Medical Cannabis in Parkinson Disease: Real-Life Patients' Experience

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Background: The use of medical cannabis (MC) is controversial. Support for its benefits is based on small clinical series.

Objective: The aim of this study was to report the results of a standardized interview study that retrospectively assessed the effects of MC on symptoms of Parkinson disease (PD) and its adverse effects in patients treated for at least 3 months.

Methods: The survey used telephone interviews using a structured questionnaire based on subjective global impressions of change for various parkinsonian symptoms and yes/no questions on adverse effects.

Results: Forty-seven nondemented patients with PD (40 men) participated. Their mean age was 64.2 ± 10.8 years, mean disease duration was 10.8 ± 8.3 years, median Hoehn and Yahr (H&Y) was stage III. The duration of MC use was 19.1 ± 17.0 months, and the mean daily dose was 0.9 ± 0.5 g. The delivery of MC was mainly by smoking cigarettes (38 cases, 80.9%). Effect size (r^2) improvement for falls was 0.89, 0.73 for pain relief, 0.64 for depression, 0.64 for tremor, 0.62 for muscle stiffness, and 0.60 for sleep. The most frequently reported adverse effects from MC were cough (34.9%) in those who used MC by smoking and confusion and hallucinations (reported by 17% each) causing 5 patients (10.6%) to stop treatment.

Conclusions: Medical cannabis was found to improve symptoms of PD in the initial stages of treatment and did not cause major adverse effects in this pilot, 2-center, retrospective survey. The extent of use and the reported effects lend support to further development of safer and more effective drugs derived from *Cannabis sativa*.

Key Words: Parkinson disease, medical cannabis, adverse effects, motor symptoms, nonmotor symptoms, therapeutics

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Current treatments of Parkinson disease (PD) and parkinsonism still provide suboptimal effects, especially regarding the patients' quality of life. This has led to the search for alternative and often unconventional therapies. There is a wealth and steadily growing body of information in the nonmedical literature on the positive effects of cannabis products on motor symptoms (tremor, rigidity, bradykinesia) as well as on nonmotor symptoms (pain, sleep, depression, anxiety, nausea, and vomiting) and quality of life. The widely discussed adverse effects of standard PD medications encourage patients with PD and physicians to try "alternative natural treatments," including the attractive option of medical cannabis (MC). We were able to find only a few small clinical trials of the effects of MC in PD, one of which reported improvement of motor (tremor, rigidity, and bradykinesia) and nonmotor (sleep and pain) symptoms, with no significant adverse effects in 22 patients with PD.[1] In contrast, the results of 2 other studies were negative: there was no improvement of tremor after smoking cannabis among 5 patients,[2] and there were no effects of oral cannabis extract on dyskinesias in a randomized, 4-week, double-blinded, crossover study on 17 patients with PD who tolerated the treatment well.[3]

The use of *Cannabis sativa* for medical purposes had been permitted in Israel since 1991, and it has expanded significantly over the past 5 to 7 years, most likely because of the increased awareness and demand of patients who are exposed to it through social media and the internet, and whose doctors recommend it. However, it is strictly regulated by the Israeli Ministry of Health (MoH), and each patient requires personal permission to use MC after the inspection of each individual case. Selected growers are allowed to produce *Cannabis sativa* for medical use. The costs of MC are not reimbursed by health providers or insurers, and they total approximately 370 NIS (approximately $100 US) per month. Given the expanding request and interest of the patients and insufficient verification from controlled clinical trials, the aim of this report was to assess the effect of MC as adjuvant symptomatic treatment for various PD symptoms, (tremor, muscle stiffness, sleep disorders, depression, pain, weight) and its adverse effects in patients who were granted a license for MC use by the MoH in response to a formal request submitted by the patients' neurologists.

METHODS

A retrospective observational telephone survey was conducted to collect data from patients with PD being treated at the Movement Disorders Clinics of the Tel Aviv Sourasky Medical Center and the Rabin Medical Center. The license for MC use was granted by the MoH for each participant.

The study was approved by the institutional review boards, and all the participating patients agreed to answer questions by telephone. The design of the structured questionnaire was based on the published MC surveys in multiple sclerosis[4] and PD.[5] It consists of 66 questions divided into 3 parts: (1) demographic data and comorbidities; (2) clinical characteristics of the patients, including motor and nonmotor features; and (3) details of MC use and subjective assessment of its effects on different symptoms, including adverse effects.

