International Journal of Research in Pharmacy and Pharmaceutical Sciences
ISSN: 2455-698X; Impact Factor: RJIF 5.22
Received: 03-09-2019; Accepted: 05-10-2019
www.pharmacyjournal.in
Volume 4; Issue 6; November 2019; Page No. 19-23

Role of cannabis in treatment of depression and suicidal symptoms of post-traumatic stress disorder: A review

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Abstract
The incidence of posttraumatic stress disorder (PTSD) is common within the population and even more so among veterans. The stress that results from traumatic events precipitates a spectrum of psycho-emotional and physiopathological outcomes. Post-traumatic stress disorder (PTSD) is a psychiatric disorder that results from the experience or witnessing of traumatic or life-threatening events. PTSD is a serious public health concern, which compels the search for novel paradigms and theoretical models to deepen the understanding of the condition and to develop new and improved modes of treatment intervention. We review the current knowledge of PTSD and introduce the role of cannabis as a new perspective in fundamental PTSD research. We discuss the domain of evidence-based research in medicine, particularly in the context of complementary medical intervention for patients with PTSD. We present arguments in support of the notion that the future of clinical and translational research in PTSD to insure the most effective and efficacious treatment for the benefit of the patient. Current medication treatment is limited primarily to antidepressants. Such medicines have shown to produce low remission rates and may require 9 patients to be treated for 1 to have a response Cannabinoids has been evaluated as an alternative and novel treatment option with 16 states legalizing its use for PTSD.

Keywords: cannabinnoids, cannabidiol, suicide, anti-depressant, posttraumatic stress disorder (PTSD)

Introduction

Post-Traumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a mental disorder that can develop after a person is exposed to a traumatic event, such as sexual assault, warfare, traffic collisions, A person with PTSD is at a higher risk for suicide and intentional self-harm, child abuse depression or other threats on a person's life. The size of the hippocampus is inversely related to post-traumatic stress disorder and treatment success; the smaller the hippocampus, the higher risk of PTSD.

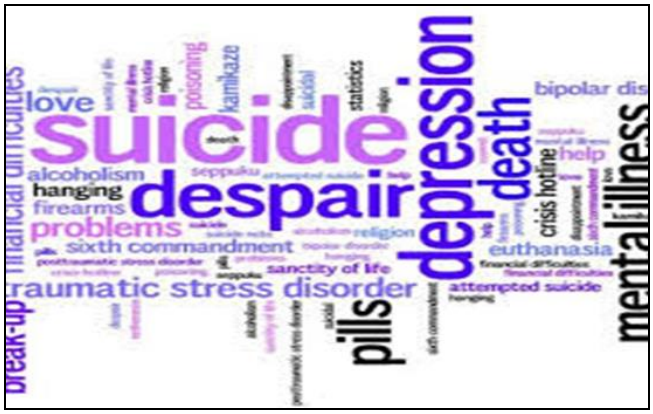

Fig 1: Over view of PTSD

PTSD is no longer considered an Anxiety Disorder but has been reclassified as a Trauma and Stressor-Related Disorder because it has a number of clinical presentations, as discussed previously. In addition, two new subtypes have been included in the *DSM-5*. The Dissociative Subtype includes individuals who meet full PTSD criteria but also exhibit either depersonalization or derealization (e.g. alterations in the experience of one's self and the world, respectively). The Preschool Subtype applies to children six years old and younger; it has fewer symptoms (especially in the "D" cluster because it is difficult for young children to report on their inner thoughts and feelings) and also has lower symptom thresholds to meet full PTSD criteria.

Cannabinoids

Cannabinoids are naturally occurring compounds found in the Cannabis sativa plant. Marijuana belongs to the Cannabaceae (hemp) plant family and is derived from the plant Cannabis sativa and Cannabis indica. Of over 480 different compounds present in the plant, only around 66 are termed cannabinoids. The most well-known among these compounds is the delta-9-tetrahydrocannabinol (Δ9-THC), which is a highly lipophilic alkaloid and is the primary psychoactive ingredient in marijuana.

Types of cannabinoids receptors

Two types of cannabinoid receptors, termed CB_1 and CB_2. The human brain has more cannabinoid receptors than any other G protein-coupled receptor (GPCR) type.

Cannabinoid receptor type 1

CB_1 receptors are found primarily in the brain, more specifically in the basal ganglia and in the limbic system, including the hippocampus and the striatum. They are also found in the cerebellum and in both male and female reproductive systems. CB_1 receptors are absent in the medulla oblongata, the part of the brain stem responsible for respiratory and cardiovascular functions. CB1 is also found in the human anterior eye and retina.

