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SHORT COMMUNICATION

Preliminary, Open-Label, Pilot Study of Add-On Oral Δ^9-Tetrahydrocannabinol in Chronic Post-Traumatic Stress Disorder

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Abstract

Background and Objectives Many patients with post-traumatic stress disorder (PTSD) achieve but partial remission with current treatments. Patients with unremitted PTSD show high rates of substance abuse. Marijuana is often used as compassion add-on therapy for treatment-resistant PTSD. This open-label study evaluates the tolerance and safety of orally absorbable Δ^9-tetrahydrocannabinol (THC) for chronic PTSD.

Methods Ten outpatients with chronic PTSD, on stable medication, received 5 mg of Δ^9-THC twice a day as add-on treatment.

Results There were mild adverse effects in three patients, none of which led to treatment discontinuation. The intervention caused a statistically significant improvement in global symptom severity, sleep quality, frequency of nightmares, and PTSD hyperarousal symptoms.

Conclusions Orally absorbable Δ^9-THC was safe and well tolerated by patients with chronic PTSD.

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1 Introduction

Many patients with post-traumatic stress disorder (PTSD) do not achieve remission with currently available treatment [1] and some turn to alcohol and substance abuse [2]. Among other substances, marijuana is often used to alleviate PTSD symptoms of avoidance/numbing and hyperarousal [2].

Following reports of its use for multiple sclerosis, anorexia in AIDS patients, chronic pain and inflammation among other medical conditions [3], marijuana has been prescribed as compassionate, add-on therapy for treatment-resistant PTSD [4], sometimes with serious undesired effects [5]. Alongside that, previous reports on medical cannabis revealed a relatively safe profile [6]. Additionally, marijuana use can unmask or worsen underlying anxiety disorders. Cannabis-induced anxiety disorders were also reported [7]. The exact amount of active compounds in inhaled or smoked marijuana vary between plants and preparations and while some homogeneity can be achieved under very strict conditions, it is mostly hard to set standards of potency and purity [8]. In an open-label study, the synthetic cannabinoid receptor agonist nabilone had been shown to have beneficial effects on treatment-resistant nightmares in PTSD [9]. Recently, a retrospective chart review on medical cannabis treatment appliers for PTSD reported up to 75 % reduction in PTSD symptoms [10].

During the last decade, human and animal studies described an important role of the cannabinoid CB_1 receptor in the extinction learning of aversive memories [11, 12], a neural process with central relevance to PTSD.

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Along these lines, a recent brain imaging study has shown elevated brain cannabinoid CB_1 receptor availability and decreased concentrations of anandamide, an endogenous cannabinoid agonist, in patients with chronic PTSD [13].

These findings make the use of this family of compounds of particular interest for the treatment of PTSD. The main psychoactive compound of marijuana is Δ^9-tetrahydrocannabinol (THC). The effect of Δ^9-THC in human PTSD patients has not been evaluated to date. This open-label study explored the tolerance, safety and preliminary clinical effects of Δ^9-THC as add-on treatment for patients with unremitting chronic PTSD.

2 Methods

This was a 3-week, open-label, adjusted doses, preliminary evaluation of the safety, tolerance, and efficacy of THC as a secondary outcome.

2.1 Participants

Ten adult outpatients from Hadassah University Hospital Outpatient Clinic and other mental health clinics in Jerusalem, Israel, took part in the study. Participants were patients with chronic PTSD diagnosed more than 1 year before entering the study and at least 3 years after the traumatic event. They were receiving stable psychotropic medication for at least 4 weeks. The Clinicians-Administered PTSD Scale (CAPS) was used to confer the diagnosis of PTSD. A symptom criterion was rated as 'present' when its frequency score was 1 or greater and its intensity score was 2 or greater. A diagnosis of PTSD required Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria A through F. Patients with frequent dissociative episodes, women who were currently pregnant or nursing or not using a reliable method of contraception, and participants with suicidal ideation and those with concurrent psychosis, alcohol or drug abuse were excluded. Prior cannabis use was a relative exclusion criterion, and no use for the last 6 months, according to information provided by the subjects, was required. One patient reported such a condition and was included in the study. No urinary drug tests were taken due to technical reasons.

Hadassah University Hospital Institutional Review Board approved and monitored the study.

2.2 Physiologic Assessment

Patients were assessed for blood pressure, heart rate, weight and body mass index (BMI) at baseline and through the trial.

2.3 Psychometric Instruments

The CAPS [14] is a structured clinical interview that evaluates the 17 DSM-IV PTSD and associated symptoms on dimensions of frequency and intensity (0–4 scale for each). It yields a categorical (present/absent) notation of each of the DSM-IV PTSD criteria and continuous symptom severity score, obtained by summing the scores of individual items.

The Clinical Global Impression Scale (CGI) [15] used in this study has two different measures: severity of illness (CGI-S), rated on a 7-point scale, using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients), and global improvement (CGI-I), with scores ranging from 1 (very much improved) through to 7 (very much worse).

