Cannabis for Post Traumatic Stress Disorder: Risk-Benefit, Ethical Issues and Proposed Guidelines for the Physician

Sol Jaworowski, MBBS, FRANZCP, Joseph Mergui, MD, and Cornelius Gropp, MD

Psychiatric Service, Shaare Zedek Medical Center, affiliated with the Hebrew University, Jerusalem, Israel

ABSTRACT

Despite the lack of controlled studies demonstrating the efficacy of cannabis for Post Traumatic Stress Disorder (PTSD), there appears to be an increasing trend to recommend this treatment without clear clinical guidelines for its use.

The physician should have an appropriate knowledge of cannabis in order to select and manage those patients with PTSD who are likely to benefit from this treatment such as patients suffering from sleep disturbance as a result of hyperarousal symptoms. The physician should be sufficiently acquainted with the patient so as to minimise the possibility of non-medical use of the cannabis such as recreational use or diversion (giving or selling the cannabis to persons without a permit). The physician should also maintain contact with the patient's family. Patients should remain in medical follow up in order to monitor side effects and potential for abuse. Urine tests should be considered for those patients with a high index of suspicion for substance abuse. Use of cannabis should be avoided in persons with a pre-existing history of substance abuse over the past 12 months, severe personality disorder or psychotic illness. Use of cannabis should be avoided in pregnancy and in persons under the age of 25.

Risk-benefit, ethical issues and proposed guidelines are presented for using cannabis in post traumatic stress disorder.

INTRODUCTION

With increasing legalization of recreational cannabis in parts of the United States, medical and retail marijuana has become the fastest growing industry in the U.S., with some analysts projecting sales to reach $22 billion by 2020 (1). Despite the increasing number of medical conditions for which cannabis has been claimed to have therapeutic effect, controlled studies have only demonstrated efficacy in the treatment of chronic pain relief, spasticity and more recently severe myoclonic epilepsy in infancy (Dravet Syndrome) (2-4).

Since medical cannabis has become legally available in Israel through medical recommendation over the last two and a half years, there has been a dramatic rise in the number of Health Department permits for medical cannabis (5). The current list of approved medical conditions for which the Israel Health Department may provide permits for medical cannabis includes cancer, autoimmune deficiency syndrome (AIDS), multiple sclerosis, Parkinson's disease, Crohn's disease, Tourette's Syndrome and post traumatic stress disorder (PTSD). This last condition is the only accepted psychiatric indication for medical cannabis. A medical specialist may apply for a permit for this substance according to his /her area of medical expertise.

The Israeli Health Ministry has documented a number of contra-indications for medical cannabis including:

1. Psychosis
2. Significant family history of mental illness.
3. Severe heart disease.
4. Permits for medical marijuana are subject to the following conditions:
   a. The patient has suffered from the disorder for at least three years.
   b. The patient has received a permanent invalid capacity of at least 30% from the National Insurance System.

Address for Correspondence: ✉ Dr. Sol Jaworowski, Psychiatric Service, Shaare Zedek Medical Center, POB 3235, Jerusalem 91031, Israel
solj@szmc.org.il

c. The patient refrains from driving a car or using the cannabis in the presence of minors or in public.

Although medical cannabis permits for PTSD in Israel currently comprise only 6% of the total number of permits issued for this substance, the number of permits for PTSD in Israel has increased over 12-fold over the last two and a half years despite the fact that there have been no controlled scientific efficacy studies of medical cannabis for PTSD (6). Patients suffering from PTSD who are assessed by a psychiatrist for a Health Department permit for medical cannabis will often acknowledge they are self medicating with cannabis as a result of medical and non-medical recommendation to do so until the permit becomes available. The psychiatrist is then faced with the dilemma of supervising medical treatment during which cannabis is acquired and used illegally without medical supervision. Since recreational use of cannabis may precede the onset of the PTSD it is essential that the supervising psychiatrist be sufficiently knowledgeable about the properties of cannabis in order to offer information and advice about the risks and benefits of this substance.

BACKGROUND ON CANNABIS

The plant *Cannabis sativa* known as marijuana has been known for its psychoactive properties in China and Egypt for thousands of years (7) and the term for "anesthesia" in the Chinese language derives from words meaning "Cannabis intoxication."