Cannabinoid receptor type 2

CB_2 receptors are predominantly found in the immune system, or immune-derived cells with the greatest density in the spleen. While found only in the peripheral nervous system, a report does indicate that CB_2 is expressed by a subpopulation of microglia in the human cerebellum. CB_2 receptors appear to be responsible for the anti-inflammatory and possibly other therapeutic effects of cannabis seen in animal models.

Cannabidiol

Fig 2: Structure of Cannabidiol

Cannabidiol, or CBD, is one of at least 85 active cannabinoids identified within the Cannabis plant. It is a major phytocannabinoid, accounting for up to 40% of the Cannabis plant's extract that binds to a wide variety of physiological targets of the endocannabinoid system within the body.

History of post-traumatic stress disorder

The term "posttraumatic stress disorder" came into use in the 1970s in large part due to the diagnoses of U.S. military veterans of the Vietnam War. It was officially recognized by the American Psychiatric Association in 1980 in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III). The psychological problems of soldiers in World War II, the Korean War, and the Vietnam War, along with the severe psychological impact of rape, fostered interest and research in the collection of symptoms that became known as posttraumatic stress disorder.

The 12-month prevalence of posttraumatic stress disorder (PTSD) in the United States is 3.5%.1 this is even higher in the veteran population with an estimated incidence of 24%.2 approximately 80% of people with PTSD have comorbid psychiatric disorders, and the associated mood,

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

Epidemiology

There is debate over the rates of PTSD found in populations, but, despite changes in diagnosis and the criteria used to Define PTSD between 1997 and 2013, epidemiological rates have not changed significantly. Most of the current reliable data regarding the epidemiology of PTSD is based on DSM-IV criteria, as the DSM-5 was not introduced until 2013.

The United Nations' World Health Organization publishes estimates of PTSD impact for each of its member states; the latest data available are for 2004. Considering only the 25 most populated countries ranked by overall age-standardized Disability-Adjusted Life Year (DALY) rate, the top half of the ranked list is dominated by Asian/Pacific countries, the US, and Egypt. ranking the countries by the male-only or female-only rates produces much the same result, but with less meaningfulness, as the score range in the single-sex rankings is much-reduced (4 for women, 3 for men, as compared with 14 for the overall score range), suggesting that the differences between female and male rates, within each country, is what drives the distinctions between the countries

As of 2007, the cross-national lifetime prevalence of PTSD was 3.9%, based on a survey were 5.6% had been exposed to trauma. The primary factor impacting treatment-seeking behavior, which can help to mitigate PTSD development after trauma was income, while being younger, female, and having less social status (less education, lower individual income, and being unemployed) were all factors associated with less treatment-seeking be

Risk factors

Persons considered at risk include combat military personnel, victims of natural disasters, concentration camp survivors, and victims of violent crime.

1. Trauma

PTSD has been associated with a wide range of traumatic events. The risk of developing PTSD after a traumatic event varies by trauma type and is highest following exposure to sexual violence (11.4%), particularly rape (19.0%).Men are more likely to experience a traumatic event, but women are more likely to experience the kind of high-impact traumatic event that can lead to PTSD, such as interpersonal violence and sexual assault

2. Intimate Partner Violence

An individual that has been exposed to domestic violence is predisposed to the development of PTSD. However, being exposed to a traumatic experience does not automatically indicate that an individual will develop PTSD. There is a strong association between the developments of PTSD in mothers that experienced domestic violence during the perinatal period of their pregnancy.

Those who have experienced sexual assault or rape may develop symptoms of PTSD.PTSD symptoms include re-experiencing the assault, avoiding things associated with the assault, numbness, and increased anxiety and an increased startle response.

3. Life threatening illness

Medical conditions associated with an increased risk of PTSD include cancer, heart attack, and stroke 22% of cancer survivors present with lifelong PTSD like symptoms Intensive-care unit (ICU) hospitalization is also a risk factor for PTSD Some women experience PTSD from their experiences related to breast cancer and mastectomy

4. Pregnancy related trauma

Women who experience miscarriage are at risk of PTSD. Those who experience subsequent miscarriages have an increased risk of PTSD compared to those experiencing only one. PTSD can also occur after childbirth and the risk

increases if a woman has experienced trauma prior to the pregnancy. Prevalence of PTSD following normal childbirth (that is, excluding stillbirth or major complications) is estimated to be between 2.8 and 5.6% at 6 weeks postpartum, with rates dropping to 1.5% at 6 months postpartum. Symptoms of PTSD are common following childbirth, with prevalence of 24-30.1% [75] at 6 weeks, dropping to 13.6% at 6 months. Emergency childbirth is also associated with PTSD.

