

VIEWPOINT

Cannabis and Cannabinoids for Pain and Posttraumatic Stress Disorder in Military Personnel and Veterans

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Cannabis is now legal for medical use in at least 37 states and the District of Columbia (DC) and for recreational use in 21 states and DC.¹ With the gradual expansion of legal access to cannabis over the past 2 decades, the prevalence of cannabis use has increased in both the general population and veterans.¹ Although the reported use of cannabis within the past year among US military personnel remains low at less than 1%,² this low rate is likely attributable to regulations that prohibit its use, with severe penalties (eg, administrative separation and potentially other-than-honorable discharge with reduced benefits) for military personnel.

While the use of nonprescribed cannabis products is uncommon and illegal in the military, 3 cannabinoids are approved by the US Food and Drug Administration and can be legally prescribed to military personnel and veterans in clinical settings. Dronabinol, in particular, is occasionally prescribed to military personnel off-label to treat pain or symptoms of posttraumatic stress disorder (PTSD). Questions remain regarding the clinical validity of these practices. Herein we summarize the current evidence regarding cannabis or cannabinoid monotherapy for pain and PTSD in military and veteran populations.

Cannabinoids for Pain Management

A meta-analysis of **36 randomized clinical trials** (RCTs) studying cannabinoids for pain management found that most trials showed no benefit.³ Two trials rated as having very low-quality evidence included a total of 231 patients and found that pain improved when cannabis was used for less than 7 days. Another 6 trials also rated as having very low-quality evidence included a total of 1484 patients and found that pain improved with nabiximols, a combination spray of 2.7-mg tetrahydrocannabinol (THC) and 2.5-mg cannabidiol (CBD) that is approved for use in the UK but not in the US. The remainder of the studies showed no benefit, had high or uncertain risk of bias, and had either low- or very low-quality evidence per GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) criteria. The meta-analysis did not correct for multiple testing protocols despite evaluating numerous cannabinoids across several different indications and subgroups, thus further limiting confidence in these findings.

Another meta-analysis of 20 studies of cannabinoids for treating pain found that cannabinoids were associated with improvements in pain in both active and placebo groups, but there were no statistically significant between-group differences.⁴ However, a statistically significant moderate to large change in effect size was detected in pain improvement in the placebo group (Hedges $g = 0.64$).⁴ This suggests that patients' subjective

report of improvement in pain while taking a cannabinoid may be attributable to the placebo effect, potentially due to favorable expectations of the cannabinoid's therapeutic potential rather than to a biological treatment effect.⁴

Cannabinoids for Treating Posttraumatic Stress Disorder

Many veterans view cannabis as a safe, nonaddictive, and therapeutic alternative to medications or other substances, and they expect cannabis to improve their symptoms of combat-related PTSD.⁵ Cannabis use by veterans also increases in relation to the severity of their PTSD symptoms and their expectations that cannabis will improve their PTSD symptoms.⁵

Unfortunately, these optimistic expectations do not align with current evidence. Cannabis has been associated with improvements in PTSD symptoms, quality of life, and overall function across 10 observational studies.⁶ However, without comparator treatment arms, these studies cannot differentiate to what extent benefits are due to a true treatment effect of cannabis vs a placebo effect potentially rooted in expectancy biases, similar to that found across studies of cannabinoids for pain management.⁴

Only 2 RCTs have been conducted that examine cannabinoids for the treatment of PTSD.^{7,8} One was a small crossover RCT of nabilone (synthetic THC) that found a statistically significant improvement in PTSD-related nightmares.⁷ However, this study recruited only 10 participants, all of whom were military personnel,⁷ and nabilone has since been discontinued in the US market.

The second RCT was a 4-arm crossover study involving 3 active arms of smoked cannabis (high THC content, high CBD content, or moderate combined THC and CBD content) and a placebo arm of smoked cannabis that contained only trace amounts of THC and CBD.⁸ This RCT recruited 80 veterans (20 in each arm), 43% of whom had test results positive for THC on initial study screening. Every participant in the high THC group and the moderate combined THC and CBD group correctly guessed their group assignment, while approximately 60% of the high CBD and placebo groups correctly guessed their assignment. Despite the issues with allocation concealment, the study found no statistically significant between-group differences among the 4 arms on reductions in PTSD symptoms measured by the CAPS-5 (Clinician-Administered PTSD Scale for *DSM-5*).⁸ However, all 4 arms had statistically significant moderate to large within-group effect sizes in the reduction of PTSD symptoms based on CAPS-5, ranging from Cohen $d = 0.79$ for the high CBD group to $d = 1.99$ for the high THC group.⁸ The placebo group had a large, statisti-

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cally significant within-group effect size of $d = 1.30$.⁸ An effect size of this magnitude in the placebo group is unusual among RCTs examining medications for treating PTSD, which suggests a placebo effect, potentially due to expectancy biases that have also been found in other studies of cannabinoids.⁴

Secondary Consequences of Cannabis Use

While clinical trial data examining cannabinoids for the treatment of pain, PTSD, and other conditions continue to emerge, a robust body of evidence already exists concerning cannabis **use as a risk factor for psychiatric morbidity and other psychosocial consequences. This is particularly true with longer-term use, which would be required for addressing chronic conditions such as pain or PTSD.**

Retrospective analysis of survey data from a national sample of veterans with subthreshold or full PTSD found that veterans who used cannabis more than once per week were more likely than those with infrequent or no use to screen positive for co-occurring depression, anxiety, and suicidal ideation; to score lower in cognitive functioning; and to endorse avoidance coping strategies, including substance use and behavioral disengagement, to manage PTSD symptoms.⁹ Furthermore, not only is cannabis use disorder associated with a greater severity of PTSD symptoms, but it is also associated with reduced effectiveness of PTSD treatment.¹⁰

Limitations of the Research

The research described herein focuses on cannabis or cannabinoids as monotherapy for pain or PTSD. More research is needed to examine these substances in individuals with comorbid conditions and when used in combination with other treatments, such as psychotherapy. Also, cannabis has many potentially active ingredients and modes of administration. Additional systematic and well-designed research is required to determine what, if any, substance in cannabis at specific dosages and modes of administration may have a treatment effect and whether this benefit outweighs the considerable risks.

Implications and Conclusions

The current body of evidence does not support the use of cannabis or cannabinoids for the treatment of pain or PTSD in military personnel or veterans. The favorable outcomes that patients report with these substances for both pain and PTSD currently are better explained by expectancy biases than by a treatment effect. Future studies examining the therapeutic efficacy of cannabinoids must take placebo effects into consideration. Additionally, given the widespread legalization of cannabis, ongoing education of veterans must highlight that these substances lack effectiveness for treating PTSD and pain and have considerable harmful effects, are associated with comorbidities, and affect treatment effectiveness for PTSD.

ARTICLE INFORMATION

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