of patients. For example, at the first-month follow-up, 79.2% (57/72) improved their anxiety, and 6.7% (48/72) bettered their sleep quality (Shannon et al., 2019). At the second follow-up, 78.1% (32/41) and 56.1% (23/41) enhanced their anxiety and sleep concerns. Thus, investigators stated that CBD treatment produced consistent results, especially in the anxiety group. For the sleep group, researchers observed mild improvement. Nevertheless, CBD was accepted, tolerated, and had minor adverse effects. The main side effect reported was fatigue.

Consequently, this study was open-label and lacked a placebo group for comparison. Other limitations included the sustained use of other medication and psychotherapy, limiting the efficacy of cannabidiol. Finally, the length of the study only monitored the acute effects of cannabidiol.

Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test

Another diagnosable anxiety, social anxiety disorder/social phobia benefited from cannabidiol in single-dose studies (Bergmaschi et al., 2011). Hence, Linares et al. 2019

conducted a study that evaluated the acute effects of three diverse doses of cannabidiol versus placebo in participants in a simulated public speaking test (Linares et al., 2019). Fifty-seven male volunteers participated in the study and orally received cannabidiol (150,300, or 600 milligrams dissolved in corn oil) or placebo (corn oil) in a double-blind and randomized fashion.

Before the test, clinicians took the patient's heart rates and blood pressures for baseline comparison. Participants also completed the Visual Analogue Mood Scale (VAMS). The VAMS is a sixteen-item list that assessed anxiety, sedation, cognitive impairment, and distress (Linares et al., 2019). Then, patients received a single oral placebo dose or cannabidiol one hour and thirty minutes before the test. For the speech, volunteers had two minutes to prepare a four-minute speech about "the public transportation system of your city" (Linares et al., 2019). The investigators also told them that the address would be recorded and later examined by psychiatrists and psychologists.

Before the speech, researchers measured anticipatory anxiety. Each volunteer stood in front of a television and began speaking. During each oration, investigators interrupted participants in the middle to assess VAMS and blood pressure. Directly after the speech and thirty minutes later, researchers completed the VAMS and blood pressure again. The public speaking test outcome exhibited that acute doses of CBD decreased anxiety (Linares et al., 2019). In particular, the VAMS indicated a U-shaped dose-response curve. This curve meant that the lowest (150 mg) or highest (600 mg) doses of cannabidiol had a negligible effect on anxiety. In comparison, the 300 mg dose had the

lowest anxiety level during the speech (Linares et al., 2019). However, the study only included men and was the major limitation.

Acute effects of cannabinoids on symptoms of obsessive-compulsive disorder: A human laboratory study

Obsessive-Compulsive Disorder (OCD) is an anxiety-related disorder described as repeated unpleasant thoughts and cyclic behaviors that causes substantial functional impairment (Gremel et al., 2016). Preclinical studies showed that the endocannabinoid system may adjust compulsive activities through CB1 projections that extend from the orbitofrontal cortex to the striatum (Kayser, Reilly R. et al., 2020). Gremel et al. (2016) reported that this connection functions in habitual and goal-directed behaviors.

Therefore, Kayser & Haney 2020 directed a placebo-controlled study that evaluated the effects of smoke cannabis in various CBD and THC concentrations in adult patients with OCD (Kayser et al., 2020). Researchers theorized that CBD and THC would reduce OCD symptoms. The study initially involved fourteen patients that were either male or female, but only twelve completed the final analysis. All participants received three different cannabis variations throughout three laboratory visits. These variants were approximately 800 mg of cannabis that were either the placebo, CBD (0.4% THC, 10.4% CBD), and THC (7.0% THC, 0.18% CBD) (Kayser et al., 2020). During each visit, 50% of a cigarette was smoked. Researchers monitored OCD symptoms during each session by using the Yale-Brown Obsessive-Compulsive Scale (YBOCS). This assessment is a ten-item checklist that rates symptom severity. Patients also did self-assessments each time through the Obsessive-Compulsive Visual Analog Scale (OCD-VAS), Spielberger

State-Trait Anxiety Inventory (STAI-S), and the YBOCS-self assessment version (Kayser et al., 2020). The OCD-VAS measures severity of obsessions.

