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Review Article Journal of Neurology, Psychiatry and Brain Research JNPBR-126
ISSN: 2641-7049

PTSD or Clinical Endocannabinoid Deficiency?

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Received Date: 31 March, 2019**; Accepted Date:** 10 April, 2019; **Published Date:** 19 April, 2019

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Abstract

Objective: A literature review was conducted supporting the theory of clinical endocannabinoid deficiency as it relates to PTSD together with a review on how to treat PTSD with medical cannabis.

Background: Posttraumatic stress disorder (PTSD) is a psychiatric disorder that can occur in people who have experienced or witnessed a traumatic event such as a natural disaster, a serious accident, a terrorist act, war/combat, rape or other violent personal assault.

The following statistics are based on the U.S. population:

- About 7 or 8 out of every 100 people (or 7-8% of the population) will have PTSD at some point in their lives.
- About 8 million adults have PTSD during a given year. This is only a small portion of those who have gone through a trauma.
- About 10 of every 100 women (or 10%) develop PTSD sometime in their lives compared with about 4 of every 100 men (or 4%).

In the United States, New Mexico was the first state to list post-traumatic stress disorder (PTSD) as a condition for the use of medical cannabis. In a study published in Journal of Psychoactive Drugs, there was greater than 75% reduction in Clinician Administered Posttraumatic Scale for DSM-IV (CAPS) and it was concluded that Cannabis is associated with reductions in PTSD symptoms in some patients. Approximately 15% of US Veterans who are treated in Department of Veterans Affairs (VA) outpatient PTSD clinics report recent (past 6 months) cannabis use.

The theory of clinical endocannabinoid deficiency (CED) was presented in 2001 in two publications, but more thoroughly explored in 2004 in an article that has subsequently been cited frequently in the literature, it is based on the concept that many brain disorders are associated with neurotransmitter deficiencies, affecting acetylcholine in Alzheimer's disease, dopamine in parkinsonian syndromes, serotonin and norepinephrine in depression, and that a comparable deficiency in endocannabinoid levels might be manifest similarly in certain disorders that display predictable clinical features as sequelae of this deficiency.

Design/Methods: A literature review was conducted of the National Center for Biotechnology Information, U.S. National Library of Medicine PubMed from 2001-2019 specific to the topic of PTSD and Clinical Endocannabinoid Deficiency.

Conclusion: This literature review supports the feasibility of cannabis-based medicine as a promising treatment option in individuals with PTSD. Based on the promising results, it is recommended that large, double blind, placebo controlled cross-over trials be launched in jurisdictions where medical cannabis can be studied without limitations from the federal government.

Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that can occur in:

- People who have experienced or witnessed a traumatic event such as a natural disaster, a serious accident, a terrorist act, war/combat, rape or other violent personal assault **[1]**.

- People who have a variant of the FKBP5 gene, which is associated with changes in the body's normal response to stress as well as anxiety, depression and PTSD **[2]**.
- People who are subjects of transgenerational trauma, which is trauma that is transferred from the first generation of trauma survivors to the second and further generations of survivors via complex post-traumatic stress disorder mechanisms **[3]**.

Epidemiology

About 8 million adults have PTSD during a given year. This is only a small portion of those who have gone through a trauma. With approximately 7 or 8 out of every 100 people (or 7-8% of the population) having PTSD at some point in their lives and broken down by gender, about 10 of every 100 women (or 10%) develop PTSD sometime in their lives compared with about 4 of every 100 men (or 4%) **[4]**.

In a study comparing the prevalence of PTSD among veterans from the Vietnam War (theatre and non-theatre), the Gulf War (Desert Storm) and Operations Iraqi Freedom (OIF) and Operations Enduring Freedom (OEF), revealed the following:

- Vietnam War Theatre Veterans (men and women who served on active duty in Vietnam, Laos, or Cambodia): Males = 30.9% and Females = 26.9% **[5]**.
- Vietnam War Veterans: Males = 15.2% and Females = 8.1%
- Gulf War (Desert Storm):12% in a given year
- Operations Iraqi Freedom (OIF) and Operations Enduring Freedom (OEF):11%-20% in a given year **[6]**.

