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REVIEW

Cannabidiol, a promising therapy for post-traumatic stress disorder and depression. A mini-review

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Post-traumatic stress disorder (PTSD) is a mental health disorder, manifesting in people who have endured traumatic events like violence, war, natural disasters, accidents, or other life-threatening situations. Essentially, PTSD is a chronic and debilitating disorder, significantly impacting mental health and psychosocial well-being, necessitating the exploration of novel treatment approaches. Although conventional therapies like psychotherapy and antidepressants have demonstrated efficacy for certain individuals, their effectiveness is limited for some and minimal for others. Consequently, researchers and clinicians are investigating alternative therapeutic methods for these conditions. Among these emerging treatments, cannabidiol (CBD) has shown promising results. Nevertheless, early studies suggest that CBD might yield positive outcomes in mitigating symptoms related to both depression and PTSD.

Keywords: cannabidiol, PTSD, antidepressants, SSRI, serotonin

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Introduction

Trauma is defined as a life event that involves negative emotions, harmful events and adverse experiences associated with death, respectively insults to physical or mental integrity [1]. Trauma can lead to changes in self-identity, spirituality, and worldviews due to changes in cognitive patterns related to trust, intimacy, safety, power, and control [2]. Such experiences, associated with feelings of helplessness, intense fear and horror, can lead to the onset and development of post-traumatic stress disorder (PTSD) [3]. PTSD is a condition observed in individuals who have experienced a trauma event like for example violence, war, natural disasters, accidents, or other life-threatening events. In other words, PTSD is a debilitating, chronic condition, with particularly pronounced negative effects on mental health and psychosocial characteristics, which is in search of new treatments [4].

PTSD was officially recognized as a diagnosable psychiatric condition in both the third edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-III) and the tenth edition of the International Classification of Diseases (ICD-10) [5]. With the debate on this topic in DSM-III and ICS-10, PTSD was defined as a biological or psychological response, variable in its complexity, to an acutely or chronically experienced stressor. More severe symptoms were seen in people who had been through prolonged exposure to a stressor, who did not have an adequate support system, and those who felt guilty for their own actions. For this reason, it is necessary to carry out research and evaluations in order to minimize and/or prevent the development of PTSD [6]. The links established in DSM-III between the traumatic moment and post-traumatic life were also debated, studied and revised in the following editions, in 1994 in DSM-IV, in 2000 in DSM-IV-TR and in 2013 in DSM-V. For this reason, to reflect reality, research is in continuous development [7].

Prevalence

Traumatic experiences are very common globally, and the chance that a person will be exposed to trauma is very high. In Romania, 29% of exposures to traumatic events represent favorable circumstances for the development of PTSD, the chances increasing to 83% for Peru and 82% for Iraq [8]. Several studies indicate that individuals experience one traumatic event during their lifetime, with a higher prevalence observed among women. Approximately 70% of women will encounter such an event at some point in their lives. Because of the increased rate of exposure to traumatic events, the collective incidence of PTSD is about 1% of the global population.

People most likely to develop PTSD are women, military personnel, police officers, firefighters, first-line disaster responders, the socially disadvantaged, and youth. The likelihood of developing PTSD varies by gender and type of trauma. For example, the probability that a male subject will develop PTSD after rape is 65%, 2% after physical assault and 6% after a major accident, respectively the probability that a female subject will develop PTSD after rape is 46%, 22% after physical assault, and 9% after a major accident. Traumas after rape are perceived differently by gender, and those caused by physical aggression represent a source of fear, horror, and helplessness, less for personnel trained in such situations compared to ordinary people [9]. Studies on financial status have shown that the population of middle- and high-income countries is more prone to develop PTSD compared to the population of low-income countries. These differences may be reflected by social roles and situational factors in the development, presentation, and persistence of PTSD symptoms [10].

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Neuroendocrine influence

The mechanisms and causes of PTSD are not fully understood, but studies hypothesized that there is an involvement of the neuro-endocrine system and also immune system in the development of this disorder. After exposure to traumatic events, the hypothalamus-pituitary-adrenal axis and the adrenergic nervous system stress response pathways are stimulated. Due to these events, an elevated secretion of cortisol and epinephrine/norepinephrine will be released [11]. Cortisol is known to have immunosuppressive properties, causes metabolic disturbances, and inhibit the hypothalamic-pituitary-adrenal axis, establishing a link between neuroendocrine modulation and disturbances of immune activity and the resulting inflammatory effects [12]. Literature studies revealed elevated plasma levels of pro-inflammatory mediators (IL-1β, IL-6, and TNFα. These results indicate that alterations in neuroendocrine function and inflammatory response might serve as an underlying biological predisposition for PTSD following trauma [13-15]. However, it has been observed that people with PTSD after a single traumatic event have lower cortisol levels compared to people without PTSD or people exposed to traumatic events but without PTSD [16]. This may be due to the sensitization of the negative feedback control of cortisol secretion [17-19].