At the beginning of a visit, patients completed a toxicology report and learned how to smoke a THC cigarette. Specifically, investigators asked patients to inhale for five seconds, hold the smoke in for ten seconds, and exhale for forty seconds between puffs until smoking 50% of the cigarette (Kayser et al., 2020). After smoking, researchers measured heart rate, blood pressure, and self-evaluation of obsessions, compulsions, and anxiety at specific timepoints. These precise intervals were 20,40,60, 90, 120, and 180 minutes after smoking (Kayser et al., 2020).

Trial outcomes indicated a decrease in scores for the YBOCCS and STAI-S. Interestingly, minute 40 displayed that STAI-S scores were significantly lower for the placebo and THC treatment phases only. However, at minute 60 and after, the STAI-S scores were relatively similar for all treatment groups (Kayser et al., 2020). Cardiovascular results revealed that THC had an increase in heart rate and blood pressure. Nevertheless, there were no severe side effects, but the most commonly reported were dry mouth and apprehension.

Overall, this study had four discoveries. First, THC, as in other preclinical and clinical studies, had an increase in cardiovascular effects. Self-assessments signified that OCD and anxious symptoms decreased over time for all three treatment groups. CBD and THC did not have a significant difference in symptoms in comparison to placebo. Participants in the placebo group had a more substantial reduction in anxiety in the first 40 mins than CBD or THC inhalation (Kayser et al., 2020). Despite these findings, the

study had a small sample size, and the trial only assessed acute doses. The latter was because the study lasted approximately two months for each participant.

Cannabinoid Augmentation of Exposure-Based Psychotherapy for Obsessive-Compulsive Disorder

First-line treatments for OCD are serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy with a focus on exposure and response prevention (EX/RP) (Kayser et al., 2020). Thus, Kayser et al. 2020 performed a trial with nabilone, a THC synthetic form (Kayser, Reily et al., 2020). The clinical trial's goal was to measure the acceptability, tolerance, and efficacy of nabilone, either alone or in combination with EX/RP in OCD adult patients. The trial lasted four weeks and included eleven patients, ages 18-60.

Patients were randomized and placed in two groups. The first only received nabilone, and the second received nabilone with EX/RP. The nabilone prescription was 1 mg initially but decreased from 0.25 to 0.5 mg because of side effects (Kayser et al., 2020). Tablets were consumed orally and taken twice a day. The EX/RP therapy sessions lasted for 90 minutes weekly and included eight exposure sessions. During exposure, patients encountered feared stimuli without making it a compulsion. At baseline, week 2, and week 4, investigators rated OCD and depression/anxiety symptoms through the YBOCS and Depression Anxiety Stress Scale, respectively (Kayser et al., 2020). For the second treatment group, therapists assessed the progress of EX/RP by utilizing the Patient EX/RP Rating Scale. Furthermore, participants met with a physician weekly to measure heart rate, blood pressure, weight, and adverse medication effects. At week 8,

investigators asked the study sample to return to complete a final follow-up that addressed the previous measures.

Data analysis indicated a more significant decrease in symptoms for the nabilone treatment group with EX/RP. Additionally, there was no significant difference in the Depression Anxiety Stress Scale between the two groups. Altogether, investigators concluded that the study participants accepted and well-tolerated nabilone. The reason for this is the absence of severe adverse effects. However, patients reported disorientation, difficulty concentrating, and a dry mouth (Kayser et al., 2020).

Moreover, the researchers gathered another sample with 21 patients who only participated in EX/RP. Investigators discovered that the amount of change in the nabilone plus EX/RP was twice as significant as EX/RP alone, which the YBOCS detected. The effects continued for another month after the study.

Conversely, this study had shortcomings. It had a minute sample size and lacked a control/placebo group for comparison. Finally, researchers noted that a larger clinical trial must occur to determine nabilone's efficacy.