In 2014, it was found that Vietnam-era Veterans with PTSD have diminished functioning and increased disability **[7]**. This poor functional status of aging combat-exposed Veterans is of particular concern to not only the veterans, but their spouses, family members and society as a whole!

About 4% of children under age 18 are exposed to some form of trauma in their lifetime that leads to post-traumatic stress disorder and according to the National Institute of Mental Health (NIMH), of those children and adolescents who have experienced trauma, about 7% of girls and 2% of boys are diagnosed with PTSD **[8]**.

PTSD and Suicide

According to the Centers for Disease Control and Prevention (CDC) Leading Causes of Death Reports, in 2016 **[9]**:

- Suicide was the tenth leading cause of death overall in the United States, claiming the lives of nearly 45,000 people.
- Suicide was the second leading cause of death among individuals between the ages of 10 and 34, and the fourth leading cause of death among individuals between the ages of 35 and 54.
- There were more than twice as many suicides (44,965) in the United States as there were homicides (19,362).
- The rates of suicide attempts increased considerably among people who had experienced multiple incidents of sexual (42.9%) or physical assault (73.5%). They also found that a history of sexual molestation, physical abuse as a child, and neglect as a child were associated with high rates of suicide attempts (17.4% to 23.9%). People with a diagnosis of PTSD are also at greater risk to attempt suicide. Among people who have had a diagnosis of PTSD at some point in their lifetime, approximately 27% have also attempted suicide **[10]**.

Conventional Treatment for PTSD

Conventional treatment can be divided in two areas, trauma-focused psychotherapies and medications **[11]**. The trauma-focused psychotherapies include:

- Prolonged Exposure (PE)
- Cognitive Processing Therapy (CPT)
- Eye-Movement Desensitization and Reprocessing (EMDR) **[12-15]**.

Prolonged Exposure (PE) teaches the client how to gain control by facing their negative feelings. It involves talking about their trauma with a provider and doing some of the things they [the client] have avoided since the trauma. Cognitive Processing Therapy (CPT) teaches the client to reframe negative thoughts about the trauma. It involves talking with their provider about their negative thoughts and doing short writing assignments. And, Eye-Movement Desensitization and Reprocessing (EMDR) helps the client process and make sense of their trauma. It involves calling the trauma to mind while paying attention to a back-and-forth movement or sound (like a finger waving side to side, a light, or a tone).

The classes of medications typically used to manage/treat individuals with PTSD include, but are not limited to:

- SSRIs (selective serotonin reuptake inhibitors)
- SNRIs (serotonin-norepinephrine reuptake inhibitors)
- Benzodiazepines **[16].**

Examples of selective serotonin reuptake inhibitors include Sertraline (Zoloft), Fluoxetine (Prozac) and Paroxetine (Paxil) and examples of serotonin-norepinephrine reuptake inhibitors include Venlafaxine (Effexor) and Cymbalta (Duloxetine). Benzodiazepines include Alprazolam (Xanax), Clonazepam (Klonopin), Diazepam (Valium), Lorazepam (Ativan) and Temazepam (Restoril).

Cost for Conventional Treatment

The United States Veterans Administration's cost of treating patients with PTSD alone averaged $8,300 the first year and $20,200 over 4 years, these average out to a treatment cost of almost $14/day over the four-year period, and a cost of almost $10.50/day by the end of year four. In total, it is estimated that the VA spent over $1.4 billon treating PTSD-diagnosed patients between 2004–2009.Extrapolating the same level of treatment to the general population would yield an eye-opening estimated treatment cost in excess of $66 billion for the first year alone, and over $166 billion over a four-year period **[17]**.