Cannabis sativa contains a large number of psychoactive substances known as cannabinoids, two of which have particular medical interest because of their pharmacological actions via the Endocannabinoid system: tetra hydrocannabinol (THC) that is the major psychotropic constituent of marijuana and cannabidiol (CBD) that has no psychoactive properties (8). The flowers of the plant contain 5% THC compared to a concentration of 20% THC found in the more concentrated resin of the plant known as hashish.

Synthetic Cannabinoids, which are known as "Nice Guy, Mabsuton, K2, Spice," were until recently freely available, are currently prohibited substances, following fatal incidents associated with their use.

Cannabinoid receptors, located throughout the body, are part of the Endocannabinoid system which is involved in a variety of physiological processes including:

- Appetite
- Pain-sensation via opiate pathway
- Mood via dopamine and noradrenaline pathways
- Memory
- Inflammation

Cannabinoid receptors are of a class of cell membrane G protein receptors which are activated by:

- Endocannabinoids which exist naturally in the body
- Plant cannabinoids such as THC
- Synthetic cannabinoids

Raphael Mechoulam, a pharmacologist and researcher at the Hebrew University was the first person to isolate THC, CBD and the Endocannabinoid: Anandamide (9).

Cannabinoid receptors are further subdivided into CB1 and CB2: the former are primarily found in the brain (hippocampus, prefrontal cortex, amygdala and cerebellum) and mediate the psychoactive properties of THC and the latter are found more peripherally in the body such as the immune system and are thought to mediate the psychoprotective properties of CBD (10). The anecdotal use of marijuana and/or preparations from *Cannabis sativa* L. (hemp) in patients with inflammatory bowel disease (IBD) has been recently confirmed by investigations in humans (11). Clearly, the most known among the phytocannabinoids is Δ^9-tetrahydrocannabinol (THC), whose possible clinical use is hindered by its psychoactivity. This obstacle has addressed further research toward non-psychotropic phytocannabinoids such as cannabidiol (CBD), One of the best studied among such extracts is the standardized *C. sativa* extract with high content of CBD, generally referred to as CBD BDS (an acronym for Botanical Drug Substance). Notably, CBD BDS is a major ingredient of the medicine known with the generic name nabiximols.

The strengths of CBD BDS for a possible clinical use in IBD patients include: (a) its intestinal anti-inflammatory activity following oral gavage administration (in contrast to pure CBD, which was ineffective); (b) its ability to reduce the degree of inflammation in a curative protocol, (c) its ability to reduce motility in the inflamed gut at doses lower than those required to affect motility in control animals. There is further support (12) for the therapeutic rationale for combining CBD with other minor constituents present in *Cannabis sativa*, also in the light of recent positive effects exerted by CBD BDS in IBD patients (13).

The potency of illicit marijuana around the world has been found to be escalating with an increasing ratio of THC/CBD (14).

Cannabis is highly fat soluble, has a half life in fat of eight days and may take up to 30 days for complete elimination from the blood. Smoking cannabis (marijuana, grass) as

compared to oral ingestion results in three to four times higher blood levels (15). There are concerns about potential carcinogenicity especially in heavy cannabis users (16), but apparently not in occasional users (17). It is difficult to gauge the exact delivered dose of cannabis after smoking as a result of variability of plasma concentrations of THC after smoking, the plant concentration of THC and the smoking method: frequency of inhalation, hold time and inhalational volume (18). Smokers titrate their exposure to achieve the desired effect so these parameters are of limited clinical significance.

