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Short Communication

Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An-Open Label, Add-On, Pilot Study

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Abstract.
Background: Tetrahydrocannabinol (THC) is a potential treatment for Alzheimer's disease (AD).
Objective: To measure efficacy and safety of medical cannabis oil (MCO) containing THC as an add-on to pharmacotherapy, in relieving behavioral and psychological symptoms of dementia (BPSD).
Methods: Eleven AD patients were recruited to an open label, 4 weeks, prospective trial.
Results: Ten patients completed the trial. Significant reduction in CGI severity score (6.5 to 5.7; $p < 0.01$) and NPI score were recorded (44.4 to 12.8; $p < 0.01$). NPI domains of significant decrease were: Delusions, agitation/aggression, irritability, apathy, sleep and caregiver distress.
Conclusion: Adding MCO to AD patients' pharmacotherapy is safe and a promising treatment option.

Keywords: Alzheimer's disease, behavioral and psychological symptoms of dementia, cannabis, tetrahydrocannabinol

INTRODUCTION

Cannabis sativa is being used medicinally for a variety of indications [1, 2]. The cannabis plant contains numerous cannabinoids, which are responsible for its physiological and psychoactive effects. The first cannabinoids to be identified were the main psychoactive compound delta-9-tetrahydrocannabinol (THC) and the non-psychoactive compound cannabidiol (CBD), a cannabinoid with strong anti-inflammatory characteristics.

Cannabinoids act primarily through CB1 receptors (which are common particularly in the hippocampus, basal ganglia, and cerebellum) and CB2 (peripheral tissues). Following the discovery of an endogenous cannabinoid system and the identification of specific cannabinoid receptors in the brain, an effort has been made to investigate whether cannabis is efficient therapy in various neurodegenerative diseases.

Many studies have been focusing on the endocannabinoid system and revealed unique effects of

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this system on neuroinflammation, neurogenesis and the pathological processes of Alzheimer's disease [3–7]. Cao et al. found that THC directly interacts with amyloid-β peptide, thereby inhibiting its aggregation [8]. The endogenous cannabinoid system is associated in the central nervous system with regulating psychomotor activation, mood, sleep-wake cycle, and eating behavior. All of these functions are impaired in moderate and severe dementia.

There are only two published small clinical trials in older adults that were given oral synthetic cannabis based drugs. The first trial reported that the synthetic THC, dronabinol 2.5 mg/day appeared to be effective in anorexia and behavioral disorders in individuals with severe Alzheimer's disease [9]. The second study reported that dronabinol reduced nocturnal agitation [10]. None of the trials reported serious adverse events.

THC could be a potential therapeutic treatment option for Alzheimer's disease. Cannabis can be a new, safe, and more effective treatment for dementia and its associated symptoms.

Recently a randomized, double blind, placebo controlled low-dose study of THC for dementia patients was conducted. Twenty-four patients received THC and 26 received placebo for three weeks. The treatment was well tolerated, but no benefit in the neuropsychiatric symptoms of dementia was noted [11].

We aimed to test medical cannabis oil (MCO) in a small group of patients suffering from Alzheimer's dementia and co-morbid behavioral and psychological symptoms of dementia (BPSD).

METHODS

Participants

Eleven consecutive inpatients at our geriatric psychiatry ward who had been diagnosed with Alzheimer's dementia accompanied by BPSD were included in this pilot open-label trial. The patients were recruited during the period February 2013 to July 2014. Diagnosis was in accordance with the DSM-IV criteria.

The study was conducted in accordance with the declaration of Helsinki and approved by the Abarbanel Mental Health Center and The Israel Ministry of Health Ethical committees. Patients' guardians provided informed consent. Patients without a guardian were evaluated for ability to provide informed consent by independent senior psychiatrist who was not a part of the research group.

Materials

The term medical marijuana refers to phytocannabinoids, the cannabinoid compounds in the *Cannabis sativa* plant, including the two most medically relevant ones, THC and CBD [12].

For purposes of this study, medical marijuana will be synonymous with botanical cannabis. MCO is a form of botanical cannabis. In our study it contained THC extract obtained from the Cannabis plant.

MCO was supplied by "Canabliss", a medical cannabis manufacturer licensed by the Israeli Ministry of Health. Canabliss produces a THC extract from Cannabis flowers and leaves to prepare an oil of 1.65% potency.

Study protocol

This study was a prospective trial in which participants were assigned to a treatment for a 4-week period. MCO was added to the patients' medication regime (mainly antipsychotic medications) as an add-on treatment.

