Effects of Marijuana on Mental Health:
Posttraumatic Stress Disorder (PTSD)

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Highlights

- The endocannabinoid system appears to play an important role in responses to stress, fear, and anxiety.
- Preclinical studies with animal models of PTSD suggest that cannabinoids may be useful for treating PTSD. However, there have been few controlled studies with humans.
- Despite the fact that 22 states have allowed the use of medical marijuana for PTSD, there are no randomized controlled trials examining the efficacy or safety of marijuana for PTSD in humans.
- Research suggests that many individuals with PTSD who use marijuana do so to cope with PTSD symptoms.
- Using marijuana to cope with PTSD puts individuals at risk of marijuana dependence and adverse reactions, as anxiety and panic are the most commonly noted negative acute effects of marijuana intoxication.

Introduction

Marijuana is the most commonly used drug of abuse in the United States.[1] As found in the 2015 National Survey on Drug Use and Health, 22.2 million people aged 12 and older had used marijuana in the past month.[1] Research suggests that marijuana use has increased over the past decade[2-4] as perceptions of risk of harm from using marijuana among adults in the general population have steadily declined.[4] As of June 2017, 26 states and the District of Columbia have enacted laws that have legalized marijuana use in some form, and 3 additional states have recently passed measures permitting use of medical marijuana.[5] Mental health conditions figure prominently among the reasons given for medical marijuana use[6], yet there is a dearth of rigorous, experimentally controlled studies examining the effects of marijuana on mental health conditions.[7] This research brief will summarize what is known about the effects of marijuana on posttraumatic stress disorder (PTSD). Formerly considered an anxiety disorder but now considered a trauma- and stressor-related disorder, PTSD is a complex mental health condition with some symptom overlap with both anxiety and depression. PTSD symptoms are grouped into four categories: intrusive re-experiencing of the trauma (e.g., nightmares and flashbacks), effortful avoidance of reminders of the trauma (e.g., not discussing the traumatic event, not going where it occurred), negative alterations in cognitions and mood following the trauma (e.g., trauma-related guilt/mistrust, anhedonia/diminished interest), and altered arousal/reactivity (e.g., difficulty concentrating, sleep disturbance).[8] These symptoms often lead to significant impairment among those with a diagnosis of PTSD.

Overview of Complexities in Specifying Marijuana Effects

Any summarization of the effects of marijuana on mental health would be lacking without a brief overview of complexities in specifying marijuana effects. Unlike, say, methamphetamine, marijuana is not a single chemical compound. As a plant, marijuana is composed of more than 500 chemical substances.[8] Only a fraction of these

Table 1. CNS and cardiovascular effects of THC and CBD.

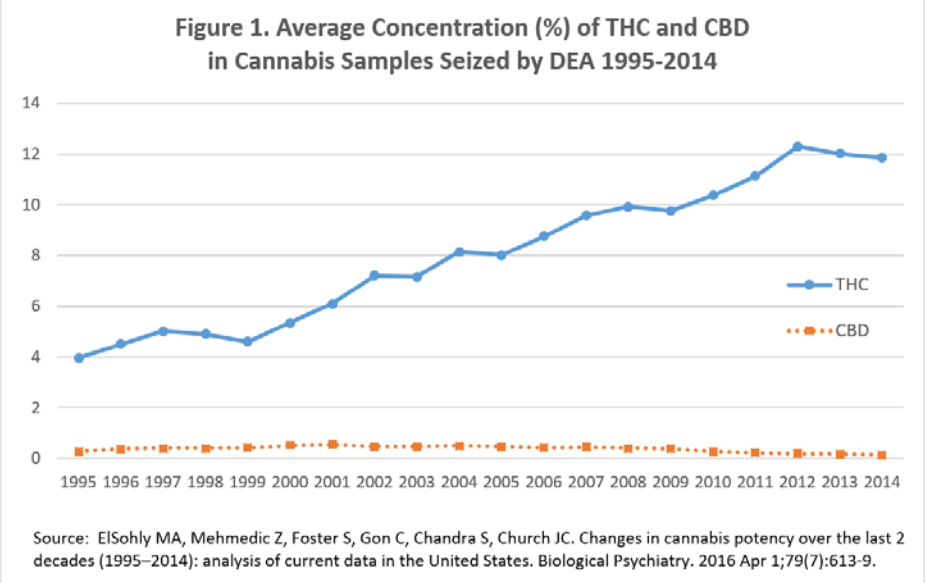
	THC	CBD
Anticonvulsant	+	++
Muscle relaxant	++	+
Analgesic	++	+
Anxiolytic	±	++
Antipsychotic	–	++
Neuroprotective	+	++
Antiemetic	++	+
Sedation	+	–
Bradycardia	–	+
Tachycardia	+	–
Hypertension	+	–
Hypotension	–	+