Cannabis, Cannabinoids, the Endocannabinoid System and Medical Cannabis

Cannabaceae is a small family of flowering plants **[18-20]** consisting of 170 species grouped under 11 genera, including Cannabis (hemp, marijuana), Humulus (hops) and Celtis (hack-berries) **[21]**. Various types of Cannabishave been described and classified as species (C. *sativa*) **[22,23]**, subspecies (*C. sativa*, *C. indica*, *C. ruderalis*) **[24]**, or varieties: **[25]** known as low- intoxicant (non-drug type), high- intoxicant (drug type) and hybridized form of any of the aforementioned types. *Cannabis* plants produce a unique family of terpenophenolic compounds called cannabinoids, some of which produce the "high/euphoria" which may be experienced from consuming a subspecies of cannabis. There are 483 identifiable chemical constituents known to exist in the cannabis plant **[26]**, and at least 85 different cannabinoids have been isolated from the plant **[27]**. The two cannabinoids usually produced in abundance are cannabidiol (CBD) and/or Δ^9-tetrahydrocannabinol (THC), but only THC is psychoactive **[28]**.

Cannabis plants are categorized by their chemical phenotype or "Chemotype", based on the overall amount of THC produced, and on the ratio of THC to CBD **[29]**. Although overall canna- binoid production is influenced by environmental factors, the THC/CBD ratio is genetically determined and remains fixed throughout the life of a plant **[30]**. Non-drug plants produce relatively low levels of THC and high levels of CBD, while drug plants produce high levels of THC and low levels of CBD. The *Cannabis plant* has a history of medicinal use dating back thousands of years in many cultures **[31]**. Medical cannabis, is cannabis and cannabinoids that are recommended by physicians for their patients **[32]**. Studies suggest that medical cannabis therapy, as an adjunct to a traditional analgesic therapy, can be an efficacious tool to make more effective the management of chronic pain with proven functional and psychological benefits **[33-35]**. The use of cannabis as medicine has not been rigorously tested due to production restrictions and other governmental regulations **[36]**.

Limited evidence suggests that cannabis can reduce nausea and vomiting during chemotherapy, improve appetite in people with HIV/AIDS, and reduce chronic pain and muscle spasms **[37-39]**.

Being a pioneer in this area in the mid-1960, Dr. Raphael Mechoulam discovered the endocannabinoid system **[40]**. Endogenous cannabinoids (Anandamide, 2-Arachidonoylglycerol (2-AG), noladin ether, Virodhamine and N-arachidonoyl-dopamine (NADA)) **[41]**, are the chemicals our own bodies make to naturally stimulate the cannabinoid receptors (CB1, CB2 and non-CB1/CB2 aka GPR55). Physical, mental or emotional stressors support the endogenous production of cannabinoids. Years after this discovery, the theory of Clinical Endocannabinoid Deficiency (CED) was presented in 2001 in two publications, but more thoroughly explored in 2004 in an article that has subsequently been cited frequently in the literature with the greatest evidence for CED being for migraine, fibromyalgia, and irritable bowel syndrome (IBS) **[42]**. The theory of CED was based on the concept that many brain disorders are associated with neurotransmitter deficiencies, affecting acetylcholine in Alzheimer's disease, dopamine in Parkinsonian Syndromes, serotonin and norepinephrine in depression, and that a comparable deficiency in endocannabinoid levels might manifest similarly in certain disorders that display predictable clinical features as sequelae of this deficiency **[43]**. All humans possess an underlying endocannabinoid tone that reflects of levels of anandamide (AEA) and 2-arachidonoylglycerol (2-AG), the centrally acting endocannabinoids; their synthesis, cata-bolism, and the relative density of cannabinoid receptors in the brain. If endocannabinoid function were decreased, it follows that a lowered pain threshold would be operative, along with derangements of digestion, mood, and sleep among the almost universal physiological systems subserved by the endocannabinoid system (ECS) **[44]**.

Clinical Endocannabinoid Deficiency (CED) and PTSD

Subjects diagnosed with PTSD may experience a decrease in their natural production of anandamide, an endogenous cannabinoid neurotransmitter, resulting in an imbalance in the brain resulting in excessive fear and anxiety. "The data reported herein are the first of which we are aware of to demonstrate the critical role of CB1 (cannabinoid) receptors and endocannabinoids in the etiology of PTSD in humans," the study's authors concluded **[45]**.

