APA Resource Document

Resource Document on APA Opposition to the Use of Cannabis for PTSD

Approved by the Joint Reference Committee, February 2019

"The findings, opinions, and conclusions of this report do not necessarily represent the views of the officers, trustees, or all members of the American Psychiatric Association. Views expressed are those of the authors." -- *APA Operations Manual*.

Prepared by the Council on Addiction Psychiatry

Abstract
The use of cannabis for medical indications has received considerable attention as several states have moved to legalize cannabis for various purposes. A growing number of patients cite post-traumatic stress disorder (PTSD) as the reason for seeking cannabis for medical purposes in states where it is legal.[1] Furthermore, approximately 15% of Veterans who are treated in Department of Veterans Affairs (VA) outpatient PTSD clinics report recent (past 6 months) cannabis use.[2] This position statement was developed through review of the evidence to date and to establish the APA's consensus on the matter.

Complexities of Cannabis
Cannabis is a complex plant with over 500 compounds, where marijuana often refers to the dried leaves, flowers, stems and seeds. There are multiple species including *sativa*, *indica* and *rudelaris*. Tetrahydrocannabinol or THC is the main psychoactive compound, and there are numerous other cannabinoids, with cannabidiol (CBD) being the most well-studied and popular one. Other compounds include tetrahydrocannabinolic acid (THCA), tetrahydrocannabivarin (THCV), cannabigerol (CBG), and cannabinol (CBN).[3] Formerly, cannabis was consumed through smoking of dried cannabis flowers or resin. However, newer methods of consumption include inhaling vaporized dried flowers or cannabis oil (known as "vaping") and orally ingesting edible products (known as "edibles"). Emerging methods of use include inhaling vaporized high-potency (THC) butane hash oil concentrate products (known as "wax" and "shatter" or "dabbing" when using a specialized glass device).[4] Here a highly concentrated THC product is vaporized, rather than just the plant product. Given the variability in product form and potency and onset, dosing as a medication is extremely difficult.[5,6] There are also synthetic cannabis-derived medications such as Marinol and Syndros (dronabinol), Cesamet (nabilone) or Epidiolex (contains purified CBD, one of more than 80 active chemicals in cannabis) which have been studied and approved by the FDA for specific indications which do not include PTSD.

Epidemiology of Use
The best available data regarding cannabis use among both the general population and individuals with PTSD comes from The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), conducted in two waves in 2001-2002 and 2004-2005 which included 34, 653 individuals who participated in both waves and were administered a structured psychiatric interview to obtain DSM-IV diagnoses of PTSD and Cannabis Use Disorder. Kevorkian et al. analyzed this data set in 2015 and identified that 24.4% of the sample had lifetime cannabis use, while 26.0% of the subset with lifetime exposure to a criterion A trauma (n=12,305, 35.7%) had used cannabis at least once in their life. Using various models to control for demographics and the presence of DSM-IV Axis I and II diagnoses other

than PTSD and cannabis use disorder, a modest increased odds of life time cannabis use was demonstrated (OR=0.997) in individuals with a history of PTSD. In a similar model only controlling for DSM-IV Axis-I diagnoses, individuals with a history of PTSD had a slightly higher odds of lifetime cannabis use disorder (OR=1.217).[7]

Summary of Studies

As of yet, there are no published high quality, randomized, controlled studies evaluating the effects of botanical cannabis or synthetic, pharmaceutical cannabinoids on PTSD outcomes.

In regard to synthetic, pharmaceutical cannabinoids, one small (n=10) open-label, pilot study assessed the effects of low dose (5 mg bid) pharmaceutical THC (dronabinol) on PTSD.[8] All participants were stable on other psychopharmacological treatments, including 80% on benzodiazepines, which are not an evidence-based, recommended treatment for PTSD. Significant improvement in self-reported nightmares and sleep quality and objectively determined arousal (but not intrusion or avoidance) symptoms were observed. However, absence of a control group and the use of other medications preclude any certain conclusions about efficacy of THC for treatment of PTSD.