Cannabidiol in the Treatment of Post-Traumatic Stress Disorder: A Case Series

In 2018, Elms et al. published a retrospective chart review to see if PTSD adult patients treated with cannabidiol had symptom reduction (Elms et al., 2019). Additionally, the objective of the study analyzed the tolerance and efficacy of cannabidiol. The review lasted for eight weeks and included eleven patients. After the preliminary evaluation, researchers distributed the Post-Traumatic Stress Disorder Checklist (PLC-5) for patients to complete every four weeks. The PLC-5 is an assessment

that physicians and scientists use to determine a patient's PTSD symptom severity. There are a total of 20 questions, with the highest score equating to eighty. Although any score on this exam confirms that a patient has PTSD, the study patients all received a baseline score of at least 33. This score indicates that they would likely benefit from treatment (Elms et al., 2019).

Besides cannabidiol, many patients continued to receive psychiatric medication and psychotherapy. Medications encompassed mood stabilizers, anxiolytics, antidepressants, stimulants, and nearly 75% of patients engaged in cognitive behavioral therapy. Nonetheless, patients obtained cannabidiol in an oral liquid spray or oral capsule. The capsules contained 22-28 mg of cannabidiol, while the liquid spray contained 425 to 575 mg of CBD, with approximately 1.5 mg of CBD per spray (Elms et al., 2019). Researchers informed patients about taking cannabidiol once or twice per day, based on their symptom severity. Thus, the median dose daily for the capsule was 25 mg and 9 mg for the liquid spray (Elms et al., 2019).

Results exhibited a baseline average score of 51.82 on the PLC-5. Nevertheless, after four weeks of treatment, ninety-one percent of patients reported a 21% decrease, 51.82 to 40.73 (Elms et al., 2019). At eight weeks, nearly 75% (73%) had an even more significant reduction in their symptoms which was 9%, and the PLC-5 indicated a new score of 37.14. During the four to eight-week period, half of the patients described an improvement in their nightmare since starting their cannabidiol dosage (Elms et al., 2019). Besides, 38% of the sample conveyed that the quality of their sleep improved.

This improvement meant that CBD resulted in patients having a better mood, increased focus, and decreased anxiety (Elms et al., 2019).

These studies indicated that patients had an overall reduction in their PTSD symptoms in two months, as evaluated by the PLC-5. Moreover, investigators did not find a difference between those taking the oral capsule or liquid spray. This study pointed out that not only does cannabidiol help reduce PTSD symptoms such as intrusive memories of traumatic experiences and an increased level of arousal, but it also reduced nightmares. CBD did not exacerbate or minimize side effects seen with other medications. The study's shortcomings included a lack of an exact CBD dose for all patients and a small sample size that was predominantly female (Elms et al., 2019).

Experiences with medical cannabis in the treatment of veterans with PTSD: Results from a focus group discussion

There are several anecdotal reports and focus groups that describe the relationship between PTSD and medicinal cannabis. Focus groups are beneficial for researchers because they allow them to draw conclusions about cannabis as a therapeutic and apply them to a larger population. For example, in 2018, the Netherlands Military Mental Health Service produced a qualitative focus group study that observed the opinion and experience of PTSD symptomatology (Krediet et al., 2020).

Ten veterans diagnosed with chronic PTSD and recurrent insomnia and nightmares participated in a focus group. They were treated by a psychiatrist on-site, and the study lasted for two hours. The psychiatrist, psychologist-researcher, and pharmacist-researcher monitored the discussion. During the talk, the veterans mostly conversed about

the use, administration, and effect of medical cannabis. Also, they discussed the comparison of medical cannabis with other psychiatric medications, the stigma of medicinal cannabis, and its availability. The results revealed that the study sample was all-male, and they were between the ages of 42 and 66 (Krediet et al., 2020). All of the patients had various prescriptions of cannabis strains with different ratios of tetrahydrocannabinol and cannabidiol. There was no exact administration route, but many administered it sublingually (Krediet et al., 2020).

In the beginning, patients first discussed their experience with previous treatments. Most were in agreement that other medications resulted in symptoms severity remaining the same and several adverse effects. Examples of side effects were stomach pain, drunkenness, and liver problems. Some were hesitant to start a prescription in terms of stigma because of drug abuse worries and getting “high.” Many of the times, this perception originated from childhood where patients encountered family members using it recreationally. Thus, patients never considered cannabis having medicinal effects.

In terms of therapeutic effects, participants conveyed an increase in sleep quality and relaxation while experiencing a reduction in nightmares and anger (Krediet et al., 2020). Additionally, participants had less pain with headaches, and many did not suffer from any adverse effects. Therefore, some patients discontinued their mood stabilizers and antidepressants.

