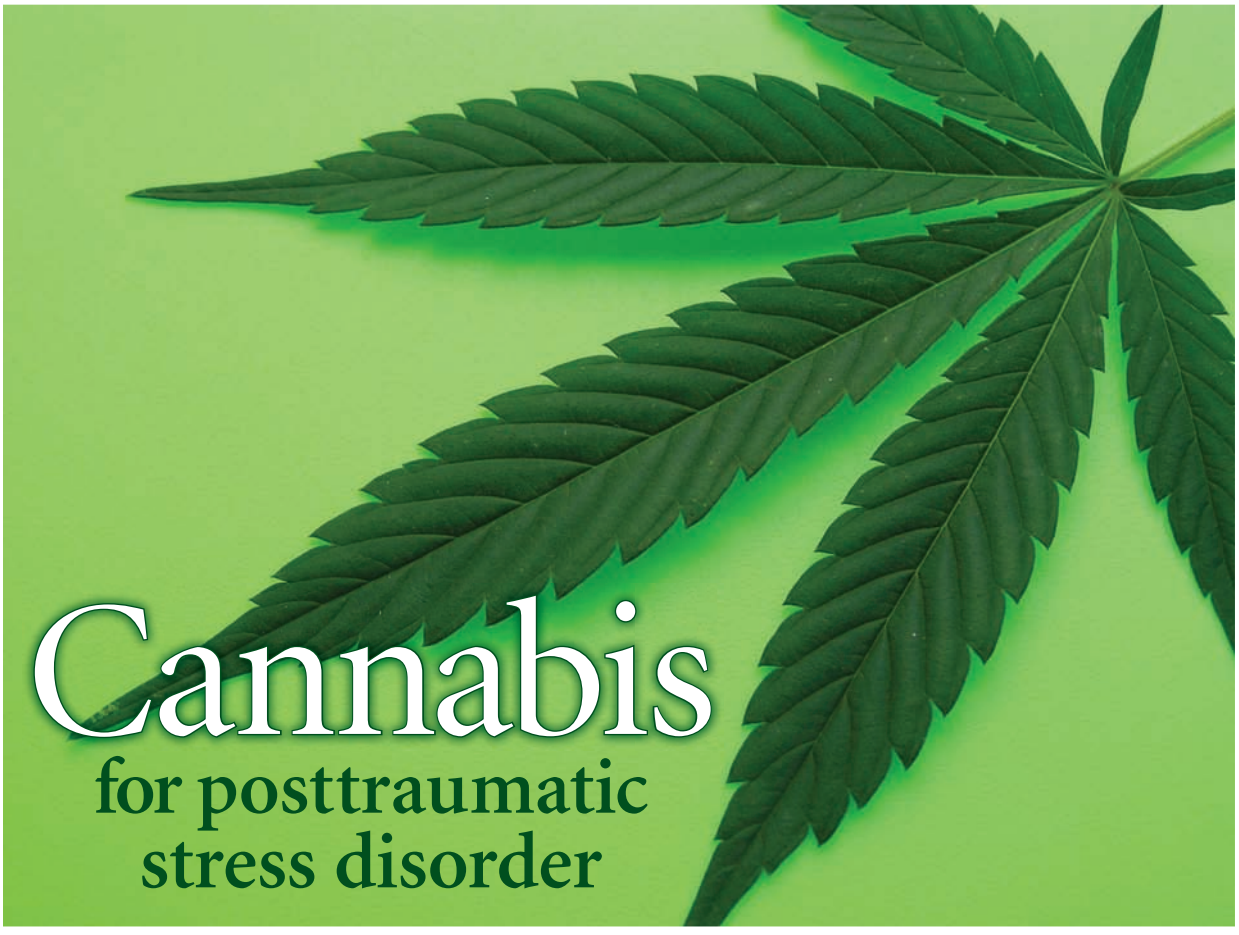

Cannabis for posttraumatic stress disorder

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A neurobiological approach to treatment

Abstract: The endocannabinoid system is intricately involved in regulation of the neurobiological processes, which underlie the symptomatology of posttraumatic stress disorder (PTSD). This article discusses the neurobiological underpinnings of PTSD and the use of cannabis for treating PTSD in the New Mexico Medical Cannabis Program.