Three Canadian studies evaluated nabilone (schedule II in the U.S.), for management of PTSD symptoms. Individuals with PTSD who had nightmares unresponsive to other medications (N=47) were placed on nabilone 0.5 to 6.0 mg nightly in an uncontrolled open-label design. Seventy-two percent had a reduction in or elimination of nightmares, but 28% stopped nabilone because of adverse effects.[9] In another uncontrolled, retrospective study the effects of daily 0.5 to 6.0 mg nabilone on insomnia and PTSD were examined among incarcerated males simultaneously being treated with other medications and psychotherapy. Self-reported improvements in sleep, frequency of nightmares, and overall PTSD symptoms were observed, with 9.6% discontinuing nabilone because of adverse effects. Given the methodologic weaknesses of these two investigations, little can be concluded about any benefits of nabilone for PTSD. A small randomized, placebo-controlled cross-over study among male Canadian military personnel (N = 10) was conducted with nabilone 0.5 to 3 mg daily or placebo for 7 weeks, followed by a 2-week washout period and 7 weeks of the cross-over treatment.[10] When on nabilone compared to placebo, participants did show significant improvement in nightmares suggesting that nabilone may warrant further investigation as a PTSD treatment.

Three observational studies have looked at the association between cannabis use and PTSD symptoms in cohorts of veterans treated in the Veterans Health Administration. A cross sectional analysis examined veterans with PTSD (N = 700) who did and did not use cannabis. Cannabis use was not associated with fewer PTSD symptoms.[11] However the cannabis users were significantly more likely to experience suicidal ideation and reported significantly more alcohol use (reporting on average approximately 6 alcoholic drinks per week compared to approximately 3 drinks per week in the comparison sample). A longitudinal observational study of veterans receiving residential PTSD care (N = 2,276) found that initiation of cannabis use following treatment discharge was associated with worse PTSD symptoms, alcohol use, and violent behavior, whereas discontinuing cannabis use during residential treatment was associated with improvement in PTSD symptoms.[12] A third study among veterans (N=94) indicated that a history of heavy cannabis use prior to entering a residential program requiring cannabis abstinence was associated with poorer PTSD outcomes compared to nonusers.[13]

In a randomized, controlled trial of prolonged exposure versus sertraline for PTSD, recent cannabis use and lifetime history of cannabis use disorder predicted treatment dropout. Recent cannabis use predicted poorer adherence to prolonged exposure but not to sertraline. Recent cannabis use did not

predict post-treatment or 6-month follow-up outcomes, but cannabis use disorder did predict worse post-treatment PTSD outcomes, although no differences were discerned at 6 month follow-up between those with and without this disorder.[14]

In an ecological momentary assessment study of individuals with PTSD symptomatology (but not necessarily PTSD diagnosis), participants with hyperarousal symptoms used cannabis in response to heightened anxiety, and cannabis use reduced anxiety. Participants with avoidance symptoms used cannabis in response to heightened anxiety, but cannabis use did not reduce anxiety.[15]

In summary, the extant literature contains very preliminary, methodologically weak evidence that synthetic, pharmaceutical cannabinoids could provide benefit for patients with PTSD, and further rigorous study is warranted. At present, no data support the use of botanical cannabis as a PTSD treatment, and, if anything suggest that individuals with PTSD who use cannabis have more severe PTSD and possibly worse outcomes than individuals who do not use cannabis. More compelling knowledge may be gained from a randomized, controlled, blinded, crossover trial now underway which will test four types of smoked cannabis as a treatment for PTSD: High THC cannabis, high CBD cannabis, high THC and CBD cannabis, and placebo cannabis.[16]

Other Consensus Statements and Reviews

The Health Services Research & Development Service within the Department of Veterans Affairs conducted a recent Systematic Review on this topic.[17] They found insufficient evidence examining the effects of cannabis in patients with PTSD. The Canadian Agency for Drugs and Technologies in Health reviewed "Medical Marijuana for Post-Traumatic Stress Disorder"[18] as well and cite one systematic review.[19] That review notes that there are no studies of cannabinoids in PTSD. In their summary they note that given evidence of poorer outcomes in PTSD patients who use cannabis, there is an urgent need for adequately powered, double blind RCTs with adequate control for effects of prior expectance and symptoms of cannabis withdrawal that overlap with symptoms of PTSD. They also suggest that studies need to examine specific PTSD symptoms that are distinct from the effects of cannabis as an avoidance strategy or coping mechanism.