5. Genetics

There is evidence that susceptibility to PTSD is hereditary. Approximately 30% of the variance in PTSD is caused from genetics alone. For twin pairs exposed to combat in Vietnam, having a monozygotic (identical) twin with PTSD was associated with an increased risk of the co-twin's having PTSD compared to twins that were dizygotic (non-identical twins). There is evidence that those with a genetically smaller hippocampus are more likely to develop PTSD following a traumatic event. Research has also found that PTSD shares many genetic influences common to other psychiatric disorders. Panic and generalized anxiety disorders and PTSD share 60% of the same genetic variance. Alcohol, nicotine, and drug dependence share greater than 40% genetic similarities.

Several biological indicators have been identified that are related to later PTSD development. Heightened startle responses and a smaller hippocampal volume have been identified as biomarkers for the risk of developing PTSD. Additionally, one study found that soldiers whose leukocytes had greater numbers of glucocorticoid receptors were more prone to developing PTSD after experiencing trauma

Pathophysiology

PTSD symptoms may result in an over-reactive adrenaline response, which creates deep neurological patterns. During traumatic experiences the high levels of stress hormones secreted suppress hypothalamic PTSD causes biochemical changes in the brain and body that differ from other psychiatric disorders such as major depression.

Most people with PTSD show a low secretion of cortisol and high secretion of catecholamines in urine with a higher level of nor epinephrine is this in contrast to the normative fight-or-flight response, in which both catecholamine and cortisol levels are elevated after exposure to a stressor

Dopamine levels in a person with PTSD: low levels can contribute to anhedonia, apathy, impaired attention, and motor deficits; high levels can contribute to psychosis, agitation, and restlessness.

Sign and Symptoms

1. Emotional distress
2. Emotional disorders
3. Repeated past memories
4. Living life in past
5. No concentration on current events
6. Dangerous dreams of past memories
7. Depression
8. Suicidal thought

Diagnosis

To diagnose post-traumatic stress disorder, your doctor will likely:

Perform a physical exam to check for medical problems that may be causing your symptoms.

Do a psychological evaluation that includes a discussion of your signs and symptoms and the event or events that led up to them.

Use the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published by the American Psychiatric Association.

Diagnosis of PTSD requires exposure to an event that involved the actual or possible threat of death, violence or serious injury.

The risk of exposure to trauma has been a part of the human condition since we evolved as a species. Attacks by saber tooth tigers or twenty-first century terrorists have probably produced similar psychological sequelae in the survivors of such violence. Shakespeare's Henry IV appears to meet many, if not all, of the diagnostic criteria for Posttraumatic Stress Disorder (PTSD), as have other heroes and heroines throughout the world's literature. The history of the development of the PTSD concept is described by Trimble

In 1980, the American Psychiatric Association (APA) added PTSD to the third edition of its Diagnostic and Statistical Manual of Mental Disorders (*DSM-III*) nosologic classification scheme

Although controversial when first introduced, the PTSD diagnosis has filled an important gap in psychiatric theory and practice. From an historical perspective, the significant change ushered in by the PTSD concept was the stipulation that the etiological agent was outside the individual (i.e., a traumatic event) rather than an inherent individual weakness (i.e., a traumatic neurosis). The key to understanding the scientific basis and clinical expression of PTSD is the concept of "trauma."

Differential diagnosis

A diagnosis of PTSD requires that the person has been exposed to an extreme, life-threatening stressor. Any stressor can result in a diagnosis of adjustment disorder and it is an appropriate diagnosis for a stressor and a symptom pattern that does not meet the criteria for PTSD.

The symptom pattern for acute stress disorder must occur and be resolved within four weeks of the trauma. If it lasts longer, and the symptom pattern fits that characteristic of PTSD, the diagnosis may be changed.

Obsessive compulsive disorder may be diagnosed for intrusive thoughts that are recurring but not related to a specific traumatic event.

In extreme cases of prolonged, repeated traumatization where there is no viable chance of escape, survivors may develop complex post-traumatic stress disorder.] This occurs as a result of layers of trauma rather than a single traumatic event, and includes additional symptomatology, such as the loss of a coherent sense of self.

