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## The Use of Medicinal Marijuana for Posttraumatic Stress Disorder: A Review of the Current Literature

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### Abstract

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#### Background:

Medicinal marijuana has already been legalized in over 23 states with more considering legalization. Despite the trend toward legalization, to date, there has been no systematic review of the existing literature for the efficacy of medicinal marijuana for many of the conditions for which it is proposed to treat. This study seeks to understand the current literature regarding the use of medicinal marijuana in the treatment of posttraumatic stress disorder (PTSD).

#### Data Sources:

PubMed and PsycINFO databases were searched until April 2014 for articles outlining outcomes of case files, control studies, and observational studies regarding the efficacy of medicinal marijuana in treating PTSD. Various combinations of the following search terms were used: *marijuana*, *medicinal marijuana*, *cannabis*, *cannabinoid*, *PTSD*, *efficacy*, *trial*, and *neurobiology*.

#### Study Selection:

Full text of each article was reviewed, and those directly addressing the question of efficacy of medicinal marijuana on PTSD symptomatology were included. Data were extracted from a total of 46 articles.

## Results:

Analysis revealed that most reports are correlational and observational in basis with a notable lack of randomized, controlled studies. Many of the published studies suggest a decrease in PTSD symptoms with marijuana use. Though the directionality of cannabis use and PTSD could not be fully differentiated at this time, there appears to also be a correlation between PTSD and problematic cannabis use. Despite this finding, there is a growing amount of neurobiological evidence and animal studies suggesting potential neurologically based reasons for the reported efficacy.

## Conclusions:

Posttraumatic stress disorder is 1 of the approved conditions for medicinal marijuana in some states. While the literature to date is suggestive of a potential decrease in PTSD symptomatology with the use of medicinal marijuana, there is a notable lack of large-scale trials, making any final conclusions difficult to confirm at this time.

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### Clinical Points

- Posttraumatic stress disorder (PTSD) is one of the approved conditions for medical marijuana in some states.
- Current literature is suggestive of a potential decrease in PTSD symptomatology with medical marijuana, but also suggests a correlation with problematic cannabis use, though directionality is not established at this time.
- Neurobiological studies in both humans and animal models are providing further insights into the reported efficacy of medical marijuana for PTSD.
- Lack of large-scale randomized controlled trials makes any final conclusions difficult.

Cannabis is currently the most widely used illicit substance, with approximately 18.1 million people reporting use within a 1-month period in 2011 within the United States alone.<sup>1</sup> The rapidly changing legal environment surrounding cannabis, both for medicinal and recreational use, is becoming increasingly relevant to patient care. While still illegal under federal law, at least 23 states have approved marijuana for medical use, and recreational use is now legal in Colorado and Washington. The approval of marijuana as a purported medication is unique, as it is done under state authority, either by ballot or by state legislature approval, without approval of the US Food and Drug Administration (FDA). Whereas the FDA requires multiple rigorous clinical trials evaluating safety and efficacy prior to the approval of a drug for a specific indication, there are no standard requirements for state approval of indications for medical marijuana. In at least 8 states, 1 of the indications for medical marijuana is posttraumatic stress disorder (PTSD).<sup>2</sup> The current circumstances create an awkward situation in which researchers must evaluate the safety and efficacy of medical marijuana after its approval for various indications, including PTSD.

## NEED FOR RESEARCH

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Despite claims of medical use, marijuana remains illegal. Currently, in the United States marijuana remains listed as a Schedule I drug, meaning that there is a high abuse potential and no accepted medical use. Despite this, there are a growing number of claims that marijuana, particularly in the smoked form, has medical benefits. Indeed, early National Institutes of Health (NIH)-sponsored studies supported the claim that marijuana decreased nausea and vomiting in chemotherapy patients, resulting in FDA approval of a synthetic form of oral cannabis. Later, FDA approval for synthetic cannabis was extended to AIDS wasting syndrome.<sup>3</sup> This approval resulted in a multitude of claims of the benefits of marijuana for other potential conditions, leading to 2 large government-sponsored studies into the use of medical marijuana.<sup>4,5</sup> While both of these studies set out to finalize views on the matter, both ultimately found that there were simply too few scientific studies to determine the utility of medical marijuana; however, both concluded further research on the matter was justified.<sup>3</sup> This article seeks to review the existent literature to help determine the current state of such studies in regard to the use of medicinal marijuana in the treatment of PTSD.

## METHOD

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Potential studies for inclusion were identified by querying PubMed and PsycINFO for various combinations of the terms *marijuana*, *medicinal marijuana*, *cannabis*, *cannabinoid*, *PTSD*, *efficacy*, *trial*, and *neurobiology* up to April 2014. Duplicate studies were removed from inclusion. Articles adopting descriptive, observational, analytic, and experimental studies of both human and animal trials were considered for establishing proposed neurobiological basis. As such, animal studies, case studies, qualitative articles, reviews, and commentaries were reviewed. Given the limited number of studies on this topic, all were considered for inclusion. Full text of each article was reviewed, and those directly addressing the question of efficacy of medicinal marijuana on PTSD symptomatology were included. Data were extracted from a total of 46 articles.

