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Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial

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Abstract

Introduction: Parkinson's disease (PD) has a progressive course and is characterized by the degeneration of dopaminergic neurons. Although no neuroprotective treatments for PD have been found to date, the endocannabinoid system has emerged as a promising target.

Methods: From a sample of 119 patients consecutively evaluated in a specialized movement disorders outpatient clinic, we selected 21 PD patients without dementia or comorbid psychiatric conditions. Participants were assigned to three groups of seven subjects each who were treated with placebo, cannabidiol (CBD) 75 mg/day or CBD 300 mg/day. One week before the trial and in the last week of treatment participants were assessed in respect to (i) motor and general symptoms score (UPDRS); (ii) well-being and quality of life (PDQ-39); and (iii) possible neuroprotective effects (BDNF and H^1-MRS).

Results: We found no statistically significant differences in UPDRS scores, plasma BDNF levels or H^1-MRS measures. However, the groups treated with placebo and CBD 300 mg/day had significantly different mean total scores in the PDQ-39 ($p = 0.05$).

Conclusions: Our findings point to a possible effect of CBD in improving quality of life measures in PD patients with no psychiatric comorbidities; however, studies with larger samples and specific objectives are required before definitive conclusions can be drawn.

Keywords
Parkinson's disease, cannabidiol, *cannabis*, treatment

Introduction

Cannabidiol (CBD) is one of the main components of *Cannabis sativa*, but it is not involved in its psychomimetic effects. Pharmacological studies on CBD have shown that the substance has a wide spectrum of action with different effects on different systems (Zuardi, 2008). The neuroprotective properties of CBD have been under increasing scientific scrutiny in the context of neurodegenerative diseases including Huntington's disease, Alzheimer's disease and Parkinson's disease (PD) (Iuvone et al., 2009). Two investigations using animal models of PD have been conducted to date to assess the neuroprotective effects of CBD. In the first one, Lastres-Becker et al. (2005) showed that the administration of CBD counteracted neurodegeneration caused by the injection of 6-hydroxy-dopamine in the medial prosencephalic bundle, an effect that could be related to the modulation of glial cells and to antioxidant effects (Lastres-Becker et al., 2005). In the next year, Garcia-Arencibia et al. (2007) tested many cannabinoid compounds following the lesion of dopaminergic neurons in the substantia nigra with 6-hydroxy-dopamine and found that the acute administration of CBD seemed to have a neuroprotective action; nonetheless, the administration of CBD one week after the lesion had no significant effects (Garcia-Arencibia et al., 2007). This study also pointed to a possible antioxidant effect with the upregulation of mRNA of the enzyme Cu-Zn-superoxide dismutase following the administration of CBD.

Despite the promising findings in animal models of PD, few clinical trials have assessed the neuroprotective effects of CBD in humans. An investigation with *Cannabis* users measured N-acetylaspartate to creatine ratios (NAA/Cr) in the brain through magnetic resonance spectroscopy (H^1-MRS) to assess the neurotoxic and neuroprotective effects of cannabinoids present in the drug and found a positive correlation between CBD and NAA/Cr in the globus pallidus and putamen ($r = 0.66$; $p = 0.004$) (Hermann et al., 2007). Furthermore, only one clinical trial has assessed the

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therapeutic use and neuroprotective effect of CBD in PD patients to date. Zuardi et al. (2009) conducted an open label study involving six patients with psychosis associated to PD and administered CBD at doses ranging from 150 mg in the first week to 400 mg in the fourth and last week of treatment according to the patients' clinical response. There was a significant improvement in psychosis and also in the total scores of a scale that measures general symptoms of PD (Unified Parkinson's disease rating scale – UPDRS) (Zuardi et al., 2009). These results, together with the findings from animal models of PD, point to the relevance of additional clinical trials with CBD in PD patients.

Thus, we designed a clinical trial to assess the effects of CBD in PD globally, including neurological assessments of motor and functional symptoms, a psychiatric assessment and complementary tests (brain-derived neurotrophic factor plasma levels and H^1-MRS).

Method

Sample

Participants were selected from an initial sample of 119 patients followed at the Movement Disorders Outpatient Clinic of the Ribeirão Preto Medical School University Hospital who were assessed by a neurologist, a psychiatrist and a neuropsychologist over a period of 24 months. The inclusion criteria for the clinical trial were: diagnosis of idiopathic PD, age above 45 years, use of stable doses of anti-Parkinson medication for at least 30 days before the trial and a score between 1 and 3 in the Hoehn and Yahr scale. Exclusion criteria consisted of the presence of atypical Parkinsonism, any previous or current psychiatric disorder, dementia diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria, relevant clinical comorbidity and previous use of cannabis. According to these criteria, we selected 23 patients to be included in the trial. Two patients refused to participate while the remaining patients were divided into three groups with seven participants each and matched according to age, gender, PD duration and total score in the UPDRS (Figure 1).