Traumatized animals have exhibited reductions in hippocampal anandamide content with respect to the controls **[46]**. In a study measuring the circulating endocannabinoid levels in individuals with post-traumatic stress disorder following exposure to the World Trade Center attacks, showed that PTSD is associated with a reduction in circulating levels of the endocannabinoid (eCB) 2-AG. Given the role of 2-AG

in the regulation of the stress response, these data support the hypothesis that deficient eCB signaling may be a component of the glucocorticoid dysregulation associated with PTSD. The negative association between anandamide (AEA) levels and intrusive symptoms is consistent with animal data indicating that reductions in anandamide promote retention of aversive emotional memories **[47]**.

The data indicates that central anandamide levels predict acute stress-induced anxiety, and that reversal of stress induced anandamide deficiency is a key mechanism sub-serving the therapeutic effects of fatty acid amide hydrolase (FAAH) inhibition. This study provides further support that endocannabinoid-augmentation is a viable pharmacological strategy for the treatment of stress-related neuropsychiatric disorders **[48]**.

Researchers have proposed that a state of endocannabinoid deficiency could represent a stress susceptibility endophenotype predisposing to the development of trauma-related psychopathology and provide biologically plausible support for the self-medication hypotheses used to explain high rates of cannabis use in patients with trauma-related disorders **[49]**.

Preclinical research in endocannabinoid biology has neglected the influential role of sex hormone differences on PTSD symptomology, which is particularly important given that PTSD is twice as common in women as in men, as was discussed earlier. In a literature review, they compiled and considered the evidence that the endocannabinoid system is influenced by ovarian hormones, with application to stress disorders such as PTSD. It is clear that therapeutic modulation of the endocannabinoid system needs to be approached with awareness of ovarian hormonal influences, and knowledge of these influences may enhance treatment outcomes for female PTSD populations **[50]**.

For generations, it has been taught, not only in the United States, but also around the world that cannabis "has no medicinal value", however, upon highlighting the components of the endocannabinoid system, it was discovered that the eCB system offers potential 'druggable' targets for "new" anxiolytic medications providing a range of plausible paths to developing novel compounds that could prove useful for treating trauma-related and anxiety disorders **[51]**.

Medical Cannabis and PTSD in the United States

According to the Department of Veterans Affairs, over one-third of patients seeking cannabis for medical purposes list PTSD as the primary reason for the request **[52]**. And, approximately 15% of veterans who are treated in Department of Veterans Affairs outpatient PTSD clinics report recent (past 6 months) cannabis use **[53]**.

What state, in the US was the first state to list post-traumatic stress disorder as a condition for the use of medical cannabis? It was New Mexico, and being that it was the first to recognize PTSD as a qualifying condition for the use of medicinal cannabis, there has been considerable amount of data demonstrating that cannabis is associated with a greater than 75% reduction in the Clinician Administered Posttraumatic Scale for DSM-IV (CAPS) symptom scores, and they concluded that prospective, placebo-controlled studies are needed to determine efficacy of cannabis and its constituents in treating PTSD with medical cannabis **[54]**.

And, of the 33 medically legal states in the United States, at the writing of this article, which state does not include post-traumatic stress as a qualifying condition? Alaska does not include PTSD as a qualifying condition and two states (California and Massachusetts), the US capital (Washington, DC) and a US territory (Puerto Rico) allow the use of medical cannabis for PTSD at the "discretion of the physician" **[55]**.

Commonly used Cannabis Chemovars in Patients with PTSD

Cannabis may dampen the strength or emotional impact of traumatic memories through synergistic mechanisms that might make it easier for people with PTSD to rest or sleep and to feel less anxious and less involved with flashback memories; evidence is increasingly accumulating that cannabinoids might play a role in fear extinction and anti-depressive effects **[56]**.