Following baseline assessments, patients received MCO (2.5 mg of THC) twice a day, at 0800 a.m. in the morning, and at 2000 p.m. in the night for 4 weeks. If no adverse events were noticed and no/minor improvement was noticed, after two days of THC treatment the dosage was increased to 5 mg THC two times a day and after two more days to the maximal dosage of 7.5 mg THC two times a day. The minimal dose of 2.5 mg bid, was given to 7 participants and only in 3 subjects there was a need for dose increase during the study.

Cannabinoid profile

Chemical analysis of the cannabinoid content of the MCO by Panaxia Ltd. laboratories was undertaken using high performance liquid chromatography HPLC [13]. The analysis showed very low levels of other phytocannabinoids, particularly CBD 0.05%, cannabichromene 0.05%, cannabinol 0.17%, tetrahydrocannabivarin 0.02%, and Tetrahydrocannabinolic acid <0.01%.

Outcome measures

Physical and neuropsychiatric outcome measures were obtained at baseline, and at 2 and 4 weeks. Participants' weight, glucose level, and both systolic

and diastolic blood pressure were assessed. Adverse effects were recorded during the study period.

The primary efficacy parameters were the change in the Neuropsychiatric Inventory (NPI) scale [14]; Mini-Mental State Examination scale (MMSE) [15]; Clinical Global Impression Improvement scale (CGI-I) [16]; and the Clinical Global Impression severity scale (CGI-S) [16]. The scales were assessed at baseline, end of week 2 and end of week 4.

Statistical analysis

Due to the small sample size, all analyses were non-parametric tests. Fridman's analysis of variance was used for the comparison of each variable change in time (k-related samples; baseline, 2 weeks, 4 weeks). The Wilcoxon signed-rank test was used for the comparison of two related samples (i.e., time comparisons). All analysis was conducted with the SPSS v20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

RESULTS

Ten patients suffering from Alzheimer's dementia completed the four weeks trial. One patient discontinued MCO treatment after three days (see adverse events section).

Five were females, and mean age for the group was 73.2 ± 8.59 years. Illness duration was on average 3.9 ± 3.5 years and mean years of education were 12.1 ± 4.4.

Six patients were born in Israel the rest immigrated from the former USSR, Morocco, and Turkey.

Patients were referred for hospitalization with severe agitation ($n = 7$) or aggressive behavior ($n = 3$). The patients were suffering from moderately to severe dementia with MMSE score of 10.3 ($\pm$9.4).

Eight patients who had completed the study received antipsychotic medications: Risperidone (5 patients), Olanzapine (2 patients), and Clozapine (1 patient).

In two patients who had received Olanzapine, the antipsychotic dosage was reduced and the rest were stable on their dosage.

Four patients received acetylcholinesterase inhibitors.

Adverse events

Only 3 of 11 patients who started the trial suffered an adverse event. One patient discontinued MCO after three days due to dysphagia, which was probably not related to MCO ingestion. A second patient had recurrent falls prior to admission and during the study he fell and suffered a broken pelvic bone, a simple fracture with no observable impairment. The third patient had been more confused with MCO dosage of THC 5 mg/day bid. MCO dose was decreased to the minimal dose of 2.5 mg/day bid, and the patient's confusion improved.

Physiological measures

No significant changes were obtained for weight (χ^2 (2) = 1.46, $p = 0.48$), glucose level (χ^2 (2) = 0, $p = 1$), and both systolic (χ^2 (2) = 4.15, $p = 0.13$) and diastolic blood pressure (χ^2 (2) = 2.57, $p = 0.28$).

Neuropsychiatric measures

The MMSE had shown a modest trend of change with time (χ^2 (2) = 4.95, $p = 0.08$), which originates from a significant increase in MMSE score between weeks 2 and 4 (W (5) = 15, $Z = 2.04$, $p < 0.05$) (Table 1).

CGI-S score has shown a significant change with time (Table 1) (χ^2 (2) = 4.95, $p = 0.08$), which originated from a decrease from baseline within two weeks (W (7) = 0, $Z = -2.53$, $p < 0.05$), and four weeks (W

Table 1
Change in physiological measures and clinical measures (MMSE and CGI)