The project was approved by the Local Ethics Committee under process number HCRP 8990/2011 and the volunteers signed an informed consent form to participate.

Study design

During a period of one week, the participants underwent psychiatric and neurological assessments. After this baseline assessment, the patients were randomly assigned to three groups in accordance with the matching variables described above. Both the participants and investigators were blind in respect to the group each subject belonged to for the whole period of the study. Patients received placebo or doses of CBD (75 mg/day or 300 mg/day) for 6 weeks, in the last of which the baseline assessment was repeated. Blood samples for plasma BDNF quantification and H^1-MRS scans were also performed in the last week of the trial.

CBD preparation

CBD was provided in powdered form with 99.9% purity by THC-Pharma (Frankfurt, Germany). The drug was dissolved in corn oil and placed in gelatin capsules containing 75 mg or 300 mg and stored in dark glass flasks at the Laboratory of Clinical Psychopharmacology of the Ribeirão Preto Medical School. Placebo consisted of capsules containing corn oil only. CBD and placebo were supplied in identical capsules. The patients were instructed to take the medication at night under the supervision of relatives/caretakers.

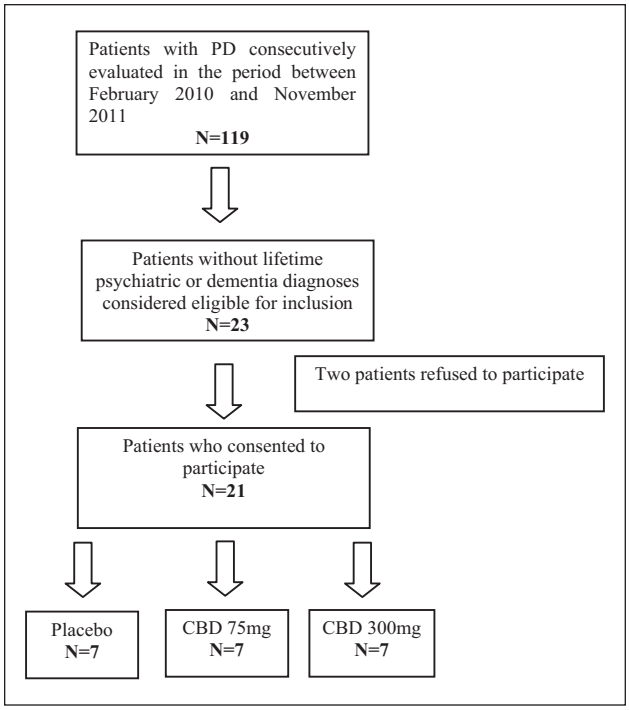

Figure 1. Flowchart describing the inclusion of patients from the Movement Disorders Outpatient Clinic in the double-blind, placebo controlled trial.

Assessment instruments

The following scales were used: (i) UPDRS to assess PD symptoms; (ii) Parkinson's Disease Questionnaire – 39 (PDQ-39) to assess functioning and well-being; and (iii) Udvalg for kliniske undersøgelser (UKU) side effect rating scale to evaluate possible adverse effects of CBD.

The UPDRS (Fahn et al., 1987) consists of 42 items that assess symptoms, signs and daily life activities of patients by means of clinical observation and patient reports. The scale has four parts: mentation, behavior and mood (Part I); activities of daily living (Part II); motor exam (Part III); and complications of therapy (Part IV).

The PDQ-39 (Jenkinson et al., 1995) is a questionnaire that assesses functioning and well-being in PD patients, covering characteristics that are specific to PD. Scores range between 0 and 100 and the questionnaire has good reliability and validity in relation to other measures of quality of life (Fitzpatrick et al., 1997; Jenkinson et al., 1997). The PDQ-39 can be divided into eight factors: mobility, activities of daily living (ADL), emotional well-being, stigma, social support, cognition, communication and bodily discomfort. The score in each factor is calculated through the sum of the scores of each item corresponding to the factor divided by the number of items and multiplied by 4. The

Table 1. Clinical and demographic data of patients in each group at baseline.