Prevention

Modest benefits have been seen from early access to cognitive behavioral therapy. Critical incident stress management has been suggested as a means of preventing PTSD, but subsequent studies suggest the likelihood of its producing negative outcomes. A review did not find any evidence to support the use of an intervention offered to everyone", and that "multiple session interventions may result in worse outcome than no intervention for some

individuals. The World Health Organization recommends against the use of benzodiazepines and antidepressants in for acute stress (symptoms lasting less than one month). Some evidence supports the use of hydrocortisone for prevention in adults, although there is limited or no evidence supporting propranolol, escitalopram, temazepam, or gabapentin

Treatment

A dysregulation of neurotransmitters is alsopresent, causing a failure in the stress response system to react, adapt, and recover from a situation. An increase in
Norepinephrine, decrease in serotonin, and increase in glutamate can contribute to physical, mental, and emotional symptoms of PTSD. To target the neurotransmitter imbalance, antidepressants are recommended to treat PTSD

Earlier Medication

While many medications do not have enough evidence to support their use, three (fluoxetine, paroxetine, and venlafaxine) have been shown to have a small to modest benefit over placebo. With many medications, residual PTSD symptoms following treatment is the rule rather than the exception.

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) may have some benefit for PTSD symptoms. Tricyclic antidepressants are equally effective but are less well tolerated. Evidence provides support for a small or modest improvement with sertraline, fluoxetine, paroxetine, and venlafaxine. Thus, these four medications are considered to be first-line medications for PTSD.

Benzodiazepines

Benzodiazepines are not recommended for the treatment of PTSD due to a lack of evidence of benefit and risk of worsening PTSD symptoms. Some authors believe that the use of benzodiazepines is contraindicated for acute stress, as this group of drugs can cause dissociation. Nevertheless, some use benzodiazepines with caution for short-term anxiety and insomnia. While benzodiazepines can alleviate acute anxiety, there is no consistent evidence that they can stop the development of PTSD and may actually increase the risk of developing PTSD 2–5 times. Additionally, benzodiazepines may reduce the effectiveness of psychotherapeutic interventions, and there is some evidence that benzodiazepines may actually contribute to the development and chronification of PTSD. For those who already have PTSD, benzodiazepines may worsen and prolong the course of illness, by worsening psychotherapy outcomes, and causing or exacerbating aggression, depression (including suicidality), and substance use.

Drawbacks include the risk of developing a benzodiazepine dependence, tolerance (i.e., short-term benefits wearing off with time), and withdrawal syndrome; additionally, individuals with PTSD (even those without a history of alcohol or drug misuse) are at an increased risk of abusing benzodiazepines. Due to a number of other treatments with greater efficacy for PTSD and less risks (e.g., prolonged exposure, cognitive processing therapy, eye movement desensitization and reprocessing, cognitive restructuring therapy, trauma-focused cognitive behavioral therapy, brief eclectic psychotherapy, narrative therapy, stress inoculation training, serotonergic antidepressants, adrenergic inhibitors, antipsychotics, and even anticonvulsants), benzodiazepines should be considered relatively contraindicated until all other treatment options are exhausted. For those who argue that benzodiazepines should be used sooner in the most severe cases, the adverse risk of disinhibition (associated with suicidality, aggression and crimes) and clinical risks of delaying or inhibiting definitive efficacious treatments, make other alternative treatments preferable (e.g., inpatient, residential, partial hospitalization, intensive outpatient, dialectic behavior therapy; and other fast-acting sedating medications such as trazodone, mirtazapine, amitripytline, doxepin, prazosin, propranolol, guanfacine, clonidine, quetiapine, olanzapine, valproate, gabapentin).

Glucocorticoids

Glucocorticoids may be useful for short-term therapy to protect against neurodegeneration caused by the extended stress response that characterizes PTSD, but long-term use may actually promote neurodegeneration.

Cannabinoids

The cannabinoid is sometimes used for nightmares in PTSD. Although some short-term benefit was shown, adverse effects are common and it has not been adequately studied to determine efficacy. Currently, a handful of states permit the use of medical cannabis for the treatment of PTSD.

Discussion and conclusion

A substance found in cannabis may be a faster-acting antidepressant than conventional medications.

Depression is a serious mental illness which affect more than 300 million people worldwide, being considered the first cause of disability in many developed and undeveloped countries.

The treatments that are currently available, although effective, suffer from partial and lacking response even after weeks of continuous treatment. These issues raise the need for better understanding of depression neurobiology, as well as developing novel and more effective treatment strategies.

CBD emerges as an interesting compound, since it has shown large-spectrum therapeutic potential in preclinical models and clinical trials.