By Bryan A. Krumm, MSN, RN, CNP, BC

The State of New Mexico has approved posttraumatic stress disorder (PTSD) as an indication for its Medical Cannabis Program, and patients with PTSD currently comprise the largest segment of any approved indication.

Cannabis remains in Schedule I of the Controlled Substances Act (CSA) in the United States, making it illegal to use under federal law. In the case of Krumm vs. Holder, the Drug Enforcement Administration argued that they did not need to defer to state laws regarding scheduling decisions for controlled substances.[1] Due to the federal prohibition against cannabis, research looking into its therapeutic value has faced significant barriers, rendering it nearly impossible to conduct controlled clinical trials of cannabis in treating PTSD. However, the U.S. Supreme Court has upheld that practitioners have a right to recommend cannabis to patients when it is deemed appropriate.[2]

PTSD can occur when a patient is exposed to one or more traumatic events leading to the development of characteristic symptoms following exposure. Patients may exhibit fear-based re-experiencing with emotional and behavioral symptoms. Others may present with anhedonic or dysphoric states and negative cognition. Patients may exhibit arousal and reactive-externalizing, while others may exhibit dissociative symptoms. Some individuals may have combinations of symptom patterns.[3] PTSD is considered the fourth most common psychiatric disorder, affecting 10% of all men and 18% of women, with rates approximately 40% in high-trauma populations, such as soldiers in combat, low-income individuals, and those

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living in inner cities.[4] PTSD often occurs comorbidly with other psychiatric disorders.[4] Originally, PTSD was considered a normative response, related primarily to stressor intensity, but individual response to trauma depends on stressor characteristics as well as neurobiological factors.[5]

The endocannabinoid system appears to be involved in the extinction of aversive memories, and patients with PTSD claim that cannabis use helps alleviate their symptoms.[6] Cannabinoids stimulate receptors in the prefrontal cortex, amygdala, and hippocampus, activating signaling pathways, which appear to inhibit anxiety.[7] Alterations in the endocannabinoid system are seen in depression, including changes in levels of cannabinoid 1 (CB1) receptors and endogenous CB1 receptor ligands.[8] Stimulation of cannabinoid receptors enhances stress-coping behaviors and increases spontaneous firing of serotonergic and noradrenergic neurons in the midbrain.[9] Phytocannabinoids, including delta 9 tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabichromene exert antidepressant-like actions and may be useful in the treatment of mood disorders.[10]

High rates of suicidal behavior have been found among patients with PTSD.[11] It appears that sensitization of CB1-receptor-mediated G-protein signaling in the prefrontal cortex contributes to the pathophysiology of suicide and likely contributes to suicidal behavior.[12] The role of the endocannabinoid system in the pathophysiology of PTSD suggests that cannabinoids may be an effective modality to treat both PTSD and suicidal behavior in patients with PTSD.[11] Many patients in New Mexico's Medical Cannabis Program for PTSD have reported reductions in frequency and severity of suicidal thoughts at Medical Advisory Board meetings. Some reported complete cessation of suicidality.

The military is currently facing an epidemic of suicide, and the U.S. Department of Veterans Affairs has called on all mental health and substance abuse healthcare providers to share responsibility for zero tolerance regarding suicide.[13] An estimated 22 veterans die via suicide daily, accounting for at least 22.2% of all reported suicides.[14] There were also 349 suicides among active duty troops in 2012, accounting for more deaths than by enemy fire.[15] Developing new treatment modalities for PTSD is critical given the number of returning veterans who require psychiatric help and are at high risk for suicide.