COGNITIVE, BEHAVIORAL AND PSYCHIATRIC SIDE EFFECTS OF CANNABIS

- Impaired cognition: Acute and chronic effects on human cognition have been demonstrated with greater impairment being associated with earlier age of use (19).
- Psychosis: Use of marijuana was found in 34% of patients with first episode psychosis (20), the risk was related to the amount of cannabis consumed and continued use after the onset of psychosis resulted in more severe symptoms and higher relapse rates (21). Onset of schizophrenia among users of cannabis occurred on average three years earlier among users of cannabis compared to non-users (22). Genetic factors as well as neurotransmitter mechanisms are implicated in the development of psychosis (23).
- Addiction: Including symptoms of withdrawal has been described in 10% of persons who experiment with cannabis, 17% of persons who started using it in their teens, up to 50% of those who use it daily and up to 95% of heavy users (24). Emerging evidence suggests that adolescents may be particularly vulnerable to the adverse neurocognitive effects of cannabis (25).
- Pregnancy: Prenatal exposure to cannabis has been associated with increased incidence of stillbirths, decreased birth weight and longer term decrease in cognitive functioning at age 6 (26). A common means of cannabis consumption is via smoking, which increases the amount of toxins and thereby amplifies harmful effects to the embryo (27).
- Automobile accidents: Use of cannabis has been associated with twice the risk of fatal car accidents, impairment of psychomotor skills in driving and a cumulative impairment in driving skills when combined with alcohol (28).

Cannabis may help with PTSD through the reduction of PTSD hyperarousal thereby reducing the frequency of nightmares and improving sleep quality (29, 30). It should therefore be considered for those PTSD patients who suffer from disturbed sleep as a result of hyperarousal.

ETHICAL ISSUES RELATED TO MEDICAL MARIJUANA

In which way should we apply the Georgetown biomedical ethical principles of autonomy, beneficence, nonmaleficence and justice (31) to the use of medical cannabis?

As with any medical treatment the physician is required to evaluate the efficacy (beneficence) of the treatment versus the potential for causing harm to the patient (nonmaleficence) which appears to be the core ethical dilemma of this topic. Furthermore the physician needs to consider the likely side effects of the treatment. Issues of autonomy (the patient's choice to use cannabis should be respected by his/her physician) and justice (a licence for medical cannabis might be easier to acquire using private medical care?) will not be discussed in the current article.

Reports of improvement in PTSD with cannabis use are correlational without randomized controlled studies (30-32). However, there also appears to be a correlation between PTSD and problematic use of cannabis (6). The current use of medical cannabis in several U.S. states and in Israel bypasses the century old scientifically based approval procedure and the carefully regulated distribution of medications through licensed pharmacies. The Food and Drug Administration (FDA) in the U.S. does not evaluate chemicals or plants like cannabis; it evaluates specific standardized products for their safety, efficacy and purity. The buyer has no way of knowing the accuracy of the claims or the purity of the product (33). Cannabis has been known to be contaminated by moulds, fungi or herbicides (34).

FDA approval has usually helped keep dangerous and ineffective but often popular drugs off the market. Substituting a politically motivated drug approval for that protection is hazardous to the nation's health and safety. It is estimated that 9% of medical cannabis users will become dependent on the drug and the number of addicted individuals will rise as the number of users increases (33).

Historically, alcohol (35) and nicotine (36) have both been used as medical remedies. Nicotine has been shown to be neuroprotective in animal models of Parkinson's disease with resulting investigations through randomized trials (37). Similarly, light to moderate use of alcohol has been shown to produce a cardio- protective effect on patients with coronary artery disease (38). Despite these apparently well demonstrated benefits, neither alcohol nor nicotine would be labelled and sold as medi-

cal preparations. Both have been demonstrated to cause extensive worldwide morbidity and mortality (39, 40).

Cannabis has been regulated differently from other comparable substances: Cannabis is produced from the leaves of the hemp plant in a comparable way that Hypericum is produced from the leaves of the St. John's Wort plant. It has proven antidepressant properties (41), but has far less potential side effects than cannabis. While cannabis is marketed in Israel in leaves or extracts produced from leaves, according to their weight or concentration, without exact quantification of its active ingredients, Hypericum is marketed in tablet form only, as a prescription medication. It would be unacceptable that an extract of the poisonous foxglove leaves would be marketed instead of Digoxin. Though "medical" cannabis in Israel is considered an officially regulated remedy, and its side effects known as significant, it is neither produced nor marketed as comparable plant based medications are, with serious repercussions on the quality of research of its use.

All things considered, it appears reasonable to suggest that cannabis may have a therapeutic role for certain patients suffering from PTSD despite the lack of evidence for its efficacy in controlled studies, its serious potential side effects, and the politicization of its therapeutic use.