Adapted from Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Medical Hypotheses. 2006 Dec 31;66(2):234-46.

have been studied. It is generally understood that the psychotropic substance in marijuana that is primarily responsible for its intoxicating effects is delta-9-tetrahydrocannabinol (THC).[9] More than 100 other compounds have been identified in marijuana that are chemically related to THC, called cannabinoids.[8] Cannabinoids exert their effects through the relatively recently discovered endocannabinoid system; only since the late 1980s has it been recognized that humans and other mammals have cannabinoid receptors throughout the body and endogenous cannabinoids that modulate the effects of neurotransmitters and other cellular mechanisms in ways that are not yet fully understood but that have generated intense interest as potential targets for therapeutic drug development, including drugs for mental health.[9] Of the two known cannabinoid receptors, CB1 and CB2, CB1 is expressed abundantly in the brain and central nervous system (CNS) while CB2 expression is low in the CNS but high in peripheral immune cells and tissues.[10] Psychoactive effects of marijuana are attributed to CB1 receptors whereas CB2 receptors are non-psychoactive.[9, 10]

Aside from THC, the most studied phytocannabinoid is cannabidiol (CBD).[11] CBD has been described as nonpsychotropic due to the fact that it appears to be non-intoxicating and non-reinforcing, but it does appear to be psychotropic insofar as it appears to have pharmacological benefits with regard to anxiety, schizophrenia, addiction, and depression.[12] Table 1 summarizes the major CNS and cardiovascular effects of THC and CBD.[11] CBD has been demonstrated to attenuate certain effects of THC, including intoxication, sedation, and tachycardia.[11] In modern clinical trials, this has permitted the administration of higher doses of THC in an effort maximize therapeutic effects while minimizing side effects.[11] It is largely unknown how the interaction of THC and CBD plays out in practical use of marijuana by medicinal and recreational marijuana users.

Research on cannabis products seized by the US Drug Enforcement Agency (DEA) shows that the potency of marijuana in common use has increased dramatically in the last 2 decades, at least in terms of THC content.[8] As shown in Figure 1, from 1995 to 2014, the average THC content of seized cannabis products virtually tripled from approximately 4% to approximately 12%.[8] On the other hand, average CBD content fell from approximately 0.28% in 2001 to < 0.15% in 2014, resulting in a change in the THC:CBD ratio of 14:1 in 1995 to approximately 80:1 in 2014.[8] This means that, on average, the cannabis products seized in 2014 were presumably far more intoxicating and than those seized in 1995 – and marijuana and cannabis products that are in common use may bear little resemblance to marijuana supplied by the federal government for marijuana research.[13] In terms of strength, the National Institute on Drug Abuse considers less than 1% to be low, 1-5% to be medium, 5-10% to be high, and over 10% to be very high.[14] An examination of the online menu of one of Seattle's most popular



recreational marijuana stores in June 2017 listed over 100 varieties of marijuana "flowers" that were labeled as 20% THC or higher, with THC content going as high as 30%. For many of these, CBD content was not listed. By comparison, there were only 20 varieties with listed THC content under 10%. Marijuana concentrates were labeled as having THC content as high as 97%. From a scientific standpoint, the effects of cannabis products with such levels of THC on mental health have largely not been studied.

Individual differences in objective and subjective effects of marijuana vary by individual, variety/strain, dosage, route of administration, personality, degree of tolerance, and other factors.[9] Many of the psychological effects of cannabis and THC are biphasic and bidirectional.[9] Acute marijuana intoxication is generally associated with euphoria, subjective quickening of associations, relaxation, decreased motor activity, a sense of calm, increased awareness of sensory experience and internal sensations of the body, transient sensory experiences, synesthesia, craving sweet and salty foods, enhanced perception of current activities, increased salience of stimuli, simultaneous focus on multiple things, impaired shifting of focus, fantasies of power, and belief of having arrived at a transcendent insight.[15] With regard to neurocognition, marijuana intoxication is associated with deficits in processing speed, attention, working memory, decision-making, motivation, time-perception, and reality testing.[15] Considering the broad range of effects, one can begin to imagine how marijuana could have beneficial or harmful effects with regard to mental health.