Raphael Mechoulam, PhD, perhaps the world's leading authority on cannabinoids and the endocannabinoid system, points out the following:

> "It has been suggested that pharmacologic treatments in psychiatry have been overly reliant on neurotransmitter systems and their agonists. In the last several decades, advances in psychopharmacology have reduced adverse reactions but have failed to lead to major disease improvement. The endocannabinoid system may shed new light on the physiologic basis of psychiatric diseases, leading to new and more effective treatments."[6]

The neurobiological basis of PTSD

After exposure to a traumatic event, patients may experience recurring memories of the event, including distressing dreams, dissociative reactions/flashbacks, or increased stress responses to external cues and physiological reactions to external cues resembling aspects of the traumatic event. They try to avoid distressing memories or external reminders of the event. They experience negative changes in mood and cognition associated with the event in addition to marked alterations in arousal and reactivity, beginning or worsening after the traumatic event. These disturbances continue for over 1 month and cause significant disturbances in social, occupational, or other important areas of function. These disturbances cannot be attributable to the physiological effects of substances or other medical conditions.[3]

The broad range of symptoms seen in PTSD have made treatment challenging. PTSD involves central neurotransmitter imbalances and neuroanatomical disruptions, with potential dysregulation of immune, autonomic, endocrine, and cardiovascular function.[16] Recent neuroimaging studies have helped elucidate the underlying neurobiological processes involved in the symptomatology of PTSD as well as the role of the endocannabinoid system in managing these neurobiological pathways. CB1 receptor availability is upregulated in an amygdala-hippocampal-cortico-striatal neural circuit implicated in PTSD and in brain regions outside this circuit. This may result from a combination of both receptor upregulation and low receptor occupancy by anandamide, an endogenous cannabioid. This suggests that abnormal CB1 receptor-mediated anandamide signaling is implicated in the PTSD etiology.[17]

PTSD is associated with amygdala dysfunction, the anterior cingulate cortex (ACC), the medial prefrontal cortex (mPFC), and the hippocampus. Structural impairments include decreased hippocampal volume and decreased ACC volume. Dysregulation in threat-related processing in response to trauma exposure leads to a cascade of neural changes, causing a state of amygdala hyperresponsivity, which triggers hyperarousal and vigilance. Inadequate top-down control by the mPFC and ACC perpetuates the state of amygdala hyperresponsivity, increasing attention to trauma-related stimuli.[18]

The hypothalamic-pituitary-adrenal (HPA) axis coordinates neuroendocrine stress response systems and has been

a major focus of scrutiny in patients with PTSD. Exposure to stress triggers neurons in the hypothalamic paraventricular nucleus to secrete a corticotropin-releasing hormone, which stimulates the production and release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH then stimulates the release of glucocorticoids from the adrenal cortex, which modulate metabolism, immune function, and brain function to manage stressors. Sustained glucocorticoid exposure leads to reduced dendritic branching, loss of dendritic spines, and impaired neurogenesis of the hippocampus.[5]

Role of the endocannabinoid system in PTSD

THC has a significant and selective impact on amygdala reactivity to threat signals in humans.[19] Endocannabinoids are crucial for the extinction of aversive memories.[20,21] Activation of CB1 receptors in the amygdala blocks reconsolidation of aversive memories, which suggests that cannabinoids might help patients with PTSD prevent relapse after a stressful experience.[22]

The endocannabinoid system plays a significant role in the function of the prefrontal cortex. The PFC receives and modulates information processing throughout the brain and projects to subcortical arousal systems, regulating monoamine and cholinergic inputs.[23] Activation of cannabinoid receptors in the mPFC enhances serotonin 5-hydroxytryptamine (5-HT) neurotransmission, eliciting potent antidepressant effects.[24] Disinhibition of excitatory projections from the mPFC to serotonergic neurons in the dorsal raphe may underlie antidepressant activity in the mPFC.[25] The endocannabinoid system may be involved not only in the extinction of conditioned fear but also adaptation to aversive situations in general.[26]

Cannabinoids have diverse effects on hippocampal memory and plasticity. The effects of cannabinoids on anxiety appear to be biphasic, with low doses being anxiolytic and high doses being ineffective or possibly anxiogenic.[27] However, chronic high-dose cannabinoid treatment has been shown to induce hippocampal neurogenesis, which may contribute to the anxiolytic and antidepressant effects of cannabinoids.[28] Modulation of hippocampal memory and plasticity by targeting the endocannabinoid system may aid in the treatment of impaired extinction-like processes seen in PTSD.[29]