Cannabis chemovars, which are commonly referred to as "strains" that are typically used for the management of patients with PTSD are:

- **Cannatonic**: This chemovar is primarily for daytime use and is exceptionally high in cannabidiol (CBD) content; it's considered a 50/50 hybrid chemovar that barely achieved a THC percentage higher than 6 percent, however, it's CBD content tests between 6 and 17 percent.This provides a relaxed and calming sensation, but they'll also notice a major improvement in their mood along with a marked reduction in anxiety. If their PTSD is causing them to get angry, this will calm them down **[57]**.
- **Blue Dream**: This Sativa-dominant Hybrid chemovar provides an element of mental invigoration, it provides a soothing full-body relaxation. It has an extremely high THC content of between 17 and 24% with a CBD content of between 0.1 and 0.2% and helps the individual ease into social interactions while promoting a significant uplift in their mood **[55]**.
- **OG Kush**: This Indica dominant hybrid is ideal for people with PTSD because it provides a pleasant and euphoric effect. Its THC content is between 20 and 24% with a CBD content of 0.2% and it does a remarkable job of calming the entire body which makes it perfect for a relaxing evening **[55]**.
- **Pineapple Express**: This sativa dominant hybrid is smooth and well-balanced; its THC content is

approximately 20%, and its CBD content is 0.1%. Users experience a feeling of clear-headedness which makes it the choice for creative individuals. For those with PTSD and want to go out and about but are feeling anxious, this chemovar will diminish their fears, it will ease their anxiety but ensure they're still a highly functioning individual **[55]**.

- **Master Kush:** This chemovar is probably not ideal for beginners because it is rather potent, i.e., it is popular in Amsterdam coffee houses which should give you some idea as to its strength. Its THC content is 20% while its CBD content is 1%, however, for those with PTSD, that have used cannabis before and have problems sleeping, this Indica could be the answer because it provides a blissful and euphoric sensation as it guides patients to sleep **[55]**.

Discussion

This literature review supports the feasibility of cannabis-based medicine as a promising treatment option in individuals with post-traumatic stress disorder; with significant improvements in reducing the seventeen core PTSD symptoms, which are generally grouped into four types: intrusive memories, avoidance, negative changes in thinking and mood, and changes in physical and emotional reactions by greater than 75% **[58]**.

Conclusion

This literature review supports the feasibility of cannabis-based medicine as a promising treatment option in individuals with PTSD. Based on the promising results, it is recommended that large, double blind, placebo controlled cross-over trials is launched in jurisdictions where medical cannabis can be studied without limitations from the federal government.

Biography of Author

After spending several years in central Florida working as an orderly, then an EMT/Paramedic and Heart Cath Lab technician, Dr. Rosado realized his passion for the medical profession. He started chiropractic school at Life College in Marietta, GA where he graduated cum laude with a BS degree in Clinical Nutrition and a doctor of chiropractic degree. After practicing for several years, he went on to the Universidad Central del Este, in San Pedro de Macoris where in 2001 he graduated summa cum laude with his medical degree. In 2005 he completed his MBA in Health Care Management from University of Phoenix, and graduated magna cum laude. In 2018 he became a Diplomate of the American Academy of Cannabinoid Medicine.

Upon completing his medical training, he has worked as a physician, clinic and hospital director, director of the communicable disease division/epidemiology and immunization departments. Presently, Dr. Rosado is a practicing physician, the Medical Director of a medical cannabis clinic in Ormond Beach, FL, the president and CEO of International Medical Consultants; the chief medical officer for Minorities 4 Medical Marijuana, Terra Nueva and marijuanadoctors.com; and volunteers once a quarter at a community clinic.

He was and is on the bureau of speakers for political campaigns, cannabis advocacy and medical cannabis dispensaries/licensed producers; as a clinician he has worked with toddlers, children, adolescents, adults and geriatric patients for primary care and the recommendation of and management with medical cannabis. As an author he has published multiple research articles and written the book "Hope and Healing-The Case for Medical Cannabis."

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Citation:

Rosado J (2019) PTSD or Clinical Endocannabinoid Deficiency? Jr Neuro Psych and Brain Res: JNPBR-126.