Conversely, the research had a small sample and lacked an exact dosage. However, this focus group indicated a span of therapeutic effects. Researchers also witnessed that many patients took medical cannabis with a higher quantity of CBD than

THC. Lastly, depending on symptom severity duration, patients either took their prescription before going to sleep or during the day.

Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs. Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial

In 2016, Miller & Ingrid performed a clinical trial to discuss the efficacy and safety of cannabidiol in children with Dravet syndrome (Miller et al., 2020). This trial was a "multicenter double-blind, randomized, placebo-controlled, parallel-group" that involved 198 patients from 43 clinical centers (Miller et al., 2020). This 34-week study consisted of a four-week baseline period, followed by a 14-week treatment period, resulting in 12 weeks of stable dosing and a four-week follow-up period.

For patients to be involved in the study, they had to be between the ages of two and eighteen and have at least four uncontrollable seizures during the four-week baseline period. Caregivers recorded these seizures at their first visit with the Independent Epilepsy Study Consortium. Once patients met the criteria, they returned for a second visit where they either received a placebo or highly purified cannabidiol, which were both supplied in 100 mL amber glass bottles (Miller et al., 2020). The trial's medication was given out twice daily for the placebo group, and the two treatment groups reached either 10 (CBD10) or 20 (CBD20) mg/kg per day. The trial started with two divided doses starting at 2.5 mg/kg/d. It then increased to 10 mg/kg/d on day seven and finally a 20 mg/kg/d dose on the eleventh day.

The trial had two significant outcomes. The first was to observe the change in sudden seizure frequency during the 14-week treatment period compared to the starting

point. Additionally, researchers were looking for changes in all seizure frequency during the treatment period, the proportion of patients with at least 50% reduction from baseline, and an overall score change in the Caregiver Global Impression of Change (CGIC) (Miller et al., 2020). The CGIC measures a difference in patient severity, which the caregiver rates on a scale from 1-7, with 1 indicating extreme improvement.

The trial results showed that within the primary outcome, the percentage reduction from baseline in convulsive seizures for the 10 mg/kg/d was 48.7. The 20mg/kg/d group and the placebo group had 45.7% and 26.9% reductions, respectively (Miller et al., 2020). Also, secondary outcome results illustrated that there was 56.4%, 47.3%, and 26.2% decreases in total seizures of the CBD10, CBD20, and placebo group (Miller et al., 2020). The percentage of patients achieving at least a 50% reduction from baseline in seizure frequency was 26.2% for the placebo group. The treatment groups had a more significant increase, 43.9%, and 49.3%, for CBD10 and CBD20 groups (Miller et al., 2020).

Despite the therapeutic effects of cannabidiol in the patients, nearly 89% of them suffered from adverse effects (AEs). The five most popular AEs were fatigue, diarrhea, decreased appetite, somnolence, and a high fever (Miller et al., 2020).

Thus, this randomized clinical trial showed that both prescriptions of cannabidiol considerably decreased convulsive seizures compared to the placebo group. However, there were a few limitations to the study. These drawbacks included patients under the age of 18, a report that lacked long-term results, and a shortage of diversity within patients' ethnicities since approximately 90% of the study sample were Caucasian.

Long-term safety and efficacy of highly purified cannabidiol for treatment-refractory epilepsy

In 2019, Gaston et al. performed an open-label study that assessed the quality of life in children and adults in Alabama with TRE for one year (Gaston et al., 2021). After researchers determined that eighty patients fell under the inclusion criteria, they started their cannabidiol dosage. The initial prescription was 5 mg/kg/day, with the dose increasing every two weeks by the addition of 5 mg/kg/day (Gaston et al., 2021).

Furthermore, researchers also incorporated three different questionnaires called the QOLIE-89, POMS, and the AEP recorded at the beginning and end of the treatment phase. The QOLIE-89 is an assessment that tests the quality of life in epilepsy. If there was a 10-point change, scientists considered it to be clinically significant. POMS tested six moods: anxiety, depression, anger, vigor, fatigue, and confusion (Gaston et al., 2021). Finally, the AEP was a survey that examined adverse events.