Following previous reports of a specific effect of nabilone on sleep, we used the Pittsburgh Sleep Quality Index (PSQI), including the PTSD addendum for the scale [16], to assess sleep quality and sleep disturbances. A total score >5 was associated with poor sleep quality.

The Nightmare Frequency Questionnaire (NFQ) [17] is a self-report, two-question retrospective survey that estimates the number of nights in which nightmares occur on a yearly, monthly, weekly or nightly basis, and the number of nightmares for the same time interval.

The Nightmare Effects Survey (NES) [18] is a clinician-administered survey and includes 11 items (sleep, work, relationships, daytime energy, school, mood, sex life, diet, mental health, physical health, leisure activities) rated on a five-point scale to assess the self-reported degree of impairment attributed to nightmares.

Descriptive statistics as frequencies, mean values and standard deviation, as well as hypotheses testing using paired *t*-tests for dependent samples, were carried out with SPSS 18 package for Windows (PASW Statistics, Inc.).

2.4 Procedure

After signing informed consent, participants went through baseline assessment, referred to as Clinical Assessment 1 (CA1). At the end of CA1, participants were given a bottle with 4 cc of THC in olive oil, concentrate 5 mg/0.2 cc. The compound was prepared by dissolving 100 mg of THC in 4 cc of olive oil. Participants were instructed to take 2.5 mg (0.1 cc) beneath the tongue twice a day, 1 h after waking up and 2 h before going to bed at night. In order to accurately measure the dose, they were given a no-needle 1 cc plastic syringe. After 2 days, participants received a phone call from the principal investigator (PR) to assess for side effects or other adverse events. If they tolerated the dose well, it was raised to 5 mg (0.2 cc) twice a day until the end of the trial. The 5-mg dose was set based on

previews reports concerning efficacy and safety [6, 16, 17], and the sublingual administration way was chosen following previous data on the field [19]. Participants went through weekly assessments in which they also received the medication for the next week. The trial period was 3 weeks

3 Results

Ten outpatients participated in the study, three females and seven males. The mean age was 52.3 years (SD 8.3). The patients had been exposed to different traumatic events, classified as war-related, road accident and assault/rape in five, three and two cases, respectively. All patients were receiving current psychopharmacological treatment, taking an average of more than four different medications, the more frequent being clonazepam in five cases (average dose 2 mg), lorazepam, escitalopram and duloxetine in three cases (average doses 3, 13.3 and 70 mg. respectively), and bupropion and mirtazapine in two cases (225 and 45 mg, respectively) (Table 1). All patients continued their current psychopharmacological treatment throughout the trial. All patients reached the maximal daily dose of THC.

3.1 Adverse Effects and Physiological Measures

Side effects were reported in four cases; dry mouth in two patients, headache in one patient and dizziness in another patient. These effects were mild and continued throughout the 3 weeks of treatment (Table 1). There were no treatment discontinuations during the trial. Blood pressure, weight, BMI and pulse were monitored throughout the trial (Table 2). No changes were noted, except in systolic blood pressure in the first week of the trial.

3.2 Preliminary Effect on Target Symptoms

A statistically significant decrease in symptom severity was observed in PTSD hyperarousal symptoms, CGI-S, CGI-I, sleep quality, frequency of nightmares, and total NES scores (Table 3).Two participants (20 %) attained complete remission of nightmares by week 3.

4 Discussion and Conclusions

This is the first report of the use of orally absorbable Δ^9-THC as add-on treatment in patients with chronic PTSD. The results show good tolerance and safety, reduction of PTSD hyperarousal symptoms, improved sleep quality and reduced frequency of nightmares.

Table 1 Clinical details of participants in the trial

Sex	7 male; 3 female
Age, years	52.3 (8.3)
Traumatic event	
War-related	5
Rape/assault	2
Road accident	3
Concomitant medication (*n*/mean dose, mg)	4.15 (1.52)
Duloxetine	3/70
Escitalopram	3/13.3
Mirtazapine	2/45
Bupropion	2/225
Clonazepam	5/2
Lorazepam	3/3
Other	17
Adverse effects	
Dry mouth	2
Headache	1
Tremor	1

Values are presented as mean (standard deviation)

The safety of oral Δ^9-THC seen in this work parallels the safety seen in previous reports in other conditions; sublingual Δ^9-THC caused only mild dizziness and sedation in patients treated for glaucoma [20] or chronic non-malignant pain [21]. In a randomized controlled study of Δ^9-THC to alleviate anorexia in cancer patients, there were no differences in side effects compared with placebo [22]. Marinol (synthetic Δ^9-THC) caused only mild to moderate xerostomia, sleepiness and anxiety in patients with spasticity due to spinal cord injury [22].

The beneficial effect of Δ^9-THC on sleep and nightmares replicates previous findings by Fraser [9], who reported on similar effects with nabilone in chronic PTSD (alleviation or cessation of nightmares). Furthermore, individuals with PTSD reported greater motivation to use cannabis for sleep compared with those without PTSD [23]. Δ^9-THC can modify sleep architecture by depleting rapid eye movement (REM) sleep, the sleep phase in which nightmares occur, and enhancing non-REM phase 4 sleep, the restoring phase of sleep [24], bringing a plausible explanation to both nightmare reduction and the improvement of sleep quality seen in our work.