## RESULTS

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### Who Uses Medicinal Marijuana?

Despite the lack of established medical use, marijuana is currently used for a number of conditions. Most commonly, medical marijuana users were found to be male, white, between 25 and 44 years of age, and employed.<sup>6</sup> Reportedly, the most commonly cited primary uses for medical marijuana were pain, ranging between 82.6% and 92.2% of subjects, followed by muscle spasm (21%–41.3%).<sup>6,7</sup> Other reported primary uses included headaches, anxiety, insomnia, relaxation, poor appetite, nausea, and vomiting.<sup>6</sup> Interestingly, in states that allow for use of medical marijuana for traumatic intrusions and PTSD, this was listed as the primary indication in 38.5% of registered users.<sup>7</sup>

### Studies Evaluating Use in PTSD

To date, there has been little research investigating the relationship between marijuana use and PTSD. Existing studies have mostly focused on the tendency of individuals who suffer PTSD symptoms to self-medicate with marijuana. Undoubtedly, marijuana has long been reported as a coping mechanism for individuals with heightened PTSD symptoms.<sup>8-10</sup> It has been suggested that individuals with less perceived ability to withstand emotional distress were more likely to attempt to self-soothe with marijuana in response to distressing emotions related to trauma. Additionally, those with more symptomatology associated with PTSD were suggested to be more likely to use marijuana with the explicit purpose of coping.<sup>11</sup> Bonn-Miller et al<sup>8</sup> suggested that patients with more severe PTSD symptoms may be more motivated to use cannabis. In their study, marijuana use positively correlated with PTSD symptoms and, according to self-reports, cannabis was used with intent to cope with these PTSD symptoms.<sup>8</sup> Indeed, the mere fact that an individual carries a diagnosis of PTSD significantly increases his or her chance of using marijuana at some point in life,<sup>12</sup> a relationship that also holds true even among teenagers.<sup>13,14</sup>

Cannabis use has been associated with a decrease in symptomatology, but may also be associated with higher risk of cannabis use disorder. Greer et al<sup>15</sup> reported a 75% reduction in Clinician Administered Posttraumatic Scale for *DSM-IV* (CAPS) scores through use of medical marijuana, and cannabis has been reported to be particularly helpful among persons with severe traumatic intrusions,<sup>16</sup> commonly referred to as flashbacks, as well as for managing hyperarousal symptoms.<sup>17</sup> Many people suffering from PTSD often have interrupted sleep, with many seeking medical marijuana as a means of helping them treat their sleep issues; however, while marijuana may help with sleep in the short term, it may also interfere with long-term sleep structure.<sup>18,19</sup> Cannabis has also been shown to have anxiolytic and anxiogenic properties depending on the primary cannabinoid.<sup>20</sup> The perceived sense of anxiolytic relief from cannabis may drive the high prevalence rates and co-occurrence between PTSD and cannabis use,<sup>17,21,22</sup> though arguments do exist that anxiety (including PTSD) and depression are associated with problematic cannabis use patterns and dependence.<sup>12,23-27</sup> Several studies have shown an increased chance of cannabis use disorders among adults suffering from, in particular, PTSD.<sup>12,23,28,29</sup> Boden et al<sup>30</sup> explained this phenomenon by suggesting "(a) the experience of PTSD predisposes affected individuals to use cannabis to cope with negative internal states, (b) discontinuation of cannabis use (even temporarily) paradoxically leads to greater PTSD symptomatology, via withdrawal, resulting in (c) heightened craving for cannabis, and (d) greater cannabis use problems as well as relapse to cannabis use to cope with increased negative internal states."<sup>(p282)</sup> Further, increasing rates of cannabis use disorder diagnoses have been documented among military veterans,<sup>22,23</sup> especially those who endorse high rates of trauma exposure and PTSD.<sup>31-35</sup> With the large number of young men and women returning from war with traumatic experiences, veterans appear to be at particular risk for potential cannabis use disorders as a result. Therefore, determining the true causal relationship has never been more important.

