

Use and effects of cannabinoids in military veterans with posttraumatic stress disorder

KEVIN BETTHAUSER, JEFFREY PILZ, AND LAURA E. VOLLMER

Cannabis and its synthetic derivatives are commonly used around the world to treat a variety of disease states.¹ However, controversy continues to surround cannabis and cannabinoid use as a primary or adjunctive therapy in the treatment of stress disorders. Conflicting results of published studies further blur the distinction between cannabis as a potentially beneficial alternative to conventional pharmacotherapy and behavioral therapies and cannabis as a substance that might worsen patient outcomes when used for self-medication.²⁻⁵ This article reviews published evidence regarding the use of cannabis to address symptoms of posttraumatic stress disorder (PTSD) among military veterans.

PTSD prevalence and pathophysiology

Prevalence. PTSD is defined as chronic activation of the stress response as a result of experiencing a traumatic event.^{6,7} It has been estimated that 60% of male and 50% of female persons will experience at least one traumatic experience in their lifetime, with a high rate of

Purpose. Published evidence regarding the use of cannabis and cannabis derivatives by military veterans with posttraumatic stress disorder (PTSD) is reviewed.

Summary. When inhaled or delivered orally or transdermally, cannabinoids (the psychoactive components of unrefined marijuana and various derivative products) activate endogenous cannabinoid receptors, modulating neurotransmitter release and producing a wide range of central nervous system effects, including increased pleasure and alteration of memory processes. Those effects provide a pharmacologic rationale for the use of cannabinoids to manage the three core PTSD symptom clusters: reexperiencing, avoidance and numbing, and hyperarousal. A literature search identified 11 articles pertaining to cannabis use by military veterans who met standard diagnostic criteria for PTSD. Cross-sectional studies have found a direct correlation between more severe PTSD symptomatology and increased motiva-

tion to use cannabis for coping purposes, especially among patients with difficulties in emotional regulation or stress tolerance. Data from 4 small studies suggested that cannabinoid use was associated with global improvements in PTSD symptoms or amelioration of specific PTSD symptoms such as insomnia and nightmares. Large well-designed controlled trials are needed in order to better delineate the potential role of cannabinoids as an adjunct or alternative to conventional approaches to PTSD management.

Conclusion. While further research into cannabinoid treatment effects on PTSD symptoms is required, the evaluated evidence indicates that substantial numbers of military veterans with PTSD use cannabis or derivative products to control PTSD symptoms, with some patients reporting benefits in terms of reduced anxiety and insomnia and improved coping ability.

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stress disorders in men caused by traumatic experiences associated with combat.⁸ In the United States, PTSD is diagnosed in approximately 5.2 million people annually, and these people suffer a wide range

of symptoms. Individuals serving combat tours in the line of military service are particularly vulnerable to PTSD. According to the Department of Veterans Affairs (VA), 11–20% of veterans of Operations Iraqi Free-

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The Clinical Consultation section features articles that provide brief advice on how to handle specific drug therapy problems. All articles are based on a systematic review of the literature. The assistance of ASHP's Section of Clinical Specialists and Scientists in soliciting Clinical Consultation submissions is acknowledged. Unsolicited submissions are also welcome.

dom and Enduring Freedom, 10% of veterans of the Persian Gulf War, and 30% of those serving during the Vietnam War have had PTSD symptoms to varying degrees.

Furthermore, patients with PTSD are at risk for other psychological disorders, including but not limited to generalized anxiety disorder, major depressive disorder, and substance use disorder, and for physical problems such as chronic pain, hypertension, and asthma.⁶

Diagnosis. PTSD symptoms are often grouped into three subgroups defined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, criteria and often assessed in veterans using the PTSD Checklist—Military Version (PCL-M): reexperiencing (also termed intrusion), avoidance and numbing, and hyperarousal.^{9,10} Reexperiencing refers to the cluster of PTSD symptoms associated with flashbacks and vividly reliving the traumatic experience. Avoidance–numbing symptoms are those that involve the patient trying to avoid emotional feelings; such behavior disrupts personal relationships. Finally, hyperarousal symptoms include irritability, difficulty concentrating, increased worrying about safety, and reduced tolerance to startling stimuli.¹⁰ PTSD diagnosis is based on patients experiencing these symptoms for at least one month to a degree that interferes with activities of daily living or reduces quality of life.