Endocannabinoid signaling negatively modulates function of the HPA axis. Short-term activation of the HPA axis is beneficial to survival; however, long-term activation can impact mood, cognition, and metabolism. Chronic activation of the HPA axis is associated with a variety of neuropsychiatric disorders.[30]

Cannabinoids, through action on both limbic and paralimbic brain areas, reduce activity of the amygdala and hypothalamus.[31] Retrograde endocannabinoid signaling in the hypothalamus is responsible for regulating HPA output.[32] Acute administration of exogenous cannabinoid ligands also activates the HPA axis indirectly through an increase in serotonergic and noradrenergic neurotransmission.[33] Chronic exposure to desipramine (and perhaps other antidepressants and therapies) has been shown to upregulate the endocannabinoid system, which, in turn, dampens the stress axis in a manner similar to habituation.[34] Endogenous cannabinoid signaling is essential for stress adaptation and is fundamental to the intrinsic regulation of the HPA axis.[35]

Discussion

Because PTSD is often difficult to treat with a single medication, it is common to see the use of "drug cocktails," which may cause significant adverse reactions. This may include treatment with combinations of antidepressants, antipsychotics, benzodiazepines, anticonvulsants, sedative/hypnotics, and antihypertensives. Cannabis may address symptoms across all 3 major symptom clusters in PTSD with few clinically significant adverse reactions.

A review by Grant and colleagues found that inhaled cannabis is a rapid and efficient method of delivery for THC, allowing for self-titration of medication.[36] Although cannabis may cause dizziness, anxiety, paranoia, dry mouth, fatigue, or weakness, tolerance to adverse reactions develops rapidly. There are no reports of fatal overdose with cannabis, and long-term use is not associated with increased risk of lung or gastrointestinal cancers. There is little evidence of important CYP 450 system drug-drug interactions, and the acute medical risks of THC as used in clinical trials are low.[36]

Inhaled cannabis is generally well tolerated and has been shown to reduce the pain intensity, decrease anxiety, and improve sleep.[37] Cannabinoids may reduce or entirely eliminate nightmares; patients using cannabinoids report improvement in sleep time, quality of sleep, and reduction of daytime flashbacks and night sweats.[38]

Alcohol abuse has been significantly linked to PTSD,[39] and cannabis has been shown to act as a substitute for alcohol.[40] Many patients with PTSD struggle with alcohol abuse, often in an attempt to self-medicate. The majority of these patients referred to the Medical Cannabis Program, who have co-occurring alcohol abuse issues, have reported significantly decreased use, and in many cases, complete cessation of alcohol. A patient survey conducted by Berkeley Patient's Group, a medical cannabis dispensary in Berkeley, CA, found that 65% of those surveyed reported using cannabis as a substitute because it has less adverse reactions than alcohol and illicit or prescription drugs.[41]

Cannabinoids have been shown to reduce aggressive behavior, which has important implications in PTSD.[42-44] Patients commonly report significant reductions in irritability and anger. Patients are often accompanied by family members, friends, and/or treatment team members who confirm reductions in aggressive behavior.

Many patients with PTSD have co-occurring psychotic disorders. Although use of cannabis in patients with schizophrenia has typically been reported to worsen psychosis, increases in population cannabis use have not been followed by increases in psychotic incidence.[45,46] THC has been shown to improve symptoms in treatment-refractory patients with schizophrenia, including reduction in core psychotic symptoms, with no clinically significant adverse effects.[45] When compared to non-using patients, patients with schizophrenia who use cannabis and patients with a history of cannabis at first episode of psychosis have superior neuropsychological functioning.[47] Medical cannabis patients with co-occurring psychotic disorders often report reductions in both positive and negative symptoms of schizophrenia, which have failed to resolve with traditional antipsychotic medications, consistent with the findings of Schwarcz and colleagues.[45]

Strains of cannabis-containing CBD in addition to THC may prevent the psychotic-like symptoms sometimes caused by strains with high levels of THC but a lack of CBD.[48] Cannabis of the *sativa* and *ruderalis* biotypes typically contain higher levels of CBD and lower levels of THC, while *indica* biotypes tend to have higher levels of THC and more variable levels of CBD.[49] Unfortunately, finding consistent access to CBD-rich strains is difficult for many patients, and finding the best strain for any individual is largely a matter of trial and error.