Psychiatric risks

When an individual is diagnosed with PTSD she/he may be experiencing many mood and behavioral symptoms, however there are four main categories of symptoms many individuals will experience[20], including:

- Reliving the traumatic event, such as having nightmares or bad memories
- Avoiding situations that remind them of the traumatic event, as well as avoiding talking or thinking about the event
- Having increased negative beliefs and feelings, including feeling shame or guilt about the event, increased feelings of distrust for others and decreased engagement in pleasurable activities
- Experiencing hyperarousal or feeling "keyed up", due to always being alert and hypervigilant of surroundings

Such symptoms may lead individuals to seek various methods to deal with their feelings. Yet, despite the evidence based treatments of Trauma-focused psychotherapy, including Cognitive Processing Therapy and Prolonged Exposure Therapy; Eye Movement Desensitization and Reprocessing; as well as medication management with selective serotonin reuptake inhibitors and serotonin norepinephrine

reuptake inhibitors, some individuals are using cannabis to deal with their PTSD symptoms.[20] These individuals use cannabis to "self-medicate" the intense and unpleasant symptoms of PTSD, which may be a form of avoidance. However, users may not be aware of the additional risks they are placing themselves in when they use this drug. It is important to note that when individuals engage in cannabis use and have PTSD, the cannabis is not dealing directly with the root cause of their symptoms. Therefore, the traumatic event is not appropriately addressed, rather cannabis becomes the main coping strategy, leading to increased used and more associated psychosocial problems, such as relationship and employment problems.[2,17]. Additionally, because of the PTSD symptoms not being adequately addressed, the potential for other mental and physical health problems in an individual's life may increase with concomitant use of cannabis.

Another key aspect of cannabis use and PTSD deals with withdrawal symptoms. As noted above, an interesting overlap exists between DSM-5 PTSD symptomatology and DSM-5 cannabis withdrawal. For example, both include irritability, sleep disturbance, disturbing dreams, anxiety, and physical symptoms such as tremor or sweating. Thus, while completely speculative, it is conceivable that even brief discontinuation of cannabis use causing cannabis withdrawal in individuals with PTSD may be misinterpreted as exacerbation of PTSD symptoms, resulting in heightened cravings for cannabis.[2,13] Cannabis use may relieve the withdrawal symptoms which the user interprets as a reduction in PTSD symptoms leading the user to feel that cannabis use is helping the PTSD.

Summary

Given the lack of evidence for cannabis use in the treatment of PTSD and the risks associated with continued avoidance and worsening of symptoms, there needs to be more studies conducted prior to instituting changes in practice and policy regarding cannabis in patients with PTSD. The APA does not endorse cannabis for treatment of PTSD.

[1] Bowles DW. Persons registered for medical marijuana in the United States. J Palliat Med. 2012;15(1):9-11.

[2] Boden MT, Babson KA, Vujanovic AA, Short NA, Bonn-Miller MO. Posttraumatic stress disorder and cannabis use characteristics among military veterans with cannabis dependence. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2013;22(3):277-284.

[3] Aizpurua-Olaizola O, Omar J, Navarro P, Olivares M, Etxebarria N, Usobiaga A. Identification and quantification of cannabinoids in Cannabis sativa L. plants by high performance liquid chromatography-mass spectrometry. Analytical & Bioanalytical Chemistry [serial online]. November 22, 2014;406(29):7549-7560. Available from: Academic Search Premier, Ipswich, MA. Accessed August 17, 2018.

[4] Meacham MC, Paul MJ, Ramo DE. Understanding emerging forms of cannabis use through an online cannabis community: An analysis of relative post volume and subjective highness ratings. Drug and Alcohol Dependence. 2018;188:364-369.