The results could provide new insights on depression neurobiology and treatment, with easy translation to the clinical scenario, since CBD is used in humans for the treatment of neurological disorders, such as epilepsy.

The researchers used rodents who had been selectively bred to develop depression-like symptoms. They found that CBD was associated with a reduction in immobility during a forced swim test, which is commonly used as a model of depressive symptoms. Antidepressants shorten the duration of immobility and lengthen the swim time. None of the treatments induced locomotor effects it showed that CBD increased animal's resilience in stress models of depression, thus indicating an antidepressant-like effect. Moreover, this effect developed rapidly Since it's effect is blocked when BDNF signaling is blocked in the brain, our results suggest that it promotes fast neurochemical and neuroplastic effects in limbic brain regions, which might favor stress coping strategies and resilience to depression development,

In another rodent study, it has been found that the

antidepressant-like effect induced by CBD were dependent on levels of the neurotransmitter serotonin. The study also indicated that it could enhance the effectiveness of traditional antidepressant medication.

In small doses, CBD allowed the effect of serotonergic antidepressants to be effective. This indicates that co-administering CBD with serotonergic antidepressants might contribute to the use of smaller doses of the latter, thus decreasing their side effects, without compromising the antidepressant effect.

It is important to highlight that CBD is only one amongst the many phytocannabinoids present in the plant *Cannabis sativa* and it is devoid of psych stimulant effects and abuse liability.

In fact, the main responsible for the psych stimulant effects induced by the plant is THC. Therefore, saying that it induces antidepressant effects is not the same as saying that marijuana is an antidepressant. Although there has been evidence for that as well, one should keep in mind that marijuana also contains many other different CBD such as THC that can actually represent risks for health.

The incidence of posttraumatic stress disorder (PTSD) is common within the population and even more**.** Current medication treatment is limited primarily to antidepressants

Marijuana has been evaluated as an alternative and novel treatment option with 16 states legalizing its use for PTSD. To target the neurotransmitter imbalance, anti-depressants are recommended to treat PTSD. According to the2010 Veterans Affairs (VA)/Department of Defense guidelines, psychotherapy and/or pharmacotherapy with selective serotonin reuptake inhibitors or serotonin and nor epinephrine reuptake inhibitors are considered firstlinetreatment.4 However, the number needed to treat with preferred antidepressants for a response is up to 9patients. Remission rates with pharmacotherapy have been reported to be 20% to 30%.

The 2005 National Institute for Health and Clinical Excellence guidelines10 do not recommend pharmacotherapy as first-line treatment. The 2009 American Psychiatric Association guideline note that pharmacotherapy is not as effective for combat-related trauma compared to civilian PTSD. Given these limitations, the investigation for more effective treatment options has been underway and the utility of marijuana in alleviating PTSD symptoms has become an area of interest.

As of November 9, 2016, 28 states and the District of Columbia legalized medical marijuana with 16 states approving its use for PTSD

However, marijuana is still classified as a schedule I controlled substance federally, meaning it has no current accepted medical use and has a high potential for abuse. An addendum was passed by the US House of Representatives allowing VA providers to recommend and share information on medical marijuana in states with approved medical marijuana programs. As of April 2017, the bill is awaiting Senate approval. Other legislation has been proposed to remove marijuana from the schedule of controlled substances.

Stimulation of the cannabinoid receptors has been shown to increase stress coping behaviors as well as serotonin and nor epinephrine firing in the midbrain. THC has the ability to activate dopaminergic neurons in the ventral tegmental area as well as stimulate release of dopamine from the nucleus accumbens. Cannabinoid receptors are absent in the brain the endocannabinoid system may play a role in PTSD. An increase in availability and decreased agonism of CB-1 receptors has been found in patients with PTSD. Alterations in the receptors have been seen in depression.

The stimulation of the receptors in the prefrontal cortex, amygdala, and hippocampus may alleviate anxiety as well as cause sensitization of CB-1 receptor–mediated G-protein signaling in the prefrontal cortex, which may play a role in suicide and suicidal behaviorstem, there is minimal risk of lethal overdose. Stimulating CB-1 receptors in the prefrontal cortex can increase serotonin and, therefore, display antidepressant properties.

Anecdotal benefit has been reported with the use of marijuana for PTSD symptoms as well as suicidality.

This study found that a wide range of PTSD increased the odds of experiencing suicide ideation. However, after controlling for psychiatric comorbidity, only disorders characterized by anxiety and poor impulse-control predict which people with suicide ideation act on such thoughts. These findings provide a more fine-grained understanding of the associations between PTSD and subsequent suicidal behavior.

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