The effect of MC on motor and nonmotor symptoms and on the activities of daily living was evaluated according to the

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Both Movement Disorders Units were responsible for patient with PD selection and providing the patient's telephone numbers. Tikun Olam Co was responsible for designing and administering the questionnaire, setting up the datasheet, and entering the data. The extraction and analysis of data and the report were performed by the first author (Y.B.). This article represents a final report on these data with the collaboration of all the authors.

Conflicts of Interest and Source of Funding: Lihi Bar-Lev Schleider is an employee of Tikun Olam Co, an Israel pharmaceutical company, which is developing cannabis-based medicinal extracts. Yehuda Baruch was a head of the Israeli Ministry of Health program for Medical Use of Cannabis in 2003 to 2012; at present, Yehuda Baruch is CSO of One World Cannabis Israel, which is a company dedicated to the research of cannabis and cannabinoids and their medical properties. All the other authors have nothing to declare.

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modified 5-point Clinical Global Impressions Scale as follows: 1 = significant improvement, 2 = moderate improvement, 3 = mild improvement, 4 = no change, and 5 = any worsening.[6] Falls before and after MC treatment were registered as yes/no. The telephone interviews were conducted (by L.B.S., J.K., and H.S.) at a prearranged date and time convenient for examinees. The interview lasted around 30 minutes, and a second call was needed to complete data collection in 9/47 cases (19.1 %).

Patients with PD who did not want to participate in the study or were not eligible according to the clinical judgment of the physicians or investigators were excluded from the study. If patients were unable to answer a question, or the question seemed inappropriate, then their response was recorded as irrelevant. All the included patients with PD answered all the questions independently. The responses were accepted as reported by the patient without any modifications, and no attempt to interpret this information was made.

Statistical Analysis

Data were analyzed using a Microsoft Excel 2007 spreadsheet. Results were expressed as means with standard deviations (SDs) or as median with interquartile range (IQR). Irrelevant answers were excluded from the statistical analysis. All the included patients with PD answered all the questions independently without any help. The data on the responses of patients with PD before and after MC were compared according to Student paired *t* test for dependent samples.[7] The effect size for the dependent samples *t* test (r^2) was calculated according to the method proposed by Morris,[8] and interpreted according to Cohen's guidelines: ≤0.5 = small; 0.5 to 0.8 = moderate; and ≥0.8 = large.[9] A higher r^2 value means stronger positive effect of MC in comparison with the period before MC was used. The level of significance was 95% for all tests.

RESULTS

Between 2013 to 2015, 98 patients with PD were suitable for study enrollment: 13 patients refused to participate, 20 could not be reached by telephone, and 4 patients had passed away. Fourteen patients were excluded from the analysis because they used MC for less than 3 months. Among them, 7 patients have not reached the necessary duration of MC treatment, and the other 7 patients interrupted treatment within 1 to 2 months because of MC inefficiency (4) or adverse effects such as loss of consciousness (1), hallucinations (1), and fatigue (1). A total of 47 patients with PD were included in the study.

Demographic Information

The mean age of the 47 subjects was 64.2 years (SD = 10.8; median = 65; IQR, [56.8–70]), of whom 40 (85.1%) were male patients. Thirty (63.8%) were retired, and the other 17 were employed. The PD duration ranged from 2 to 39 years (average, 10.8 years) (SD = 8; median = 8; IQR, [5–15]), and their H&Y stages ranged from I to IV, median = III, IQR of II to III (Table 1). Unclear answers were excluded from the statistical analysis, leading to variations in the total number of the responses.

PD Status Before MC Treatment

The major PD symptoms were reported as follows: 29/45 had rest tremor (64.4%), 24/45 had muscle stiffness (53.3%), 24/45 had freezing of gait (53.3%), 24/45 had gait disorders (53.3%), and 22/47 (46.8%) had recurrent falls (Table 2). Motor fluctuations were reported by 36/46 patients (78.73%): 25/47 (53.2%) complained of "off" times lasting from 0.5 to 24 hours a day, mean of 9.3 hours (SD = 5.8; median = 8; IQR, 4.0–12).

TABLE 1. Demographic Characteristics of 47 Parkinsonian Patients Treated by MC

Variable	Number	%
Age y		
39–55	9	19.1
56–65	15	31.9
66–75	16	34.1
76–87	7	14.9
Sex		
Male	40	85.1
Female	7	14.9
PD duration, y		
2–5	11	23.4
5–9	15	31.9
10–15	10	21.3
16–39	11	23.4
Employed (n = 47)		
Yes	17	36.2
No	30	63.8
H&Y stages (n = 40)		
I	2	5
II	17	42.5
III	12	30
IV	9	22.5

Total "on" times lasted for an average of 11.8 hours (SD = 6.9; median = 12 hours; IQR, 6–16) in 32/47 patients (68.1%). Peak of dose dyskinesias were reported by 21/45 individuals (46.7%).