Pathophysiology. The pathophysiology of these symptoms, while not fully understood, is thought to

be related to increased sympathetic nervous system activity due to a traumatic experience compounded by changes in memory processing. Physical manifestations of PTSD are linked to increased levels of norepinephrine but also activity at α_2 -adrenergic receptors, which counteractively impede the release of neurotransmitters from adrenergic presynaptic neurons.⁶ Alteration in memory processing is hypothesized by several sources to be the cause of psychological reliving and continued response to triggering stimuli.^{6,10,11} Involved in central processing of fear and anxiety processes as well as sympathomimetic stimulation, the amygdala and hypothalamic structures are thought to be key components of PTSD symptomatology, although their roles are not fully understood.^{10,12}

The changes in memory function associated with PTSD differ from those seen in other forms of stress.¹³ The significant difference is the lack of increased cortisol levels in persons with PTSD. One group of researchers hypothesized that the changes in neural functioning seen in patients with PTSD reduce the ability to remove traumatic memories and the remembered response to those stimuli.¹¹

Cannabinoid pharmacology

Endogenous cannabinoid ligands, or endocannabinoids, exist naturally in the body to stimulate activity at cannabinoid receptors. Drugs delivering cannabinoid compounds also activate these receptors. Specifically, cannabinoid-1 (CB-1) and cannabinoid-2 (CB-2) G-coupled protein receptors are activated by cannabis compounds, leading to the production of secondary messengers that modulate the release of neurotransmitters from presynaptic sites through both excitatory and inhibitory actions.¹⁴ CB-1 receptors are diffusely distributed within the central nervous system, which helps to explain the wide range of effects seen

with cannabinoid receptor activation; CB-1 receptors are the primary target for modification of PTSD symptoms. With cannabinoid use, pleasure is increased, while memory and concentration can be inhibited, due to the release of acetylcholine, norepinephrine, dopamine, serotonin, and glutamate neurotransmitters. CB-2 receptors are concentrated in the peripheral nervous system and elicit immunosuppressive and antiinflammatory responses when activated. Cannabinoids are highly lipophilic compounds that rapidly cross lipid membranes and the blood-brain barrier, leading to a fast onset of effect, especially when cannabinoids are inhaled. In murine models, it was demonstrated that correcting a deficiency of endogenous cannabinoids enabled mice subjected to traumatic shock treatments to overcome their conditioned response by allowing removal of the harmful stress-inducing memories through inhibition of γ -aminobutyric acid pathways in the amygdala. This mechanism is thought to explain human responses to cannabinoids as well.

Cannabinoid classification and legal status

Perhaps the most known connotation of the term *cannabinoid* to the layperson pertains to marijuana, which can deliver cannabinoids via respiratory, transdermal, and oral routes. Formally, marijuana refers to the unrefined leaves and flowers of *Cannabis sativa*, which contain over 460 active substances and no fewer than 60 cannabinoids.¹⁴ Delta-9-tetrahydrocannabinol (δ -9-THC) is the cannabinoid responsible for the majority of effects seen with marijuana use. The active compounds in marijuana produce the same activity in the messenger systems linked to cannabinoid receptors as that produced by endocannabinoids.

Cannabinoid-containing substances differ in terms of route of administration and active chemical

ingredients. Marijuana and select synthetic cannabinoids are classified by the Drug Enforcement Administration as Schedule I drugs under the Controlled Substances Act of 1970.¹⁵ This is largely due to the effects of δ -9-THC, which causes a “high” sensation and impaired cognition when inhaled or absorbed via the gastrointestinal tract. However, cannabinoids synthesized for specific disease therapies or available in other dosage forms, such as a hard-shell capsule, may be subject to other legal classifications. As of January 2014, 19 states and the District of Columbia allowed medicinal use of cannabis in select patients with certain disease states, most commonly seizure disorders and chronic pain.¹⁴

The addiction potential and stigma of marijuana use are important considerations, and the benefits of cannabinoid therapies for PTSD must be weighed against the associated adverse drug events (some of which can be life-threatening).¹⁴ The purpose of this review is to analyze current relevant literature surrounding the use of cannabis and cannabinoids for PTSD symptom control by military veterans, with the goal of providing insights on whether these treatments improve or worsen patient outcomes.