[5] Smart R, Caulkins JP, Kilmer B, Davenport S, Midgette G. Variation in cannabis potency and prices in a newly legal market: evidence from 30 million cannabis sales in Washington state. Addiction. 2017;112(12):2167-2177. doi:10.1111/add.13886.

[6] Newmeyer et al., 2017. Newmeyer M.N., Swortwood M.J., Abulseoud O.A., and Huestis M.A.: Subjective and physiological effects, and expired carbon monoxide concentrations in frequent and occasional cannabis smokers following smoked, vaporized, and oral cannabis administration. Drug Alcohol Depend. 2017; 175: pp. 67-76

[7] Kevorkian S, Bonn-Miller MO, Belendiuk K, Carney DM, Roberson-Nay R, Berenz EC. Associations among trauma, posttraumatic stress disorder, cannabis use, and cannabis use disorder in a nationally representative epidemiologic sample. Psychology of Addictive Behaviors. 2015;29(3):633-638.

[8] Roitman P, Mechoulam R, Cooper-Kazaz R, Shalev A. Preliminary, Open-Label, Pilot Study of Add-On Oral Δ9-Tetrahydrocannabinol in Chronic Post-Traumatic Stress Disorder. Clinical Drug Investigation. 2014;34(8):587-591.
[9] Fraser GA. The Use of a Synthetic Cannabinoid in the Management of Treatment-Resistant Nightmares in Posttraumatic Stress Disorder (PTSD). CNS Neuroscience & Therapeutics. 2009;15(1):84-88.
[10] Jetly R, Heber A, Fraser G, Boisvert D. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. Psychoneuroendocrinology. 2015;51:585-588.
[11] Johnson MJ, Pierce JD, Mavandadi S, et al. Mental health symptom severity in cannabis using and non-using Veterans with probable PTSD. Journal of Affective Disorders. 2016;190:439-442.
[12] Wilkinson ST, Stefanovics E, Rosenheck RA. Marijuana Use Is Associated With Worse Outcomes in Symptom Severity and Violent Behavior in Patients With Posttraumatic Stress Disorder. The Journal of Clinical Psychiatry. 2015:1174-1180.
[13] Bonn-Miller MO, Boden MT, Vujanovic AA, Drescher KD. Prospective investigation of the impact of cannabis use disorders on posttraumatic stress disorder symptoms among veterans in residential treatment. Psychological Trauma: Theory, Research, Practice, and Policy. 2013;5(2):193-200.
[14] Bedard-Gilligan M, Garcia N, Zoellner LA, Feeny NC. Alcohol, cannabis, and other drug use: Engagement and outcome in PTSD treatment. Psychology of Addictive Behaviors. 2018;32(3):277-288.
[15] Buckner JD, Jeffries ER, Crosby RD, Zvolensky MJ, Cavanaugh CE, Wonderlich SA. The impact of PTSD clusters on cannabis use in a racially diverse trauma-exposed sample: An analysis from ecological momentary assessment. The American Journal of Drug and Alcohol Abuse. 2018;44(5):532-542.
[16] Study of Four Different Potencies of Smoked Marijuana in 76 Veterans With PTSD - Full Text View. Search of: Spain - List Results - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02759185?term=cannabis&cond=PTSD&rank=1. Accessed September 17, 2018.
[17] Kansagara D, O'Neil M, Nugent S, et al. Benefits and Harms of Cannabis in Chronic Pain or Post-traumatic Stress Disorder: A Systematic Review [Internet]. Washington (DC): Department of Veterans Affairs (US); 2017 Aug. Available from: https://www.ncbi.nlm.nih.gov/books/NBK476449/
[18] Medical Marijuana for Post-Traumatic Stress Disorder: A Review of Clinical Effectiveness and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Jan. CADTH Rapid Response Reports.
[19] Wilkinson ST, Radhakrishnan R, D'Souza DC. A Systematic Review of the Evidence for Medical Marijuana in Psychiatric Indications. The Journal of Clinical Psychiatry. 2016:1050-1064.
[20] https://www.ptsd.va.gov/public/PTSD-overview/basics/what-is-ptsd.asp