Current pharmacological treatments

Even though in PTSD, non-pharmacological therapy is considered first-line, in cases where this does not give results, pharmacological therapy is resorted to [20]. There are several medications that are used to treat PTSD. These can be prescribed by a psychiatrist or family doctor with experience in the treatment of mental disorders. Medication used in PTSD includes both antidepressants and antipsychotics and anxiolytics. Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are often prescribed to avoid and/or treat symptoms such as reexperiencing, avoidance, and hypervigilance.

Among the most widely used SSRIs are fluoxetine, sertraline, and paroxetine [21]. Venlafaxine, a selective serotonin-norepinephrine reuptake inhibitor (SNRI), has also been used, showing comparable results to SSRIs. However, in terms of efficacy, only 20–30% of PTSD patients maintained a significant clinical response after using this class of medication [22]. Clonazepam and alprazolam may be prescribed to reduce symptoms of hypervigilance and anxiety. However, these drugs have a high risk of abuse and as a result, should be prescribed and administered with caution because they can cause addiction. Also, antipsychotic drugs are prescribed to reduce symptoms of paranoia, aggression and irritability. Examples of antipsychotics used include risperidone and quetiapine [23].

Endocannabinoid system

The endocannabinoid system (ECS) serves as a crucial neuromodulatory system involved in CNS development, synaptic plasticity, and the response of various internal and external stimuli. Comprising cannabinoid receptors, endocannabinoids and enzymes involved in cannabinoid synthesis and breakdown [24], this system is pivotal in regulating physiological processes. While the CB1 receptors are most prevalent, the cannabinoid agonists (anandamide, 2-arachidonoylglycerol) interact also with CB2 receptors (for anti-inflammatory and immunosuppressive effects) [25], and transient receptor-potential channels, and peroxisome-activated receptors [26]. Also, exogenous cannabinoids (cannabidiol, CBD, tetrahydrocannabinol, THC) produce their biological effects by interacting with these receptors. The CB1 receptor is of increasing interest to researchers in PTSD, depression, and post-withdrawal depression, with an abundant density in the central nervous system, with roles in regulating appetite, memory, and pain [27]. The influence of CB1 receptors on cognitive functions is widely recognized. Disorders associated with CB1 receptors (due to their polymorphism) include psychiatric disorders (addiction, depressive disorders, bipolar disorders, anxiety) [28]. In addition to the brain, CB1 receptors are found in various tissues (blood vessels, heart, adipose tissue, gonads, bones, liver). CB1 receptors are Gi/o protein-coupled receptors. Their stimulation lead to the stimulation of mitogen-activated protein kinases, decrease in adenylyl cyclase activity, activation of potassium channels and closure of calcium channels, and modulation of NO signaling [29]. Conversely, the CB2 receptors predominantly resides in immune cells (B, T cells, neutrophils, eosinophils, basophils, monocytes, and macrophages). This explains the influence on the immune response and inflammation. CB2 receptors modulate the inflammatory response, enhance immuno-regulatory function, the activity of immune system cells and suppress excessive immune reactions [30]. In addition, this receptor is expressed in several peripheral tissues, including the spleen, lymphoid tissues, tonsils, reproductive organs, and the peripheral nervous system, and it is also coupled to G proteins, especially Gi proteins, but can also be also coupled to Gs or Gq proteins [31].

Novel therapy in PTSD

While conventional and traditional therapies such as psychotherapy and antidepressant medications have been shown to be helpful for some patients, they are only partially effective in some patients and minimally effective in others. Therefore, researchers and clinicians are studying alternative therapeutic approaches for these disorders. Among these emerging treatments, the following have shown promising results: cannabidiol (CBD) [32], ketamine [33], 3,4-methylenedioxymethamphetamine (MDMA) [34], and hallucinogenic mushrooms [35]. The discovery, development, and use of new drug therapies involves extensive study and research to determine their safety and efficacy. Research regarding the application of CBD for addressing PTSD and depression are currently underway and more data are needed to assess its effectiveness. However, preliminary research has shown