Methods and results of literature review

During the period February 10–October 1, 2014, a comprehensive literature search covering the period January 1, 1995, to October 1, 2014, was conducted using PubMed (MEDLINE) and Academic Search Complete (EBSCO Industries, Inc., Ipswich, MA). Both Medical Subject Headings (MeSH) terms and the subheadings feature of PubMed were used. Keywords were searched separately in combination with appropriate Boolean operators.

Keywords in searches included *PTSD*, *post traumatic stress disorder*, *medical marijuana*, *cannabis*, *medical cannabis*, *marijuana*, and *combat vet-*

erans (appendix). For the purposes of this review, the term *cannabinoid* was considered to apply to endocannabinoids. On identification of articles that met the inclusion criteria, the references cited therein were analyzed for additional relevant articles not identified in the original keyword and MeSH term searches.

The article/study inclusion criteria that were applied to each item retrieved in the search were as follows:

- Reported outcome(s) related to the general use of cannabinoids among persons with a diagnosis of PTSD associated with military experience or the use of cannabinoids for the amelioration of PTSD symptoms associated with military experience
- Pertained to research in humans
- Was written in the English language
- Pertained to individuals with PTSD diagnosed via a standard scale (e.g., *DSM-IV* or *DSM-5* criteria, Impact of Event Scale—Revised)

Editorials and opinion pieces were excluded from the review.

Each article identified for inclusion in the review was analyzed by the authors individually and collaboratively in order to determine its clinical relevance and relative standing in the realm of data supporting or militating against medicinal cannabis use for PTSD symptoms.

A total of 59 articles were identified through PubMed and the EBSCO database. Pursuant to application of the inclusion and exclusion criteria, 11 articles were included in this review. A variety of study designs were represented in the list of selected articles, and all evaluated research supported two general concepts: (1) many people suffering from PTSD use cannabis for symptom alleviation, and (2) some people find it of benefit in that regard.

Cannabinoids and coping mechanisms

Several studies supported the

relationship between cannabinoid use and coping behavior, with usage tending to increase with PTSD symptom severity.^{2,5,16-18} Bonn-Miller et al.¹⁶ conducted a cross-sectional study that examined the relationship between PTSD symptom severity and motives for marijuana use among 103 young adult marijuana users who reported at least one traumatic event in their lifetime. The study concluded that symptom severity was significantly related to coping-oriented marijuana use motives. Furthermore, levels of post-traumatic stress were not related to other motives for marijuana use, providing evidence of “discriminant validity” (a construct aimed at showing that things that should not be related are, in fact, not related) and empirical evidence of coping motives for marijuana use.

In other research, Bonn-Miller and colleagues⁵ used a cross-sectional study design to examine the correlation between difficulty in emotional regulation and use of cannabis as a coping mechanism in patients who have experienced traumatic life events. The study surveyed a fairly homogeneous sample of adults who reported marijuana use within the previous 30 days. A multitude of surveys were used to determine marijuana use, the presence of PTSD symptoms, and each participant’s level of difficulty with emotional regulation. The investigators found that PTSD symptom severity and difficulty in emotional regulation were both significantly predictive of coping-oriented marijuana use. Furthermore, PTSD symptom severity predicted the degree of difficulty in emotional regulation even when the frequency of marijuana use was controlled.

Bonn-Miller et al.¹⁷ subsequently hypothesized that patients with PTSD using medical marijuana for sleep might increase their use in an attempt to cope with more severe symptoms. As in their previous research, the investigators chose a

cross-sectional study design, evaluating coping-use motivations, cannabis and alcohol use, and other outcomes in a convenience sample of male and female adult patients buying cannabis from a licensed dispensary. Based on PCL-M scores, two groups were formed: patients without PTSD (defined as a PCL-M score of ≤ 30 [$n = 95$]) and patients with PTSD (defined as a score of >30 [$n = 75$]). The study results showed that patients with PTSD had a greater motivation to use cannabis for sleep and coping reasons than the non-PTSD group regardless of comorbid alcoholism or depressive symptoms. This study was limited by its narrow focus on patients who were already using medical marijuana. As the researchers noted, the fact that tolerance to marijuana's sleep-inducing effects can develop seemed inconsistent with the finding that PTSD led to increased use of cannabis.