A comprehensive study of 4 legal, medical cannabis patients in the federal Investigational New Drug Program found only mild changes in pulmonary function associated with long-term, heavy use. No functionally significant adverse effects were noted in any other physiologic system examined in the study.[50] Although changes in pulmonary function can be seen with chronic high use of cannabis, occasional and low cumulative marijuana use of up to 1 joint a day for 7 years is not associated with adverse effects on pulmonary function.[51]

New Mexico incorporated a definition of "practitioner" that allows advanced practice nurses with prescriptive authority to refer patients to the Medical Cannabis Program.[52] Unfortunately, most states with medical cannabis programs do not allow advanced practice nurses to refer patients. Many providers are not able to refer patients to medical cannabis programs due to institutional regulations. Some providers may have concerns about potential adverse reactions reported with cannabis. However, for those who are able and willing to refer patients to medical cannabis programs, these programs offer a unique opportunity to investigate the safety and efficacy of cannabis while providing relief from pain and suffering.

Marijuana as medicine

Cannabis is effective in treating PTSD, even when there are other co-occurring psychiatric and/or medical disorders. The broad range of therapeutic effects seen in treating PTSD with cannabis suggests that it may be beneficial in treating other disorders as well. Rather than targeting neurotransmitter systems and their agonists, cannabinoids target the underlying neurobiological processes that lead to imbalances in these neurotransmitter systems, helping to return them to a state of homeostasis.

As with any medication, caution must be used when recommending medical cannabis. Patients should be warned of potential risks, including the potential legal and occupational repercussions that can arise the use of cannabis. Some patients may experience increased levels of sedation, anxiety, or paranoia, and cannabis may induce psychosis in certain individuals. Many patients may opt to use cannabis in spite of these risks.

PTSD is considered the fourth most common psychiatric disorder, affecting 10% of all men and 18% of women.

"Based on evidence currently available, the Schedule I classification is not tenable; it is not accurate that cannabis has no medical value or that information on safety is lacking."[36] Healthcare providers have an obligation to provide the best possible care based on the best available scientific evidence. Until cannabis is removed from Schedule I of the federal CSA, the barriers to controlled clinical trials of cannabis in treating PTSD and other medical conditions will remain. NP

REFERENCES

1. U.S District Court, District of New Mexico. Krumm V Holder No. CIV 08-1056 JB/WDS, 2009. www.nmcourt.fed.us/Drs-Web/view-file?unique-identifier=0002337252-0000000000.
2. Conant v. Walters, 309 F.3d 629, 639 (9th Cir. 2002). Cert denied Oct. 14, 2003.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. Arlington, VA, American Psychiatric Association, 2013; 271-280.