Tolerance to certain effects of marijuana develops with regular use, within several days in some cases,[9] as a function of CB1 receptor expression downregulation.[10] Research suggests that after tolerance develops it can take several weeks of THC-free recovery for CB1 receptor expression to return to baseline levels.[10] Because of tolerance, the eventual downregulation of CB1 receptors with chronic use means that any benefit derived from THC with regard to mental health could result in symptom exacerbation when users are not under the influence of THC.[10]

The Role of the Endocannabinoid System in PTSD

The endocannabinoid (eCB) system is expressed in all brain regions that are important for the processing of anxiety, fear, and stress and has been identified as playing an important role in these responses.[17] ECB signaling appears to constrain the magnitude of the stress response.[18] Both for anxiety and fear memory processing, the eCB system is thought to ensure an appropriate reaction to stressful events and to serve as a regulatory buffer system for emotional responses.[20] In preclinical studies, CB1 receptor activation impairs the retrieval of aversive memories and enhances their extinction, which suggests potential to ameliorate flashbacks and nightmares in PTSD.[8] Relatedly, CB1 receptor activation following stressor exposure has been shown to prevent the occurrence of PTSD-like behaviors.[8]

In human recreational marijuana users with no history of psychiatric illness, a placebo-controlled fMRI study showed that THC significantly reduced reactivity to threatening stimuli in the amygdala,[19] an area of the brain that is associated with PTSD.[20] Basal eCB signaling appears to be reduced in individuals afflicted with stress-related psychiatric conditions, such as PTSD, suggesting that impaired eCB signaling is related to the development of these conditions. It is unknown whether this reduction in eCB signaling is a pre-existing risk factor to the development of PTSD or an effect of PTSD.[18]

Effects of Marijuana Intoxication on PTSD-related symptoms

There exists quite a bit of anecdotal and case-report evidence that smoking marijuana can reduce PTSD-related flashbacks, nightmares, anxiety, and hyperarousal.[21] However, very little high quality research evidence exists to demonstrate this. At this time, no reported randomized controlled trials have shown benefits of cannabis in PTSD, anxiety disorders, or depression.[11] There have been human studies of the relationship between marijuana

intoxication and anxiety that is relevant to PTSD, and there does exist some low quality evidence with respect to treatment of PTSD with cannabinoids,[22] described below.

Research suggests one of the primary reasons individuals use marijuana regularly is to take the edge off stressful life events, reduce feelings of tension, and promote relaxation.[23] However, anxiety and panic reactions are the most commonly noted negative acute effects of marijuana intoxication.[24] While the likelihood of marijuana intoxication to reduce or increase anxiety appears to depend on a variety of factors, including individual and genetic vulnerability, personality traits, gender, use frequency, dose, THC:CBD ratio, history of previous anxiety reaction, presence of anxiety disorder/symptoms, basal anxiety state, abstinence states, and environment and context of use, all other things being equal, THC appears to decrease anxiety at lower doses and increase anxiety at higher doses .[24] CBD, on the other hand, appears to have robust anxiolytic effects without anxiogenic effects at higher doses.[24] Similarly, whether marijuana has pro- or antitherapeutic effects on PTSD symptoms is likely to be a function of dose, phytocannabinoid constituent ratio, individual differences and other factors.[8]

Medicinal Use of Marijuana for PTSD

In 2009, New Mexico became the first state to explicitly authorize the use of medical marijuana (MM) for people with PTSD.[25] As of June 2017, PTSD is expressly listed as a qualifying condition in 22 states that allow for medicinal use of marijuana.[26] Research indicates that 19% of MM users report they use MM to manage PTSD.[27] In states that allow for use of MM for PTSD, this was listed as the primary indication by 38.5% of registered users.[28]

There are no randomized controlled trials examining the efficacy or safety of marijuana in PTSD.[22] Available research on treatment of PTSD with marijuana primarily includes studies of THC and synthetic THC analogs, rather than whole plant marijuana.[8] A 2014 study examined retrospectively self-reported PTSD symptoms on the Clinician Administered Posttraumatic Scale for DSM-IV (CAPS) with and without marijuana use among 80 individuals being evaluated by a psychiatrist to use MM for PTSD in the New Mexico Medical Cannabis Program.[25] The researchers found that those being evaluated reported significant improvements in re-experiencing, avoidance, and hyperarousal symptoms when they were using marijuana compared to when they were not. Across the three symptom clusters, participants reported a greater than 75% reduction in their symptoms while using cannabis. The researchers note their sample consisted of self-selected individuals who had already found that cannabis reduced their PTSD symptoms and who sought entry to the Medical Cannabis Program to avoid criminal penalties for possession, potentially biasing the results.[24] Unfortunately, at this time, this is the only available treatment outcome data on whole plant marijuana for PTSD that is not a case report.[8]