These considerations help to reconcile the balance between beneficence versus non-malfeasance in the treatment of PTSD with cannabis. It is all the more important that physicians be committed to practicing evidence-based medicine and to lifelong learning (42).

PROPOSED PRAGMATIC GUIDELINES FOR THE PHYSICIAN REGARDING USE OF MEDICAL CANNABIS IN PTSD:

1. The physician should have an appropriate knowledge of cannabis so as to select and manage those patients who are likely to benefit from this treatment such as those PTSD patients suffering from sleep disturbance as a result of hyperarousal symptoms. Risk –benefit issues should be discussed with the patient and his/her family.
2. Patients should be sufficiently known by the physician/ clinic so as to be relied upon not to engage in non-medical use of the substance such as recreational use or giving/ selling the marijuana to others. Wherever possible contact with the patient's family should be pursued and maintained.
3. Patients should remain in medical follow up in order to monitor side effects and potential for abuse. Urine tests for illicit use of prescription and non prescription drugs should be considered for those patients where there is a high index of suspicion for recent substance abuse such as inappropriate mood or behavior.
4. Use of cannabis should be avoided in persons with a pre-existing history of substance abuse over the past 12 months, severe personality disorders or psychotic disease.
5. Use of cannabis should be avoided in pregnancy.
6. Use of cannabis should be avoided under the age of 25.

References

1. The Guardian, November 9, 2016.
2. Whiting P, Wolff R, Deshpande S, Kleijnen J. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 2015; 313: 2456-2473.
3. National Academies of Sciences, Engineering, and Medicine. Board on Population Health and Public Health Practice, Health and Medicine Division, 2017. The health effects of cannabis and cannabinoids: Current state of evidence and recommendations for research. Washington DC: The National Academies Press.
4. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet Syndrome. N Engl J Med 2017;376:2011-2020.
5. Medical Cannabis Unit, Ministry of Health, Jerusalem, Israel.
6. Yarnell S. The use of medicinal marijuana for posttraumatic stress disorder: A review of the current literature. Primary Care Companion CNS Disorders 2015;17(3): doi 10. 4088/PCC 15roi786.
7. Kalant H. Medicinal use of cannabis : History and current status. Pain Res Manag 2001; 6: 80-91.
8. Elsohly MA, Slade D. Chemical constituents of marijuana: The complex mixture of natural cannabinoids. Life Sci 2005; 78:539-548.
9. Mechoulam R. The endocannabinoid system - a fifty years trip. Int J Neuropsychopharmacology, June 2014. Conference: 29th CINP World Congress of Neuropsychopharmacology. Vol. 17.
10. Pertwee RG. Cannabinoid pharmacology: The first 66 years. Br J Pharmacology 2006; 147:S163-171.
11. Naftali T, Mechoulam R, Lev L B, Konikoff F M. Cannabis for inflammatory bowel disease. *Dig Dis* 2014; 32: 468-474. 10.1159/000358155.
12. Pagano E, Capasso R, Piscitelli F, et al. An orally active cannabis extract with high content in cannabidiol attenuates chemically-induced intestinal inflammation and hypermotility in the mouse. Front Pharmacol 2016;7:341. eCollection 2016.
13. Irving P M, Iqbal T, Nwokolo C, et al. Sa1264, A randomised, double-blind, placebo-controlled, parallel group, multi-centred pilot study to assess the symptomatic treatment of ulcerative colitis with cannabidiol. *Gastroenterology* 2015; 148: S275 10.1016/S0016-5085(15)30904-5.
14. Cascini F, Aiello C, Di Tanna G. Increasing Δ-9-tetrahydrocannabinol (Δ-9-THC) content in herbal cannabis over time: Systematic review and meta-analysis. Curr Drug Abuse Rev 2012;5:32-40.
15. Sharma P, Murthy P, Bharath S. Chemistry, metabolism, and toxicology of cannabis: Clinical implications. Iran J Psychiatry 2012; 7: 149-156. PMCID: PMC3570572.
16. Aldington S, Harwood M, Cox B, et al. Cannabis use and risk of lung cancer: A case–control study. European Respiratory J 2008 31: 280-286. doi: 10.1183/09031936.00065707.
17. Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. *JAMA* 2012;307:173-181.
18. Cooper ZD, Haney M. Comparison of subjective, pharmacokinetic and physiological effect of marijuana smoked as joints and blunts. Drug Alcohol Depend 2009; 103:107-113.
19. Broyd SJ, Van Hell HH, Beale C, et al. Acute and chronic effects of cannabinoids on human cognition - A systematic review. Biological Psychiatry 2016; 79: 557-567.
20. Myles H, Myles N, Large M. Cannabis use in first episode psychosis. Meta analysis of prevalence and the time course of initiation and continued use. ANZJP doi: 10.1177/0004867415599846b 2015.