4. Jovanovic T, Norrholm SD. Neural mechanisms of impaired fear inhibition in posttraumatic stress disorder. *Front Behav Neurosci*. 2011;5:44.
5. Sherin JE, Nemeroff CB. Post-traumatic stress disorder: the neurobiological impact of psychological trauma. *Dialogues Clin Neurosci.* 2011;13(3):263-278.
6. Mechoulam R. Endocannabinoids and psychiatric disorders: the road ahead. *Rev Bras Psiquiatr*. 2010;32(suppl 1):S5-S6.
7. Rubino T, Sala M, Viganò D, et al. Cellular mechanisms underlying the anxiolytic effect of low doses of peripheral Delta9-tetrahydrocannabinol in rats. *Neuropsychopharmacology*. 2007;32(9):2036-2045.
8. Mangieri RA, Piomelli D. Enhancement of endocannabinoid signaling and the pharmacotherapy of depression. *Pharmacol Res.* 2007;56(5):360-366.
9. Gobbi G, Bambico FR, Mangieri R, et al. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proc Natl Acad Sci U S A.* 2005;102(51):18620-18625.
10. El-Alfy AT, Ivey K, Robinson K, et al. Antidepressant-like effect of delta9-tetrahydrocannabinol and other cannabinoids isolated from Cannabis sativa L. *Pharmacol Biochem Behav.* 2010;95(4):434-442.
11. Sher L. Neurobiology of suicidal behavior in post-traumatic stress disorder. *Expert Rev Neurother.* 2010;10(8):1233-1235.
12. Vinod KY, Hungund BL. Role of the endocannabinoid system in depression and suicide. *Trends Pharmacol Sci.* 2006;27(10):539-545.
13. Pellerin C. VA boosts staffing, programs to prevent suicide. *American Forces Press Service,* June 22, 2012. U.S. Department of Defense website. www.defense.gov/news/newsarticle.aspx?id=116868.
14. Kemp J, Bossarte R. Suicide Data Report, 2012. Department of Veterans Affairs Mental Health Services. www.va.gov/opa/docs/Suicide-Data-Report-2012-final.pdf.
15. Robert Burns, R. 2012 military suicides hit record high of 349. Jan 14, 2013 www.military.com/daily-news/2013/01/14/2012-military-suicides-hit-record-high-of-349.html.
16. Krystal JH, Neumeister A. Noradrenergic and serotonergic mechanisms in the neurobiology of posttraumatic stress disorder and resilience. *Brain Res.* 2009;1293:13-23.
17. Neumeister A, Normandin MD, Pietrzak RH, et al. Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emission tomography study. *Mol Psychiatry.* 2013;18(9):1034-1040.
18. Garfinkel SN, Liberzon I. Neurobiology of PTSD: a review of neuroimaging findings. *Psychiatr Ann.* 2009;39(6):370-381.
19. Phan KL, Angstadt M, Golden J, Onyewuenyi I, Popovska A, de Wit H. Cannabinoid modulation of amygdala reactivity to social signals of threat in humans. *J Neurosci.* 2008;28(10):2313-2319.
20. Azad SC, Monory K, Marsicano G, et al. Circuitry for associative plasticity in the amygdala involves endocannabinoid signaling. *J Neurosci.* 2004;24(44):9953-9961.
21. Zhu PJ, Lovinger DM. retrograde endocannabinoid signaling in a postsynaptic neuron/synaptic bouton preparation from basolateral amygdala. *J Neurosci.* 2005;25(26):6199-6207.
22. Lin HC, Mao SC, Gean PW. Effects of intra-amygdala infusion of CB1 receptor agonists on the reconsolidation of fear-potentiated startle. *Learn Mem*. 2006;13(3):316-321.
23. Gamo NJ, Arnsten AF. Molecular modulation of prefrontal cortex: rational development of treatments for psychiatric disorders. *Behav Neurosci.* 2011;125(3):282-296.
24. Bambico FR, Katz N, Debonnel G, Gobbi G. Cannabinoids elicit antidepressant-like behavior and activate serotonergic neurons through the medial prefrontal cortex. *J Neurosci.* 2007;27(43):11700-11711.
25. Moreira FA. Serotonin, the prefrontal cortex, and the antidepressant-like effect of cannabinoids. *J Neurosci*. 2007;27(49):13369-13370.
26. Lin HC, Mao SC, Su CL, Gean PW. The role of prefrontal cortex CB1 receptors in the modulation of fear memory. *Cereb Cortex.* 2009;19(1):165-175.
27. Akirav I. The role of cannabinoids in modulating emotional and non-emotional memory processes in the hippocampus. *Front Behav Neurosci.* 2011;5:34.