However, the most important outcome that researchers studied was seizure frequency and severity. Before the treatment period, caregivers or patients completed a seizure calendar for three months. Once the study started, patients were required to visit researchers nearly every two weeks. During the biweekly visits, clinicians used the Chalfont Seizure Severity Scale (CSSS) to measure seizure severity. Precisely, the CSSS measures the unsettling aspects of seizures: the length of the seizure, the amount of time it takes to return to baseline, and any related injuries (Gaston et al., 2021). A higher score correlated with an increase in seizure severity and a ten-point improvement designated clinical significance.

After a year, researchers discovered clinically significant improvements in total seizure count, QOLIE-89, POMS, and AEP scores. For example, the QOLIE-89 score at the start of the study was 49.4, and it increased to 57 (Gaston et al., 2021). Although the improvement was not exactly ten points, researchers observed clinically and statistically significant improvements. Conversely, there was a negative correlation between the POMS score and mood.

Moreover, at the start of research analysis, 28.3% of patients had more than fifty seizures every two weeks, but at one year, only 13.2% remained at that amount (Gaston et al., 2021). Approximately 30% of the sample had 14-50 seizures every two weeks before treatment, and now only 24.5% have that same amount a year later. Finally, 41.5% of patients had < 14 seizures/2 weeks at the beginning of the study, and now over half, 62.3%, have this quantity at follow-up (Gaston et al., 2021). These changes were significant as the CSSS score decreased from 80.9 to 28.9, which signified clinical efficacy.

Altogether, researchers concluded that cannabidiol treatment demonstrated clinically significant results in seizure severity, frequency, and duration. Nonetheless, the medication increased mood, which directly led patients to document that their quality of life increased overall (Gaston et al., 2021). Despite the success of the treatment plan, the study was an open-label trial. Thus, the lack of a placebo or control group did not allow researchers to fully understand the effectiveness of cannabidiol in terms of seizure severity and frequency, quality of life, mood, and unfavorable side effects.

Cognitive function and adaptation skills after a one-year trial of cannabidiol (CBD) in a pediatric sample with treatment-resistant epilepsy

Additionally, behavioral effects in TRE patients require testing. In 2019, Thompson et al. analyzed a study that observed functional or cognitive effects in TRE pediatric patients using cannabidiol as a remedy for one year (Thompson et al., 2020). Participants in the study ranged in age from 3 to 19 years old and began taking 5 mg/kg/day of Epidiolex (CBD) split into two doses taken during the morning and evening. Hence, the study sample took their Epidiolex at the same time as their antiepileptic treatments.

The NIH Toolbox Cognition Battery (NIHTB-CB) assessed the cognitive functioning of patients. Notably, this exam measures participants' sensory, motor, mental, and emotional function by looking at brain functions such as attention, memory, executive functioning, and language (Thompson et al., 2020). Researchers implemented the Adaptive Behavior Assessment System- Second Edition (ABAS-II) that examined functional status by looking at three domains: practical, social, and conceptual. Practical evaluated self-care and home living skills. Social assessed engagement in leisure and social behaviors and conceptual was the caregiver's rating of the patient's ability to function in communication and academic environments (Thompson et al., 2020).

Though the open-label study commenced with 87 children, only 38 completed assessments at the beginning and follow-up. Researchers determined an insignificant change in cognition and functional adaptive skills, but there was an overall improvement in life quality (Thompson et al., 2020). This development is due to cannabidiol's

effectiveness in decreasing seizure frequency. Additionally, researchers concluded that cannabidiol did not cause any adverse effects that affected cognitive function. However, drawbacks for this research included a smaller number of patients. Besides, some participants could not take the NIHTB-CB because they had nonverbal impairments (Thompson et al., 2020). Therefore, caregivers rated those patients using the ABAS-II solely.

RECOMMENDATIONS FOR FUTURE STUDIES

Researchers are currently implementing clinical tests with larger samples to address medicinal cannabis's effects on anxiety disorders, PTSD, and epilepsy. For instance, in April 2021, at McMaster University in Hamilton, Ontario, Canada, investigators estimated that they would begin an eight-week randomized, placebo-controlled trial to evaluate the effects of CBD in generalized and social anxiety disorder, panic disorder, and agoraphobia (Van Ameringen et al., 2020).