The observed improvement in PTSD hyperarousal symptoms is similarly in line with a previous report of marijuana use in combat veterans with PTSD [25]. The effect on PTSD symptoms can be interpreted as involving an activation of unoccupied CB_1 receptors in the hippocampus, amygdala, prefrontal and anterior cingulate cortex by exogenous Δ^9-THC. The endocannabinoid system (eCB) in these cerebral areas may play a critical role in

Table 2 Blood pressure, weight, BMI and pulse measurements over 3 weeks

Parameter	CA1	CA2	CA3	CA4	Group comparison
Pulse	79.4 (12.0)	75.4 (8.6)	77.2 (11.2)	76.7 (13.1)	NS
Systolic BP	137.0 (16.2)	129.8 (17.1)	133.4 (20.0)	138.6 (25.6)	$p < 0.05$[a]
Diastolic BP	85.0 (15.5)	81.4 (9.9)	79.7 (11.0)	85.3 (14.0)	NS
Weight	88.380			88.340	NS
BMI	28.8			28.9	NS

Values are presented as mean (SD). p value <0.05 was considered statistically significant

BMI body mass index, *BP* blood pressure, *CA1* clinical assessment at the start of the trial, *CA2*, *3 and 4* clinical assessment at the end of the first, second and third weeks, respectively, *NS* not significant

[a] Only between CA1 and CA2 assessments

Table 3 Average psychometric scores

Parameter	CA1	CA4	*t*-Test (degrees of freedom)	*p*-Value[a]
CAPS total score	94.0 (13.42)	78.0 (23.60)	1.81 (9)	>0.1
CAPS intrusion score	24.2 (7.75)	18.7 (7.97)	1.65 (9)	>0.1
CAPS avoidance score	37.5 (6.36)	35.0 (6.36)	0.64 (9)	>0.5
CAPS arousal score	32.3 (4.73)	24.3 (9.11)	3.07 (9)	<0.02
CGI-S	6.0 (0.47)	4.9 (0.99)	2.90 (9)	<0.02
CGI-I	3.5 (0.52)	2.7 (1.25)	2.75 (9)	<0.03
NFQ nights frequency	0.50 (0.30)	0.37 (0.33)	1.31 (9)	>0.2
NFQ frequency of nightmares	0.81 (0.55)	0.44 (0.41)	2.45 (9)	<0.04
NES score	32.2 (11.29)	22.9 (8.7)	4.74 (9)	<0.002
PSQI score	17.20 (2.65)	13.9 (4.48)	2.32 (9)	<0.05

Values are presented as mean (standard deviation)

CAPS Clinician-Administered PTSD Scale, *CGI-S* Clinical Global Impression–Severity Scale, *CGI-I* Clinical Global Impression–Improvement Scale *NES* Nightmare Effects Survey, *NFQ* Nightmare Frequency Questionnaire, *PSQI* Pittsburgh Sleep Quality Index (see text), *CA1* clinical assessment at the start of the trial, *CA4* clinical assessment at the end of the third week

[a] A p-value <0.05 was considered statistically significant

stress-induced emotions and etiology of PTSD [4, 26]. Working in a homeostatic way, it prevents extreme cortical inhibition or excitation through modulation of GABAergic and glutamatergic neurotransmission [27]. Moreover, recent neuroimaging studies [13] showed higher availability of CB_1 receptors and lower concentrations of anandamide in patients with chronic PTSD.

The findings of this study should be interpreted in light of its limitations. By being a pilot study, the small sample size is a major drawback and seriously affects the generalizability of the psychometric results. The open-label design and no placebo control make it difficult to determine whether the changes observed were due to oral Δ^9-THC or to variability in the course of PTSD. Although this sample of chronic patients with high levels of ongoing PTSD symptoms despite continuous and stable psychoactive medication make the last unlikely, this is also an important limitation to take into account.

A 3-week follow-up period does not allow conclusions to be drawn regarding the long-term impact of oral THC on sleep. Previous studies of chronic users of smoked marijuana found that tolerance developed to the sleep-inducing effects but not to the REM-suppressing effects in the EEG [24]. Notwithstanding this, those studies were based on very high and variable, mostly uncertain, doses of Δ^9-THC, and the implications of these to fixed and low doses of oral Δ^9-THC are unclear. Finally, there is an uneven sex distribution (70 % male), which also affects inference about the effect among female patients.

This exploratory study was meant to provide preliminary evidence on the tolerance and tentative effect of add-on Δ^9-THC in PTSD, general distress and sleep symptoms.

The results of this pilot trial provided preliminary evidence on the safety and tolerance of Δ^9-THC as add-on treatment for chronic PTSD, and the results support further studies regarding the therapeutic effect of Δ^9-THC in chronic and acute PTSD.

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