The emotional condition of the patients was self defined as depression by 43/47 patients (91.5%): it was mild in 10 patients (21.3%), moderate in 20 (42.5%), and severe in 13 (27.7%). Memory impairment was reported by 33/44 patients (71.7%): it was mild in 8 (17.4%), moderate in 18 (39.1%), and severe in 7 (15.2%). Thirty-three of the 47 patients (70.2%) reported having problems in concentration: 8 considered them as being mild (17.0%), 17 as being moderate (36.2%), and 8 as being severe (17%). Thirty-one (67.4%) patients reported experiencing chronic pain, and 31 (66%) patients reported having sleep disorders (Table 2).

Delivery of MC

Most (38/45, 84.4%) of the patients preferred smoking *Cannabis sativa* flowers and leaves (5/45, 11.1%), or oil ingestion (4/46, 8.7%). Cigarettes or "joints" was the most common means of administration, reported by 42/46 (91.3%) of the MC users. The other modes of administration were oil (6/46, 13 %), vaporizer (2/46, 4.3%), and bong (a bong is a filtration device generally used for smoking cannabis, tobacco, or other herbal substances) (1/46, 2.2%). Four patients (4/46, 8.7%) reported using a combination of means of delivery, and 46/47 subjects (97.9%) reported using MC for medical purposes only. Only 1 subject (2.2%) reported that, in addition to medical reasons related to PD, he used MC for recreation.

The daily dose of MC ranged from 0.2 to 2.25 g/d, mean of 0.9 g (SD = 0.5; median = 0.75; IQR, 0.5–1.0) among the 43 subjects who responded to this item in the questionnaire. The duration of MC treatment in the entire study group of 47 persons ranged from 3 to 84 months, average of 19.1 months (SD = 17.0; median = 12; IQR, 6–24). Ten patients reported a need to increase the MC dose for better effects (21.3%). Five patients (5/47, 10.6%)

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TABLE 2. The Motor and Nonmotor Symptoms at Baseline of Parkinson's Disease Reported by 47 Patients Treated by MC

Variable	Number	%
Rest tremor	29/45	64.4
Muscle stiffness	24/45	53.3
Gait disorders	29/45	64.4
Freezing of gait	24/45	53.3
Falls	22/47	46.8
Motor fluctuations	36/46	78.3
Depression	43/47	91.5
Memory impairment	33/46	71.7
Mental concentration complaints	33/47	70.2
Chronic pain	31/47	66
Sleep disorder	31/47	66

decided to stop MC treatment 3 to 12 months after initiating it (average, 7 months [SD = 3.9; median = 6; IQR, 4–10]). The reasons that were given for stopping the use of the MC were lack of desirable effect in 2 patients (4.3%), hallucinations in 2 (4.3%), and postural instability in 1 (2.2%).

Effects of MC on PD Symptoms

General Satisfaction and Overall Effectiveness

Most of the patients (37/45, 82.2%) reported that MC improved their overall symptoms, 2 reported no difference (4.4%), and 6 (13.3%) reported feeling worse (Table 3).

Main Effects of MC on Motor and Nonmotor Symptoms of PD

The MC treatment led to a reduction in complaints of falling (from 22/47 [46.8%] to 6/18 [33.3%]) ($P < 0.05$, $r^2 = 0.89$). Reduced general stiffness of the muscles and tremor were reported by 32/44 and 30/41 individuals (72.7% and 73.2%, respectively), whereas 12 persons with stiffness and 11 those with tremor reported no change, and none reported worsening ($P < 0.001$, for both; $r^2 = 0.62$ and 0.64, respectively). Pain reduction was reported by 35/43 individuals (81.4%), and 8 others reported no change (18.6%) ($P < 0.001$, $r^2 = 0.73$). Three quarters of the subjects (35/46, 76.1%) reported an improvement in mood, 10 reported no change (21.7%), and 1 (2.2%) reported a worsening of mood ($P < 0.001$, $r^2 = 0.64$). Most of the patients reported an improvement in sleep quality (33/46, 71.7%), 13 reported no change (28.3%), and 1 (2.2%) reported worsening of sleep ($P < 0.001$, $r^2 = 0.60$). The MC treatment had no subjective effects on memory in 23/40 patients (57.5%), it improved in 10 (25%), and worsened in 7 (17.5%). Urinary symptoms were not changed in most patients (24/33, 72.7%), were improved in 6 (18.2%), and worsened in 3 (9.1%) ($P > 0.05$ for both, $r^2 = 0.03$) (Table 3).