In 2016, Wilkinson et al.[28] reviewed the evidence for treatment of PTSD with medical marijuana. While nabilone, a synthetic THC analog, has been associated with improvements in functioning, sleep duration, sleep quality, nightmares, and flashbacks, the researchers noted that the strength and quality of the evidence in this area is very low.[28] Steenkamp et al.[8] reviewed the same evidence and drew a similar conclusion, noting that the few available studies have not consistently established the clinical significance of observed symptom reductions while they are beset with methodological limitations, including uncontrolled designs, use of non-representative samples, small sample sizes, lack of long-term follow-up, and confounding by concurrent pharmacological treatment. On this basis, these researchers stated that conclusions cannot currently be drawn about the therapeutic effects of marijuana and related cannabinoids for PTSD.[8]

Relationship between PTSD and Marijuana Use

Epidemiological studies have found associations between PTSD and marijuana abuse or dependence in adolescents and adults. A study published in 2000 examining a national household probability sample of 4,023 adolescents aged 12 to 17 years found that, controlling for age, gender, race, ethnicity, familial alcohol and drug problems, and characteristics of trauma, PTSD was significantly associated with marijuana use/dependence.[29] A study published in 2002 using data from the National Comorbidity Survey, based on a national probability sample of individuals aged 15 to 54 years, found lifetime comorbidity of cannabis dependence and PTSD was 18.5%.[30] A 2011 study examining PTSD and marijuana use in a subsequent National Comorbidity Survey found that both lifetime and current diagnoses of PTSD were associated with increased likelihood of ever having used marijuana and likelihood of having used marijuana daily in the past year.[31] Approximately half of the sample with a lifetime PTSD diagnosis who reported lifetime marijuana use indicated that their PTSD onset preceded or occurred at the same age as their first cannabis use.

A study of veterans with and without PTSD who were undergoing treatment for cannabis use disorder (CUD) indicated that, having a PTSD diagnosis and PTSD symptom severity was positively associated with use of cannabis to cope, severity of cannabis withdrawal, and levels of craving related to compulsivity and emotionality. The researchers suggest that, as the experience of PTSD predisposes some individuals to use marijuana to cope with negative internal states, discontinuation of marijuana use leads to exacerbated symptomatology, in part due to marijuana withdrawal, resulting in heightened craving and proneness to relapse to cope with negative internal states, which in turn exacerbates cannabis use disorders.[32]

Relationship between Marijuana Use and PTSD Treatment

A longitudinal study of 2,276 veterans undergoing inpatient treatment for PTSD classified the veterans according to their marijuana use and examined treatment outcomes accordingly. Overall, marijuana use was associated with greater PTSD symptom severity, more violent behavior, and more alcohol and drug use. Initiating marijuana use after treatment discharge was associated with greater PTSD symptoms, alcohol use, and violent behavior. Those who had not used before or after treatment or who discontinued use during treatment exhibited the lowest PTSD symptoms. The researchers concluded that marijuana use may actually worsen PTSD symptoms or nullify the benefits of intensive treatment and that, therefore, prevention and cessation of use may be important goals of treatment.[33]
Another study found that, among veterans participating in a residential PTSD program requiring substance abstinence, those who had a CUD diagnosis prior to starting the program showed reduced improvement in total PTSD symptoms, PTSD hyperarousal symptoms, and PTSD avoidance-numbing symptoms as compared to those without a CUD diagnosis.[34]

Conclusions

In summary, effects of marijuana on PTSD are complex. The eCB system appears to play an important role in responses to stress, fear, and anxiety. Preclinical studies with animal models of PTSD suggest that cannabinoids may be useful for treating PTSD, but very little evidence in humans exists and the extant research is of low quality. Anxiety and panic reactions are the most commonly noted negative acute effects of marijuana intoxication. There are no randomized controlled trials examining the efficacy or safety of marijuana in PTSD; however, marijuana is listed as a qualifying condition for the medicinal use of marijuana in 22 states. Research suggests that many individuals with PTSD who use marijuana do so to cope with PTSD symptoms. Using marijuana to cope may put those with PTSD at risk of becoming dependent on marijuana as discontinuing marijuana potentially produces not only marijuana withdrawal symptoms but also a re-emergence of PTSD symptoms. Cannabis dependence is associated with reduced improvement in abstinence-oriented PTSD treatment. Overall, despite the fact that 22 states have allowed and perhaps, to some, seemingly endorsed the use of MM for PTSD, benefits have not yet been empirically demonstrated. On the other hand, though not

reviewed here, risks of using marijuana are well established. As Steenkamp et al.[8] conclude, "the most clearly defensible statement to be made at this time is that rigorous research on the effects of marijuana and cannabinoids on PTSD is very overdue"; in the meantime, known risks would seem to outweigh unknown benefits.

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