Mean (SD) (min–max)	CBD 75 mg/day	CBD 300 mg/day	Placebo	ANOVA (*F; p*) or Kruskal-Wallis test (*p*)
Gender (M/F)	5/2	5/2	5/2	
Age (years)	65.86 (±10.59) (51–82)	63.43 (±6.48) (53–71)	67.29 (±7.23) (57–75)	$F_{2.18}$=0.387; *p*=0.685
Age at PD onset (years)	57.71 (±13.52) (37–79)	56.57 (±8.56) (46–68)	57.43 (±7.72) (50–69)	$F_{2.18}$=0.024; *p*=0.977
UPDRS total (*on* state)	30.39 (±11.91) (14–49)	38.86 (±13.99) (17–62)	40.17 (±11.20) (21–50)	$F_{2.18}$=1.245; *p*=0.313
PDQ-39	47.14 (±23.63) (11–69)	47.29 (±26.27) (10–86)	23.83 (±6.43) (18–33)	$F_{2.18}$=2.514; *p*=0.111
PD duration (years)	8.14 (±5.64) (2–15)	6.86 (±3.72) (3–12)	9.86 (±4.71) (5–17)	$F_{2.18}$=0.702; *p*=0.509
Education (years)[a]	8.14 (±6.20)	10.71 (±7.18)	5.71 (±3.59)	*p*=0.337

[a]Nonparametric distribution.

result is then multiplied by 100 so that each factor has a score ranging between 0 and 100.

Lastly, the UKU (Lingjaerde et al., 1987) is a detailed instrument for the assessment of adverse medication effects including psychic, neurologic, autonomic and other manifestations. Each item is rated between 0 (absent) and 3 (severe). The rater has the additional possibility of recording causal relations between medications and relevant clinical events and interference with the patient's daily life.

Complementary tests

BDNF. Approximately 10 ml of blood were collected in the baseline week through venipuncture into tubes with sodium heparin. The samples were then centrifuged twice for 10 minutes at 4ºC and plasma was stored at –74ºC. Plasma BDNF levels were measured by ELISA according to the manufacturer's instructions (DuoSet, R&D Systems, Minneapolis, MN, USA) with concentrations described in pg/mL.

H^1-MRS. Proton magnetic resonance scans were made at the Center of Imaging Sciences and Medical Physics of the Ribeirão Preto Medical School University Hospital by an experienced technician. The scans were made using a Philips Achieva X-series unit with a 3 T superconducting magnet (high field), 25 mT gradient coils and a comercially-available circular-polarized head coil. The different software used in the acquisition were provided by the manufacturer together with the equipment.

Spectroscopy data were acquired using a single voxel (CSI hybrid), point-resolved spectroscopy (PRESS) sequence and presaturation for water supression with a MOIST sequence. The bilateral basal ganglia (putamen) were defined as the volume of interest (VDI). Echo time was short for the putamen (35 ms). Post-processing included the application of a smooth Gaussian filter and Fourier transformation.

Spectroscopy data were processed using software installed in an auxiliary console of the acquisition equipment. The resonance intensities of individual spectra were determined by the calculation of the integral of areas under the peaks of chemical dislocation graphs.

Statistical analysis

We used one-factor ANOVA to compare the three groups when variables had a normal distribution. When normality tests for the whole sample or for specific groups did not indicate a normal distribution, we used the Kruskal-Wallis test. Normality requirements for data distribution were confirmed using the Shapiro-Wilk test. The groups were matched in respect to gender, age and total UPDRS score. To analyze group differences in UPDRS and PDQ-39 scores, we calculated the variations between baseline and final (6 weeks) values and ran an ANOVA or Kruskal-Wallis test according to the data distribuition. When the null hypothesis was rejected, we used Bonferroni post-hoc tests to determine differences across groups.

Results

Table 1 presents the clinical and demographic data of the three groups, which were matched according to gender, age and total UPDRS scores.

In respect to the UPDRS, we found no statistically significant differences between mean score variations in the three groups. However, in regard to the PDQ-39, we found significant differences between the total score of the placebo and CBD 300 mg/day groups (p=0.05). The scores in factors "ADL" and "stigma" also had statistically significant differences between groups taking placebo and CBD 300 mg/day (p=0.02) and CBD 75 mg/day and 300 mg/day (p=0.04). Variations between baseline and final mean scores in the UPDRS, PDQ-39, BDNF and NAA/Cr are shown in Table 2.

There were no differences between the groups treated with CBD and placebo in respect to BDNF levels at baseline and after 6 weeks, nor in the different measures using H^1-MRS (NAA/Cre). Also, no significant side effects were recorded in any of the groups assessed with the UKU or through verbal reports.

Discussion

The endocannabinoid system has recently been implicated in the neurobiology of PD, with possible neuroprotective effects. We found significant improvements in measures of functioning and well-being of PD patients treated with CBD 300 mg/day compared to a group that received placebo. Despite this, we found no differences across groups in what concerns the other measures, including motor score as assessed with the UPDRS (Part III).