### Proposed Neurobiological Mechanisms

Marijuana is not just a single drug; it is a mixture of leaves from the *Cannabis sativa* plant and contains more than 400 chemicals with over 60 of these referenced as cannabinoids. Perhaps the most well-known and well-studied, delta-9-tetrahydrocannabinol (THC), is the main psychoactive cannabinoid. While ingested in a number of forms, once in the body, THC interacts with the

cannabinoid receptors. There are 2 main cannabinoid receptors. Cannabinoid receptor 2 (CB2) is thought to exist primarily external to the central nervous system (CNS). CB2 is thought to exert its main effects on the immune and reproductive systems<sup>3,36,37</sup> and is thought responsible for the reported alleviating effects of cannabis on autoimmune dysfunction and potentiation of inflammatory reactions.<sup>37</sup> Given the limited neurologic interaction of CB2, this article will focus on cannabinoid receptor 1 (CB1), which is believed to be responsible for most, if not all, of the psychoactive effects of THC.<sup>3,37</sup>

Purportedly the most abundant receptor in the brain, the actual density of CB1 receptors varies. Brain regions with the highest concentrations of CB1 receptors are in areas primarily involved in memory formation (hippocampus), motor coordination (the cerebellum), and emotionality (prefrontal cortex).<sup>37</sup> This distribution correlates well with reported effects of THC on human behavior: modulation of pain, regulation of appetite, regulation of pleasure, memory formation, concentration, sensory and time perception, and coordination of movement and motor function, as well as abuse and addictive potential.<sup>3,37,38</sup> An example of such an effect on human behaviors is the reported correlation between cannabis and decreased hyperarousal states. The modulation of the “fight or flight” response occurs largely in the amygdala; animal studies have demonstrated that electrical stimulation of various regions of the amygdala can send the animal into states of terror or surreal calm. There is a heavy concentration of CB1 receptors and endocannabinoids in the amygdala, which may help explain why low-dose cannabinoid stimulation is generally felt as calming.<sup>39</sup> Indeed, transgenic mouse models have shown that CB1 overexpression decreases excessive excitatory neurotransmission in these brain areas, which may explain the decreased arousal symptoms, as well as reduction of anxiety associated with cannabis use.<sup>40</sup> Given that hypervigilance and hyperarousal are symptoms of PTSD, this correlation may help explain, at least in part, the proposed benefit of cannabis for patients with PTSD.<sup>17,23</sup>

One commonly reported side effect of chronic cannabis abuse is impairment in short-term memory. At first this may sound unwanted, but at times, it may be desirable to forget negative traumatic events and so may be potentially useful in treatment of PTSD.<sup>3</sup> Animal experiments have demonstrated that it took cannabinoid-deficient CB1 knock-out mice significantly longer to forget an association with painful foot shocks and bell ringing than wild-type controls, but both groups continued to make positive associations, suggesting THC may facilitate the extinction of negative memory without affecting positive memory formation.<sup>41-43</sup> Reciprocally, when the endocannabinoid system was activated through slowing of breakdown of endogenous cannabinoids, animal models demonstrated the ability to dissociate negative associations faster than in their normal state, leading to proposed involvement of the endocannabinoid system in the extinction of aversive memory.<sup>43</sup> Indeed, it may be this trait of cannabis that drives persons with PTSD to seek out and, at times, abuse cannabis.<sup>16</sup> However, this correlation has not yet been investigated in a well-structured clinical setting.<sup>16,37,43</sup>

External stimulation of CB1 may not fully explain extinction of aversive memories. While CB1 knockout mice may require more time to forget adverse memories, so do mice with blockade of the endocannabinoid system.<sup>41,42</sup> Indeed administering THC on a chronic basis reduces the number of available cannabinoid receptors by 20%–60%, which effectively leaves the body’s natural endocannabinoids with fewer sites to activate, which may reduce their overall impact.<sup>44</sup> Some

have attempted to reconcile this incongruity by suggesting the extinction response is due to fatty acid amide hydrolase, the enzyme that degrades endocannabinoids.<sup>45</sup> Clearly, more studies are needed on this matter. Another argument against mere stimulation of CB1 focused on the exclusive use of classical conditioning in the extinction studies, as this is seen as far removed from the experiences that result in PTSD in which the stressor is often seen as being of “human design.”<sup>44</sup> Indeed, as critics of medical marijuana have observed, no amount of numbing of PTSD is likely to help veterans process the deep grief and pain of having participated in the human tragedy of war.<sup>44,46</sup>

## CONCLUSION

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In summary, cannabis is the most widely used illicit substance in the United States. With a growing number of states seeking to legalize marijuana for medicinal purposes, there is a need for a better understanding regarding the mechanism of action and efficacy of cannabis for the conditions for which it is prescribed. This article sought to review the existing literature regarding the use of cannabis for PTSD. To date, there is no large-scale, randomized, controlled study investigating efficacy of marijuana and PTSD symptomatology; however, the literature that exists suggests that it may have an effect on decreasing PTSD symptoms, and the neurobiological and animal studies seem to suggest potential underlying mechanisms consistent with these findings. However, PTSD may also be related to problematic, pathological use of cannabis. Additionally, the overall literature may be limited by publication bias, and the lack of standardized, large-scale controlled trials at this time makes any final conclusions on the efficacy uncertain. As the number of people seeking medical marijuana as well as those self-medicating for PTSD continues to rise, there is a clear need for more research trials and monitoring of the long-term effects of using cannabis for the treatment of PTSD and other medical conditions. Until then, given the limited evidence, physicians need to use their own clinical judgment when weighing the potential risks and benefits for a particular patient.

### Potential conflicts of interest:

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