Duration of the MC treatment in the group of 47 persons ranged from 3 to 84 months, average of 19.1 months (SD = 17; median = 12; IQR, 6–24). Ten patients reported the need to increase MC dose after starting for better effects (21.3%).

A total of 5/46 patients (10.9%) spontaneously stopped MC treatment in the interval from 3 to 12 months, on average after 7 months, (SD = 3.9; median = 6; IQR, 4–10). Reasons given for no longer using MC were lack of desirable effect in 2 subjects (4.3%), hallucinations in 2 subjects (4.3%), and postural instability in 1 subject (2.2%).

Adverse Effects of MC

Twenty-eight patients (28/47, 59.6%) noted undesirable effects of MC, among them are mental problems (18/47, 38.3%) like confusion (8/47, 17%), anxiety (8/47, 17%), hallucinations (8/47, 17%), and short-term amnesia (3/46, 6.5%), and 1 patient (1/47, 2.1%) claimed to have developed psychosis (2.1%). Cough associated with MC smoking was reported by 15/43 patients (34.9%), 2/43 (4.7%) experienced dyspnea, 6/47 experienced dizziness (12.8%), and 7/45 experienced unsteadiness (15.6%) (Table 4).

DISCUSSION

This is a real-life survey based on reports of the patients under observation in 2 large movement disorder clinics in Israel. It was performed in the form of a standardized telephone interview. As expected, improvement in pain, sleep, and mood were reported by a significant percentage of patients. In the context of PD, the report of significant reduction of falls is an important finding, along with significant subjective improvement in muscle stiffness and tremor. We propose that this improvement is either an indirect effect of MC for example through its positive effect on fear of falling, as well as relaxation effect on mood and attention, which may improve executive function and decrease falls. This effect may also be associated with the euphoric, analgesic, and sedating effects of MC,[10] which may be different in different strains of the *Cannabis sativa* plant or, alternatively, be related to a placebo effect.[11]

The use of MC in clinical practice is controversial because of its psychotropic and antimotivational effects,[12,13] as well as the risk of addiction, reaching 9%,[14] and possible posttreatment abstinence phenomena.[15,16] Another concern with the use of the herbal form of MC relates to various concentrations of the main active ingredients (Δ-9-tetrahydrocannabinol and cannabidiol) in different strains of *Cannabis sativa* and/or *indica*.[17]

The MC treatment was accompanied by numerous adverse effects, as reported by 60.4% of our study participants, with negative psychotropic effects reported by 39.6% of them. However, no hospitalizations or severe adverse effects were reported. Treatment with MC was continued for a year or more in most cases, which may indicate a preponderance of benefits and satisfaction from this therapy. Importantly, the large percentage of subjects (10/47, 21.3%) who spontaneously increased the dose of MC might indicate a potential for addiction and abuse. In total, 12/61 patients (7/14 excluded and 5/47 included individuals, 19.7%) stopped using MC because of ineffectiveness or intolerable adverse effects.

Although a pathogenetic rationale for treating PD with MC is currently lacking, animal data support a role for cannabinoids in motor control, because of the high density of cannabinoid receptors in the basal ganglia.[18] The highest density of CB1 receptors was found in the globus pallidus and substantia nigra pars reticulata,[19] where the endocannabinoid anandamide concentration is 3 times higher in comparison with other brain regions.[20] There is colocalization of CB1 and D1/D2 receptors in striatal neurons,[21] and locomotor activity was found to be reduced by CB1 inhibition.[22] Controlled clinical studies on the therapeutic potential of MC are few and small, whereas pressure for expanding cannabis use spread by media and patients' communities and families is increasing. Currently, until further controlled studies are performed, and until the long-term results are known, the use of MC should remain limited to patients who failed the best possible established medical treatment.[23]

We acknowledge potential limitations of this study. The sample of patients was not selected through any systematic procedure or by random recruitment. The questionnaire was administered by telephone, and the rate of agreement to participate (61/98 patients,

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TABLE 3. The Effects of at Least 3 Months of MC Treatment on Motor and Nonmotor Symptoms of Parkinson's Disease Reported by 47 Patients