Potter et al.¹⁸ conducted a cross-sectional study ($n = 142$) of adults in Vermont with PTSD to investigate the role of distress tolerance in relation to PTSD symptom severity and marijuana use. The researchers found that PTSD symptom severity was positively correlated with marijuana-use coping motives ($r = 0.37, p < 0.01$) and negatively correlated with distress tolerance ($r = -0.47, p < 0.01$). Their overall conclusion was that distress tolerance may play a partial role in mediating the relationship between PTSD symptom severity and coping-oriented marijuana use.

Cannabinoids, worsening of PTSD symptoms, and substance abuse

Studies included in this review examined the possible link between cannabis use and worsening of PTSD symptoms or concomitant substance abuse.^{2,19} Bonn-Miller et al.² used a prospective cohort study design to analyze cannabis use in relation to PTSD symptom severity in a population of 432 male military veterans (mean \pm S.D. age, 51 ± 4

years) admitted to a VA residential treatment program for patients with PTSD. Cannabis use four months after the completion of the rehabilitation program was significantly more likely in program participants with lower levels of improvement from intake to discharge in PCL-M scores for avoidance–numbing and hyperarousal symptom clusters ($p < 0.05$). The researchers concluded that lower improvement in PCL-M scores at program completion was significantly predictive of an increased risk of cannabis use within the four months after discharge.

Although this study lacked generalizability (i.e., it involved only patients seen in a VA residential rehabilitation program), it suggested that specific symptoms have more influence than others on PTSD patients' desire to use cannabis. A major limitation of this study was that patients in the rehabilitation program were required to quit marijuana use for the duration of their treatment, but the effect of cannabinoid withdrawal was not included in the analysis. Furthermore, the study involved a nonrandomized sample, raising the possibilities of high subjectivity and bias.

Bremner et al.¹⁹ conducted a similar cross-sectional study of Vietnam War military veterans ($n = 61$) in the northeastern United States. This study aimed to measure the progression of some PTSD symptoms and related alcohol and substance abuse symptoms, as well as the effects of abused substances on those PTSD symptoms. The researchers found that PTSD symptoms were increased among veterans using substances such as alcohol, heroin, cocaine, and marijuana. Further, the study showed that veterans using said substances reported benefits with regard to PTSD symptoms.

Cannabinoids and reduction of PTSD symptoms

Research also has examined the reduction of PTSD symptom sever-

ity after treatment with cannabis products.^{3,4} A study by Mashiah⁴ examined the use of medical cannabis in Israeli military veterans ($n = 29$) with diagnosed chronic PTSD. Study participants were given no more than 100 g of cannabis per month and instructed to smoke the cannabis daily at frequencies and amounts of their own choosing. Patients were reassessed three times throughout one year by their psychiatrists. At each reassessment, the study found that the average total Clinician-Administered PTSD Scale (CAPS) score was reduced relative to previously assessed and baseline scores. However, all patients still met the criteria for moderate-to-severe PTSD. This report did not describe the baseline cannabis-use characteristics of the evaluated patients. Additionally, only 10 participants were reassessed after the second follow-up, with no explanation provided by the study author.

Greer et al.³ performed a chart review–based study of 80 patients with PTSD participating in New Mexico's Medical Cannabis Program. The total CAPS score and CAPS symptom-cluster scores for reexperiencing, avoidance–numbing, and hyperarousal symptoms were significantly reduced ($p < 0.0001$) when patients were using cannabis relative to scores obtained under the no-cannabis condition. Overall, patients reported more than 75% reductions in all three areas of PTSD symptoms while using cannabis. It should be noted that participants in this study had already found cannabis to reduce their PTSD symptoms and, partly for that reason, sought entry into the cannabis program (they also sought to avoid criminal penalties for marijuana possession); as a result, they might have been predisposed to report reduced symptoms. Further, it is possible that subjects exaggerated their PTSD symptoms during initial CAPS assessment in hopes of qualifying for the program. While this study

sheds some light on the possibility of medical cannabis being an effective treatment for PTSD, it lacked a control sample of PTSD sufferers with no prior experience with cannabis and involved a large potential and motives for bias.