Specifically, clinical trials need to have an extended treatment period. The majority of studies in this review lasted for less than a year, which limited the efficacy of cannabidiol. However, this could be partly due to adverse effects and lack of a safety profile for cannabis. In addition to this, many of the studies did not include a placebo group. It is hard to determine if cannabis is well-tolerated and accepted for a larger patient population without a group for comparison.

In the future, studies should observe if different routes of administration lead to various effects. Many patients in this literature review consumed treatments sublingually, but smoking or dermal creams may produce a faster or more long-term impact. Additionally, researchers should continue investigating different forms of cannabis and their effects. In the PTSD study with oral cannabidiol, investigators did not observe a difference in the liquid spray and capsule response. Still, an oral tablet or drinkable liquid could produce diverse effects.

Moreover, researchers need to continue investigating an effective dose that can apply to a multitude of patients. In the Dravet Syndrome study, researchers found that both prescriptions, 10 and 20 mg/day were efficacious. Yet, lower dosages may be more effective when used with routine medication, leading to reduced symptoms and improved quality of life.

REFERENCES

1. Abizaid, A., Merali, Z., & Anisman, H. (2019). Cannabis: A potential efficacious intervention for PTSD or simply snake oil? *Journal of Psychiatry & Neuroscience, 44*(2), 75-78. 10.1503/jpn.190021
2. Ali, S., Scheffer, I. E., & Sadleir, L. G. (2019). Efficacy of cannabinoids in pediatric epilepsy. *Developmental Medicine & Child Neurology, 61*(1), 13-18. 10.1111/dmcn.14087
3. Arnold, J. C. (2020). Prescribing medicinal cannabis
4. Bahji, A., Meyyappan, A. C., & Hawken, E. R. (2020). Efficacy and acceptability of cannabinoids for anxiety disorders in adults: A systematic review & meta-analysis. *Journal of Psychiatric Research, 129*, 257-264. 10.1016/j.jpsychires.2020.07.030
5. Bergmaschi, M. M., COSTA QUEIROZ, R. H., MARTIN-SANTOS, R., CECILIO HALLAK, J. E., WALDO ZUARDI, A., CRIPPA, J. A. S., NISIHARA CHAGAS, M. H., GOMES DE OLIVEIRA, Danielle Chaves, SPINOSA DE MARTINIS, B., KAPCZINSKI, F., QUEVEDO, J., ROESLER, R., SCHRÖDER, N., & NARDI, A. E. (2011). Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients. *Neuropsychopharmacology (New York, N.Y.), 36*(6), 1219-1226. 10.1038/npp.2011.6
6. Bonaccorso, S., Ricciardi, A., Zangani, C., Chiappini, S., & Schifano, F. (2019). Cannabidiol (CBD) use in psychiatric disorders: A systematic review. *Neurotoxicology, 74*, 282-298. 10.1016/j.neuro.2019.08.002
7. Corey, G. (2018). Theory and Practice of Counseling and Psychotherapy (10th ed.). Cengage Learning.
8. Dor, M., & Ben-Zeev, B. (2020). *Medical Cannabis for Intractable Epilepsy in Childhood: A Review*. Rambam Health Corporation. 10.5041/rmmj.10387
9. Elms, L., Shannon, S., Hughes, S., & Lewis, N. (2019). Cannabidiol in the Treatment of Post-Traumatic Stress Disorder: A Case Series. *Journal of Alternative & Complementary Medicine, 25*(4), 392-397. 10.1089/acm.2018.0437
10. Gaston, T. E., Ampah, S. B., Martina Bebin, E., Grayson, L. P., Cutter, G. R., Hernando, K., & Szaflarski, J. P. (2021). *Long-term safety and efficacy of highly purified cannabidiol for treatment-refractory epilepsy*. Elsevier BV. 10.1016/j.yebeh.2021.107862
11. Gremel, C., Chancey, J., Atwood, B., Luo, G., Neve, R., Ramakrishnan, C., Deisseroth, K., Lovinger, D., & Costa, R. (2016). Endocannabinoid Modulation of Orbitostriatal Circuits Gates Habit Formation. *Neuron (Cambridge, Mass.), 90*(6), 1312-1324. 10.1016/j.neuron.2016.04.043
12. Hillard, C. J., Weinlander, K. M., & Stuhr, K. L. (2011). Contributions of endocannabinoid signaling to psychiatric disorders in humans: genetic and

biochemical evidence. *Neuroscience*, *204*, 207-229. 10.1016/j.neuroscience.2011.11.020