	Time (weeks)			Friedman's test	Change in weeks (Wilcoxon's test)		
	0	2	4		0 to 2	2 to 4	0 to 4
Weight (kg)	66.57 (14.02)	67.31 (12.76)	67.64 (11.92)	1.46	0.42	1.18	0.94
Glucose (mg%)	114.9 (27.61)	110.0 (21.29)	117.8 (23.41)	0.00	–0.05	0.46	–0.25
Systolic BP	151.6 (23.19)	142.0 (23.05)	139.4 (17.87)	4.16	–2.19*	–0.31	–1.66
Diastolic BP	82.9 (9.31)	79.4 (7.98)	75.1 (8.37)	2.58	–1.42	–1.22	–1.72
MMSE	10.30 (9.38)	10.00 (8.89)	11.00 (8.67)	4.95	–0.41	2.04*	0.89
CGI-Severity	6.5 (.52)	5.7 (.48)	5.7 (.48)	14.00**	–2.53*	0.00	–2.53*
CGI-Improvement		2.3 (0.67)	2.2 (0.78)				

*$p < 0.05$, **$p < 0.01$.

Table 2
Change in NPI scales

	Time (weeks)			Friedman's test	Change in weeks (Wilcoxon's test)		
	0	2	4		0 to 2	2 to 4	0 to 4
Delusions	3.3 (3.94)	0.6 (1.26)	0.2 (0.42)	8.38*	–1.82	–1.34	–2.03
Hallucinations	1.7 (3.83)	0.5 (1.26)	0.3 (0.48)	0.67	–1.00	–0.45	–1.07
Agitation/Aggression	8.6 (3.77)	2.9 (2.18)	2.6 (2.11)	13.86**	–2.53*	–0.68	–2.52*
Depression/Dysphoria	1.9 (4.01)	0.1 (0.31)	0.3 (0.67)	3.50	–1.61	1.00	–1.10
Anxiety	2.4 (4.19)	0.5 (1.26)	0.1 (0.31)	5.63	–1.60	–1.34	–1.63
Elation/Euphoria	1.8 (3.82)	0.8 (1.31)	0.7 (1.33)	2.00	–0.82	–1.00	–1.34
Apathy/Indifference	3.7 (4.32)	1.0 (1.33)	1.4 (2.01)	6.91*	–2.21*	0.38	–1.79
Disinhibition	5.3 (3.49)	2.0 (2.00)	1.6 (1.95)	12.97**	–2.52*	–0.74	–2.37*
Irritability/Lability	5.9 (3.54)	2.0 (1.76)	1.7 (1.63)	12.87**	–2.52*	–0.55	–2.52*
Aberrant motor behavior	4.6 (4.71)	2.1 (2.42)	1.9 (1.96)	6.42*	–2.03*	–0.48	–1.99*
Sleep and night time behavior disorders	3.8 (3.70)	1.8 (2.74)	0.9 (1.66)	6.12*	–1.46	–1.34	–2.02*
Appetite and eating changes	1.4 (2.50)	0.6 (1.34)	0.8 (1.93)	0.80	–1.07	1.00	–0.82
Care giver distress	20.7 (5.92)	10.5 (6.02)	9.4 (5.85)	13.87**	–2.52*	–1.02	–2.67**
NPI total	44.4 (23.31)	14.9 (8.77)	12.8 (9.99)	14.81**	–2.52*	–1.58	–2.67**

*$p < 0.05$, **$p < 0.01$.

(7) = 0, $Z = -2.26$, $p < 0.05$). A similar decrease was not observed between the second week and the fourth week (W (0) = 15, $Z = 0$, $p = 1$).

CGI-I measures of change were compared to a no change score of 4 (indicating no change in CGI). Both CGI change after two weeks (D (9) = 3.09, $p < 0.001$), and CGI change after 4 weeks (D (9) = 2.77, $p < 0.001$) were found to be significantly different from a state of no change (Table 1).

Each NPI sub-scale was analyzed separately (Table 2). Significant decreases were observed in symptoms of Delusions, Agitation/Aggression, Apathy, Irritability, Aberrant motor behavior, Sleep and night time behavior disorders, Caregiver distress, and the NPI total score.

DISCUSSION

There is no FDA-approved treatment for BPSD, but antipsychotic drugs are frequently prescribed off-label yielding only modest improvements and associated with increased mortality [17].

Recently a double blind study demonstrated no improvement in NPI score with THC. This study included vascular and mixed dementia patients and the administered dose was low (1.5 mg three times daily) [11]. The present study included only Alzheimer's dementia patients and the starting dose was 2.5 mg daily with possibility of dose increase as needed.

Limitations of the present study are the small sample size and the lack of a control group. Our small pilot open label study and also the other three studies that were previously published [8–10] indicate that MCO can be safely administered to patients suffering from Alzheimer's dementia and comorbid BPSD. The positive results warrant further double blind research.

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