21. Schoeler T, Petros N, Di Forti M, et al. Association between continued cannabis use and risk of relapse in first episode psychosis. A quasi-experimental investigation within an observational study. JAMA Psychiatry 2016; 73: 1173-1179.

22. Helle S, Ringen PA, Melle I, et al. Cannabis use is associated with 3 years earlier onset of schizophrenia spectrum disorder in a naturalistic, multi-site. Schizophr Res 2016;170:217-221. doi: 10.1016/j.schres.2015.11.027.

23. Sherif M, Radhakrishnan R, D'Souza DC, Ranganathan M. Human laboratory studies on cannabinoids and psychosis. Biol Psychiatry 2016;79:526-538. doi: 10.1016/j.biopsych.2016.01.011.

24. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med 2014;370:2219-2227. doi: 10.1056/NEJMra1402309.

25. Volkow ND, Swanson JM, Evins AE, et al. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: A review. JAMA Psychiatry 2016;73:292-297.

26. Gunn JKL, Rosales CB, Center KE, et al. The effects of prenatal cannabis exposure on fetal development and pregnancy outcomes: A protocol. BMJ Open 2015;5:e007227. doi: 10.1136/bmjopen-2014-007227.

27. Friedrich J, Khatib D, Parsa K, Santopietro A, Gallicano GI. The grass isn't always greener: The effects of cannabis on embryological development. BMC Pharmacol Toxicol 2016;17:45.

28. Asbridge Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: Systematic review of observational studies and meta-analysis. BMJ 2012;344:e536.

29. 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. Clin Drug Investig 2014; 34: 587.

30. Bonn-Miller MO, Babson KA, Vandrey R. Using cannabis to help you sleep: Heightened frequency of medical cannabis use among those with PTSD. Drug Alcohol Depend 2014;136:162-165.

31. Beauchamp TL. Methods and principles in biomedical ethics. J Medical Ethics 2003;29:269-274.

32. Greer GR, Grob CS, Halberstadt AL. PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. J Psychoactive Drugs 2014;46:73-77.

33. Kleber H, Dupont RL. Physicians and medical marijuana. Am J Psychiatry 2012; 169:6.

34. Ruchlemer R, Amit-Kohn M, Raveh D, Hanuš L. Inhaled medicinal cannabis and the immunocompromised patient. Support Care Cancer 2015; ;23:819-822. doi: 10.1007/s00520-014-2429-3.

35. Gesundheit B, Or R, Gamliel C, Steinberg A. Treatment of depression by Maimonides: Rabbi, physician and philosopher. Am J Psychiatry 2008;165: 425-428.

36. Charlton A. Medicinal uses of tobacco in history. J R Soc Med 2004;97:292-296.

37. Ascherio A, Schwarzchild MA.The epidemiology of Parkinson's disease: Risk factors and prevention. Lancet Neurology 2016; doi: org/10.1016/S1474-4422(16)30230-7.

38. Klatsky AL. Alcohol and cardiovascular diseases: Where do we stand today? J Intern Med 2015; 278: 238-250.

39. World Health Organization. Global status report on alcohol and health. 2014 World Health Organization.

40. World Health Organization. Tobacco fact sheet, 2017. World Health Organization.

41. Apaydin EA, Maher AR, Shanman R, et al. A systematic review of St. John's wort for major depressive disorder. Systematic Reviews 2016; 5:148. doi: 10.1186/s13643-016-0325-2.

42. Brett AS, McCullough LB. Addressing requests by patients for non beneficial interventions. JAMA 2012; 307:149-150.