13. Kayser, R. R., Haney, M., Raskin, M., Arout, C. C., & Simpson, H. B. (2020). *Acute effects of cannabinoids on symptoms of obsessive-compulsive disorder: A human laboratory study*. Wiley. 10.1002/da.23032

14. Kayser, R., Raskin, M., Snorrason, I., Hezel, D., Haney, M., & Simpson, H. B. (2020). Cannabinoid Augmentation of Exposure-Based Psychotherapy for Obsessive-Compulsive Disorder., 207-210. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7206660/

15. Krediet, E., Janssen, D. G., Heerdink, E. R., Egberts, T. C., & Vermetten, E. (2020). Experiences with medical cannabis in the treatment of veterans with PTSD: Results from a focus group discussion. *European Neuropsychopharmacology*, *36*, 244-254. https://doi.org/10.1016/j.euroneuro.2020.04.009

16. Leo, A., Russo, E., & Elia, M. (2016). Cannabidiol and epilepsy: Rationale and therapeutic potential. *Pharmacological Research*, *107*, 85-92. https://doi.org/10.1016/j.phrs.2016.03.005

17. Linares, I. M., Zuardi, A. W., Pereira, L. C., Queiroz, R. H., Mechoulam, R., Guimarães, F. S., & Crippa, J. A. (2019). *Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test*. FapUNIFESP (SciELO). 10.1590/1516-4446-2017-0015

18. Markle, M., & Nativio, D. G. (2019). Medical Marijuana in the Pediatric Population With Epilepsy—What You Should Know. *Journal of Pediatric Health Care*, *33*(6), 626-632. https://doi.org/10.1016/j.pedhc.2019.03.002

19. Martin, E. I., PhD, Ressler, Kerry J., MD, PhD, Binder, Elisabeth, MD, PhD, & Nemeroff, Charles B., MD, PhD. (2009). The Neurobiology of Anxiety Disorders: Brain Imaging, Genetics, and Psychoneuroendocrinology. *The Psychiatric Clinics of North America*, *32*(3), 549-575. 10.1016/j.psc.2009.05.004

20. *Medical Marijuana Patient and Caregiver Resources* . (2016). Pennsylvania Department of Health. https://www.health.pa.gov/topics/programs/Medical%20Marijuana/Pages/Patients.aspx

21. Miller, I., Scheffer, I. E., Gunning, B., Sanchez-Carpintero, R., Gil-Nagel, A., Perry, M. S., Saneto, R. P., Checketts, D., Dunayevich, E., & Knappertz, V. (2020). Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs. Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. *JAMA Neurology*, *77*(5), 613-621. 10.1001/jamaneurol.2020.0073

22. Mitelpunkt, A., Kramer, U., Hausman Kedem, M., Zilbershot Fink, E., Orbach, R., Chernuha, V., Fattal-Valevski, A., Deutsch, L., Heffetz, D., & Sacks, H. (2019). The safety, tolerability, and effectiveness of PTL-101, an oral cannabidiol formulation, in pediatric intractable epilepsy: A phase II, open-label, single-center study. *Epilepsy & Behavior*, *98*(Pt A), 233-237. 10.1016/j.yebeh.2019.07.007

23. Mostafavi, M., & Gaitanis, J. (2020). Autism Spectrum Disorder and Medical Cannabis: Review and Clinical Experience. *Seminars in Pediatric Neurology, 35*, 100833. 10.1016/j.spen.2020.100833

24. Ong, K. S., Carlin, J. B., Fahey, M., Freeman, J. L., Scheffer, I. E., Gilman, L., Anderson, M., Huque, M. H., Legge, D., Dirnbauer, N., Lilley, B., Slota-Kan, S., & Cranswick, N. (2020). Protocol for a single patient therapy plan: A randomized, double-blind, placebo-controlled N-of-1 trial to assess the efficacy of cannabidiol in patients with intractable epilepsy., 1918-1923. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7820972/pdf/JPC-56-1918.pdf