that CBD may have beneficial effects in reducing both depressive and PTSD symptoms. Thus, CBD is able to reduce anxiety and stress-related behaviors, but this depends on many factors such as species, age, doses, or treatment (acute or chronic). Although CBD is acting on different receptors, the receptor which appear to be the most relevant for the anxiolytic effect is 5-HT_{1A} [36]. Administration of CBD shows interesting effects on 5-HT_{1A} receptors [37] by temporarily inhibiting the release of serotonin from neurons of the dorsal raphe nucleus (DRN), reducing its hyperreactivity, and reducing amygdala excitation. This reduces the imbalance of activity between the amygdala and the medial prefrontal cortex (mPFC). In the DRN, CBD inhibits fatty acid amide hydrolase in serotonergic neurons. Anandamide is released by serotonergic neurons from the DRN in the amygdala, inhibiting neurotransmitter release. CBD administration promoted the favorability of glutamatergic synapses in mPFC, restoring mPFC activity. This decreases the intensity of PTSD symptoms by restoring inhibitory control of the mPFC to allow the fear extinction process to take place [38]. The chronic mechanism of CBD at the synapse of the serotonergic DRN and glutamate in the mPFC enhances the activity of this region to reinstate its inhibitory function and support fear extinction and stress adaptation [39, 40, 41]. Chronic use of cannabidiol leads to the availability of anandamide, which in turn regulate the glutamate release to prevent hyperreactivity in the DRN [42].

In animal models, high doses of CBD (100 mg/kg) were shown to have no effect, while low doses (10 mg/kg) had anxiolytic effects [43, 44]. The effects of CBD are complex, so in animal models of unstressed rats, CBD administration triggered anxiety reactions in the Elevated Plus Maze test, via 5-HT_{1A} receptors, while after exposure to a stressor (acute restraint stress), it was shown to be anxiolytic [45]. Also, in various models of PTSD or depression, subchronic and chronic administration of CBD reduced anxiolytic behavior, via activation of 5-HT1A and CB1, with increased levels of AEA [46].

In clinical studies, the anxiolytic effects of CBD have been shown in the context of controlling the anxiogenic effect of THC. However, when administered alone, the anxiolytic effect could not be observed, as demonstrated by other studies [47, 48, 49]. There are multiple clinical studies in which the effect of CBD is studied, some of them being focused on the anxiolytic effect in PTSD and/or other stress-related pathologies [50-53]. In doses between 300 and 600 mg, CBD reduced anxiolytic symptoms in healthy patients who were given anxiety. Also, acute use of CBD reduced fear, thus representing a substance that can be used in cognitive behavioral therapy.

New directions for the use of cannabidiol in anxiety and depression from drug addiction and substance use disorder

Drug therapies available for addressing drug addiction and substance use disorders face various limitations (efficacy, lack of approval, relapse). These hurdles contribute to the complexity of clinical outcomes and negatively impact life for patients, highlighting the significance of innovating novel pharmacological therapies. Recent findings indicate that CBD use might provide advantageous effects in addressing neurological conditions (Parkinson's and Alzheimer's disease, multiple sclerosis, epilepsy). Furthermore, a significant amount of research suggests that CBD improves cognitive function, stimulates neurogenesis, and has neuroprotection properties. These findings imply that CBD could have potential benefits in the treatment of substance use disorders, and post-withdrawal depression [54]. There are various studies that have investigated and emphasized the anti-addiction properties of CBD. In experimental models based on self-administration of cannabis, opioids, alcohol and nicotine, treatment with CBD resulted in increased resistance to withdrawal. The effects of CBD have been evaluated in heroin intoxication and morphine withdrawal syndrome. Although CBD did not show significant effects on heroin use, a reduction in heroin-seeking behavior and an attenuation of opioid reward were observed. Similarly, it was concluded that CBD significantly reduces abstinence and withdrawal symptoms and reduces relapse behavior in experimental models of THC and alcohol dependence [55].

It has been noted that CBD has various therapeutic attributes, encompassing the reduction of anxious and depressive symptoms, but also reduces inflammation, and has antiemetic and analgesic properties. All of the bear relevance to opioid withdrawal. Furthermore, some trials revealed that CBD is a well-tolerated medication. No notable adverse effects have been reported, even when given concurrently with potent opioid agonists. Growing body of results shows that CBD could complement the conventional opioid detoxification protocol by easing both the acute and prolonged withdrawal symptoms [56].

Conclusion

PTSD, comorbid and non-comorbid depression, and post-withdrawal depression are increasingly common conditions that threaten quality of life and are in search of new treatment options. Therefore, the demand for cannabinoids is growing.

Chronic use of CBD is able to restore mPFC activity through enhanced release of 5-HT by DRN neurons, as seen in models of depression in animals. In case of PTSD, the use of cannabidiol will reduce the hyperactivity of the amygdala and will restore mPFC activity. Although, more studies are needed in order to understand the mechanism of CBD in the treatment of PTSD.

Some of these therapies include the use of cannabidiol, due to the promising results from different trials. Also, another aspect to mention is that the use of this substance, and also other hallucinogenic substances is no available widespread because they are the subject of strict regulations.

Author's contribution

GJ – Conceptualization, Supervision, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing, funding acquisition

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Conflicts of Interest

None to declare.

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