Nabilone, a synthetic endocannabinoid receptor agonist, has been studied for potential usefulness in mitigating PTSD symptoms, particularly insomnia and nightmares.^{20,21} Cameron et al.²⁰ conducted a retrospective chart review–based study of patients with mental illness ($n = 104$) who received nabilone while admitted to a correctional and treatment facility in Canada (90% of the patients had PTSD). The researchers looked at indications for nabilone use, effectiveness and safety outcomes, and medications discontinued when cannabinoids were added to patients' regimens. Nabilone was used to treat a mean of 3.5 indications per patient, most commonly nightmares, insomnia, and chronic pain. Improvement in PTSD symptoms was assessed via analysis of scores on the PTSD Checklist—Civilian (PCL-C), which is very similar to the PCL-M, and the Global Assessment of Functioning (GAF). On average, posttreatment PCL-C scores were significantly decreased ($p = 0.001$) from pretreatment scores, allowing many cases initially classified as moderate-severity PTSD to be reclassified as borderline or mild cases; the mean GAF score increased significantly ($p = 0.001$), indicating improved functioning and decreased symptoms. Thirty-one patients reported adverse events during treatment with nabilone, the most serious being psychosis; of those 31 patients, 10 chose to abandon the study. The authors concluded that nabilone can potentially decrease PTSD symptoms, including insomnia and nightmares, in patients with diagnosed cannabis dependence.

Another investigator conducted an open-label clinical trial to

evaluate the effects of nabilone on treatment-resistant nightmares in patients ($n = 47$) with PTSD.²¹ Patients were reviewed after adjunctive treatment with 0.5 mg of nabilone one hour before bedtime. Thirty-four patients (72%) receiving nabilone experienced either cessation of nightmares or a significant reduction in nightmare intensity. The researcher also found subjective improvements in terms of sleep time and daytime flashbacks. The results of the study indicated the potential benefits of nabilone in patients with PTSD experiencing poor control of nightmares with standard pharmacotherapy.

Discussion

All articles evaluated in this review indicated that individuals suffering from PTSD symptoms related to military experiences often use cannabis or cannabinoids as a means of coping, with some reporting benefits. The studies also suggested that the pathogenesis of PTSD—and, most likely, effective treatment—is multifactorial.

Of note, the research described in the reviewed articles was generally limited by the use of small nonrandomized and/or self-selected samples that lacked control groups and carried a high potential for recall bias and type II error. These limitations should be the catalyst for further research through large, randomized, placebo-controlled trials. With growing evidence that patients with PTSD use cannabis and its derivatives as a means of symptom alleviation, it is becoming necessary for the healthcare community to better understand this phenomenon.

There is a growing need for research comparing the effects of cannabinoids with those of conventional pharmacotherapies currently used in PTSD (e.g., prazosin, selective serotonin reuptake inhibitors, second-generation antipsychotics) and cognitive-behavioral therapy. Head-to-head comparisons of the

conventional therapies with cannabinoids are needed in order to demonstrate whether one treatment is superior to another in terms of safety or efficacy. Like cannabinoids, all current pharmacotherapies used for PTSD carry known risks that potentially outweigh benefits from use. With the rising number of veterans returning from recent conflict zones, and a subsequent rise in PTSD cases, the need for quality research in this area is great.

Conclusion

While further research into cannabinoid treatment effects on PTSD symptoms is required, the evaluated evidence indicates that substantial numbers of military veterans with PTSD use cannabis or derivative products to control PTSD symptoms, with some patients reporting benefits in terms of reduced anxiety and insomnia and improved coping ability.

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Appendix—Keyword strings used in literature search

(medical marijuana OR medical cannabis OR marijuana OR cannabis) AND PTSD
 medical marijuana AND PTSD
 medical cannabis AND PTSD
 marijuana AND PTSD
 cannabis AND PTSD
 medical marijuana AND PTSD NOT depression
 medical marijuana AND combat veterans
 medical cannabis AND combat veterans
 marijuana AND combat veterans
 cannabis AND combat veterans