25. Park, Y. D., Linder, D. F., Pope, J., Flamini, J. R., Moretz, K., Diamond, M. P., & Long, S. A. (2020). Long-term efficacy and safety of cannabidiol (CBD) in children with treatment-resistant epilepsy: Results from a state-based expanded access program. *Epilepsy & Behavior, 112*, 107474. 10.1016/j.yebeh.2020.107474

26. Premoli, M., Aria, F., Bonini, S. A., Maccarinelli, G., Gianoncelli, A., Pina, S. D., Tambaro, S., Memo, M., & Mastinu, A. (2019). Cannabidiol: Recent advances and new insights for neuropsychiatric disorders treatment. *Life Sciences, 224*, 120-127. 10.1016/j.lfs.2019.03.053

27. Rong, C., Lee, Y., Carmona, N. E., Cha, D. S., Ragguett, R., Rosenblat, J. D., Mansur, R. B., Ho, R. C., & McIntyre, R. S. (2017). Cannabidiol in medical marijuana: Research vistas and potential opportunities. *Pharmacological Research, 121*, 213-218. 10.1016/j.phrs.2017.05.005

28. Shannon, S., Lewis, N., Lee, H., & Hughes, S. (2019). Cannabidiol in Anxiety and Sleep: A Large Case Series. *Permanente Journal, 23*, 18-041. 10.7812/TPP/18-041

29. Shannon, S., & Opila-Lehman, J. (2016). Effectiveness of cannabidiol oil for pediatric anxiety and insomnia as part of post-traumatic stress disorder: a case report. *Permanente Journal, 20*(4), 16-005. 10.7812/TPP/16-005

30. Shishko, I., Oliveira, R., Moore, T. A., & Almeida, K. (2018). A review of medical marijuana for the treatment of post-traumatic stress disorder: Real symptom re-leaf or just high hopes? *The Mental Health Clinician, 8*(2), 86-94. 10.9740/mhc.2018.03.086

31. *State Medical Marijuana Laws.* (2020). National Conference of State Legislatures. https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

32. Steenson, S., & Chambers, L. (2019). Cannabidiol: A budding industry! *Nutrition Bulletin, 44*(3), 228-240. 10.1111/nbu.12395

33. Thompson, M. D., Martin, R. C., Grayson, L. P., Ampah, S. B., Cutter, G., Szaflarski, J. P., & Bebin, E. M. (2020). Cognitive function and adaptive skills after a one-year trial of cannabidiol (CBD) in a pediatric sample with treatment-resistant epilepsy. *Epilepsy & Behavior, 111*, 107299. 10.1016/j.yebeh.2020.107299

34. Turna, J., Patterson, B., & Ameringen, M. (2017). Is cannabis treatment for anxiety, mood, and related disorders ready for prime time? *Depression & Anxiety (1091-4269), 34*(11), 1006-1017. 10.1002/da.22664

35. Turna, J., Simpson, W., Patterson, B., Lucas, P., & Van Ameringen, M. (2019). Cannabis use behaviors and prevalence of anxiety and depressive symptoms in a cohort of Canadian medicinal cannabis users. *Journal of Psychiatric Research, 111*, 134-139. 10.1016/j.jpsychires.2019.01.024

36. Van Ameringen, M., Zhang, J., Patterson, B., & Turna, J. (2020). The role of cannabis in treating anxiety: An update. *Current Opinion in Psychiatry, 33*(1), 1-7. 10.1097/YCO.0000000000000566

37. Viana, T. G., Bastos, J. R., Costa, R. B., Hott, S. C., Mansur, F. S., Coimbra, C. C., Resstel, L. B., Aguiar, D. C., & Moreira, F. A. (2019). Hypothalamic endocannabinoid signaling modulates aversive responses related to panic attacks. *Neuropharmacology, 148*, 284-290. 10.1016/j.neuropharm.2019.01.022

38. Wilsey, B. (2018). *Effects of Vaporized Marijuana on Neuropathic Pain* . (). https://www.clinicaltrials.gov/ct2/show/results/NCT01037088?term=medical+cannabis&recrs=e&draw=2&rank=27