Symptom	Considered As Relevant Item (n)	Reported As Not Relevant* (n)	Reported Improvement (n)				Reported As No Change** (n)	Reported Worsening** (n)	*P*	Effect Size (r^2)
			High	Moderate	Mild	Total**				
Motor symptoms										
Falls (yes/no)	18	2 (10%)	-	-	-	12 (66.7%)	6 (33.3%)	0	<0.001	0.89
Tremor	41	5 (10.9%)	10	9	11	30 (73.2%)	11 (26.8%)	0	<0.001	0.64
Muscle stiffness	44	3 (6.4%)	8	10	14	32 (72.7%)	12 (27.3%)	0	<0.001	0.62
OFF time	29	12 (29.3%)	2	7	9	18 (62.1%)	10 (34.5%)	1(3.4%)	<0.001	0.49
ON time	32	6 (15.8%)	1	9	7	17 (53.1%)	14 (43.8%)	1(3.1%)	<0.001	0.45
Dyskinesias	29	15 (34.1%)	3	4	7	14 (48.3%)	15 (51.4%)	0	<0.001	0.40
Freezing of gait	28	15 (34.9%)	4	6	3	13 (46.4%)	14 (50%)	1(3.6%)	<0.001	0.39
Gait disorder	40	7 (14.9%)	3	8	12	23 (57.5%)	14 (35%)	3(7.5%)	<0.001	0.34
Nonmotor symptoms										
Pain	43	3 (6.5%)	11	16	8	35 (81.8%)	8 (18.6%)	0	<0.001	0.73
Depressed mood	46	1 (2.1%)	15	13	7	35 (76.6%)	10 (21.7%)	1 (2.2%)	<0.001	0.64
Insomnia	46	1 (2.1%)	20	11	1	32 (69.6%)	13 (28.2%)	1 (2.2%)	<0.001	0.60
Appetite	31	1 (3.1%)	5	3	3	11 (35.5%)	20 (64.5%)	0	<0.001	0.31
Libido	36	2 (5.3%)	4	4	4	12 (33.3%)	24 (66.7%)	0	<0.001	0.28
Sexual life	34	3 (8.1%)	3	1	5	9 (26.5%)	25 (73.5%)	0	<0.01	0.21
Nausea	28	18 (39.1%)	1	3	2	6 (24.1%)	22 (78.6%)	0	<0.05 > 0.01	0.18
Constipation	33	12 (26.7%)	2	2	2	6 (18.2%)	26 (78.8%)	1 (3.0%)	<0.01	0.12
Attention	42	3 (6.7%)	3	5	6	14 (33.3%)	21 (50%)	7 (16.7%)	0.01	0.11
Memory	40	4 (9.1%)	2	2	6	10 (25%)	23 (57.5%)	7 (17.5%)	>0.05	0.04
Urination	33	9 (21.4%)	1	2	3	7 (18.2%)	24 (72.7%)	3 (9.1%)	>0.05	0.03

r^2 = effect size for the dependent samples *t* test: ≥0.2 small, ≥0.5 moderate, and ≥0.8 large.

*Proportion (%) from total number of responses (considered as relevant and not relevant together).

**Proportion (%) from considered as relevant only.

62.2%) suggests that this was a highly motivated population. Therefore, there is a potential for a bias to inflate the reports of effectiveness and to minimize adverse effects. Other limitations were the retrospective self-evaluations of the examinees regarding their status over time, given the memory and concentration problems of the elderly patients with PD. We did not take into consideration the time of the interview regarding "off" and "on," or the impact of the euphoric effect after MC. Formal neurocognitive assessment of the interviewed patients was not performed. There could also be possible errors in the interviewer-patient communications because of the difficulty to verify full comprehension of the questions during a telephone conversation. All subjects were chronically ill patients with PD with a range of related conditions, and the need for additional symptom relief may explain the reported positive MC effect.

In conclusion, the results of our study demonstrate that most of the users had found MC to improve their condition, and that MC treatment was safe, without major adverse effects. This pilot, 2-center survey reflects in part the current state of MC treatment for PD in Israel. The extent of use and the reported effects lend support to further development of safer and more effective drugs derived from the now intensively bred and widely cultivated *Cannabis sativa*.

TABLE 4. Adverse Effects Reported by 47 Parkinsonian Patients Treated by MC

Variable	Number	%
Confusion	8/47	17
Anxiety	8/47	17
Hallucinations	8/47	17
Amnesia	3/46	6.5
Psychosis	1/47	2.1
Any kind of psychotropic adverse effects	18/47	38.3
Cough	15/43	34.9
Dizziness	6/47	12.8
Unsteadiness	7/45	15.6
Breathlessness	2/43	4.7
Any physical adverse effects	21/47	44.7
Any adverse effects	28/47	59.6

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