28. Jiang W, Zhang Y, Xiao L, et al. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. *J Clin Invest*. 2005;115(11):3104-3116.
29. Abush H, Akirav I. Cannabinoids modulate hippocampal memory and plasticity. *Hippocampus.* 2010;20(10):1126-1138.
30. Patel S, Roelke CT, Rademacher DJ, Cullinan WE, Hillard CJ. Endocannabinoid signaling negatively modulates stress-induced activation of the hypothalamic-pituitary-adrenal axis. *Endocrinology*. 2004;145(12):5431-5438.
31. Crippa JA, Zuardi AW, Garrido GE, et al. Effects of cannabidiol (CBD) on regional cerebral blood flow. *Neuropsychopharmacology*. 2004;29(2):417-426.
32. Wamsteeker JI, Kuzmiski JB, Bains JS. Repeated stress impairs endocannabinoid signaling in the paraventricular nucleus of the hypothalamus. *J Neurosci.* 2010;30(33):11188-11196.
33. McLaughlin RJ, Hill MN, Gorzalka BB. Monoaminergic neurotransmission contributes to cannabinoid-induced activation of the hypothalamic-pituitary-adrenal axis. *Eur J Pharmacol.* 2009;624(1-3):71-76.
34. Hill MN, Ho WS, Sinopoli KJ, Viau V, Hillard CJ, Gorzalka BB. Involvement of the endocannabinoid system in the ability of long-term tricyclic antidepressant treatment to suppress stress-induced activation of the hypothalamic-pituitary-adrenal axis. *Neuropsychopharmacology*. 2006;31(12):2591-2599.
35. Hill MN, McLaughlin RJ, Bingham B, et al. Endogenous cannabinoid signaling is essential for stress adaptation. *Proc Natl Acad Sci U S A.* 2010;107(20):9406-9411.
36. Grant I, Atkinson JH, Gouaux B, Wilsey B. Medical marijuana: clearing away the smoke. *Open Neurol J.* 2012;6:18-25.
37. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ.* 2010;182(14):E694-E701.
38. Fraser GA. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). *CNS Neurosci Ther*. 2009;15(1):84-88.
39. Coughlin SS, Kang HK, Mahan CM. Alcohol use and selected health conditions of 1991 Gulf War veterans: survey results, 2003-2005. *Prev Chronic Dis*. 2011;8(3):A52.
40. Mikuriya TH. Cannabis as a substitute for alcohol: a harm-reduction approach. *Cannabis Therapeutics*. 2004;4(1):79-93.
41. Reiman, A. Cannabis as a substitute for alcohol and other drugs. *Harm Reduction.* 2009. 6(35):1-5
42. Passmore MJ. The cannabinoid receptor agonist nabilone for the treatment of dementia-related agitation. *Int J Geriatr Psychiatry*. 2008;23(1):116-117.
43. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry*. 1997;12(9):913-919.
44. Walther S, Mahlberg R, Eichmann U, Kunz D. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology (Berl).* 2006;185(4):524-528.
45. Schwarcz G, Karajgi B, McCarthy R. Synthetic delta-9-tetrahydrocannabinol (dronabinol) can improve the symptoms of schizophrenia. *J Clin Psychopharmacol*. 2009;29(3):255-258.
46. Frisher M, Crome I, Martino O, Croft P. Assessing the impact of cannabis use on trends in diagnosed schizophrenia in the United Kingdom from 1996 to 2005. *Schizophr Res*. 2009;113(2-3):123-128.
47. Yücel M, Bora E, Lubman DI, et al. The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample. *Schizophr Bull.* 2012;38(2):316-330.
48. Morgan CJ, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br J Psychiatry*. 2008;192(4):306-307.
49. Hillig KW, Mahlberg PG. A chemotaxonomic analysis of cannabinoid variation in Cannabis (Cannabaceae). *Am J Bot*. 2004;91(6):966-975.
50. Russo E, Mathre ML, Byrne A, et al. Chronic cannabis use in the Compassionate Investigational New Drug Program: an examination of benefits and adverse effects of legal clinical cannabis. *Cannabis Therapeutics*. 2002;2(1):3-57.
51. Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. *JAMA*. 2012;307(2):173-181.
52. The Lynn and Erin Compassionate Use Act, NMSA § 26-2B-1 et.seq. 2007.

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