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

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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.
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: tetrahydrocannabinol (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:

- 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 Δ9-tetrahydrocannabinol (THC), whose possible clinical use is hindered by its psychoactivity. This obstacle has addressed further research toward non-psychoactive 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/clinician 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**

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