Quality of life is an important measure in clinical trials because it refers to a number of areas related to personal well-being. It is known that many therapies are able to improve the core symptoms of a given disease without corresponding

Table 2. Variations in the scores of UPDRS, PDQ-39, BDNF levels and NAA/Cr between baseline and final assessment.

	Placebo	CBD 75 mg/day	CBD 300 mg/day	ANOVA (*F; p*) or Kruskal-Wallis test (*p*)
	Variation/Baseline-Final (DP)	Variation/Baseline-Final (DP)	Variation/Baseline-Final (DP)	
UPDRS total *on*	3.83 (±6.85)	3.00 (±5.97)	6.57 (±5.83)	*F*=0.631; *p*=0.544
UPDRS part I	0.17 (±0.75)	0.86 (±1.07)	0.29 (±1.38)	*F*=0.737; *p*=0.493
UPDRS part II[a]	2.50 (±4.18)	−1.29 (±3.45)	2.85 (±4.14)	*p*=0.146
UPDRS part III[a]	2.17 (±8.23)	3.85 (±5.37)	3.00 (±5.16)	*p*=0.675
UPDRS part IV	−1.00 (±2.19)	−0.43 (±1.99)	0.43 (±2.64)	*F*=0.644; *p*=0.538
PDQ-39 total	6.50 (±8.48)[b]	10.00 (±12.15)	25.57 (±16.30)[b]	*F*=4.142; *p*=0.034
Mobility	4.17 (±9.70)	5.71 (±12.89)	19.64 (±17.22)	*F*=2.574; *p*=0.106
ADL	−0.69 (±6.68)[b]	16.07 (±16.21)	21.43 (±13.91)[b]	*F*=4.847; *p*=0.022
Emotional well-being	2.78 (±13.09)	5.36 (±10.12)	17.85 (±11.21)	*F*=3.339; *p*=0.060
Stigma[a]	3.13 (±5.23)	−4.46 (±16.42)[b]	15.18 (±14.37)[b]	*p*=0.038
Social support[a]	0.00 (±10.54)	2.38 (±12.47)	5.95 (±12.47)	*p*=0.694
Cognition[a]	13.57 (±30.72)	14.29 (±21.56)	7.14 (±4.31)	*p*=0.332
Communication	0.00 (±11.79)	0.00 (±23.57)	9.52 (±14.77)	*F*=0.657; *p*=0.531
Physical discomfort	13.89 (±15.52)	5.95 (±25.78)	23.81 (±18.28)	*F*=1.323; *p*=0.292
BDNF levels	−1,385.25 (±6,814.65)	822,67 (±7,884.29)	−3,522.97 (±18,993.18)	*F*=0.158; *p*=0.855
H^1-MRS				
NAA/Cre right[a]	0.11 (0.18)	0.11 (0.18)	0.10 (0.18)	*p*=0.875
NAA/Cre left	0.19 (0.18)	−0.01 (0.07)	0.07 (0.22)	*F*=1.890; *p*=0.183

[a]Nonparametric distribution; [b]$p<0.05$, Bonferroni's post hoc test.

improvements in quality of life. The PDQ-39 is a self-report instrument that assesses several dimensions of PD providing a detailed picture of the disease with little influence of symptom oscillations throughout the day, especially in what refers to treatment with levodopa. The score reduction in the PDQ-39 seen in the group of patients treated with CBD 300 mg compared to the mean variation of the placebo group seems to be mostly related with the 'daily life activities' factor ($p<0.05$) but the relationship with 'emotional well-being' and 'mobility' factors also tended to be statistically significant.

Although we excluded patients with comorbid psychiatric disorders, basal symptoms with no clinical significance or related to the impairments of the disorder could be present and be somehow connected with the observed improvement in emotional well-being. A study on *Cannabis* and PD showed that the use of the drug could be associated with subjective reports of emotional well-being, even in the absence of significant improvement in motor symptoms (Venderova et al., 2004). Recently, another study revealed significant improvement in specific motor symptoms after treatment with *Cannabis* (Lotan et al., 2014). In addition, CBD's possible anxiolytic (Bergamaschi et al., 2011; Crippa et al., 2009), antidepressant (Saito et al., 2010; Zanelati et al., 2010), antipsychotic (Zuardi et al., 1991; 1995) and sedative (Chagas et al., 2013; 2014; Monti, 1977) properties could explain the reports of improvements in emotional well-being, daily life activities and, hence, quality of life, as a result of its action in the non-motor symptoms of PD. It should be noted that the main active component of *Cannabis* is Δ9-tetrahydrocannabinol (THC), which was not investigated in this clinical trial. Nonetheless, there is evidence of the effects of THC and *Cannabis* in clinical trials (Lotan et al., 2014) and in animal models of PD (van Vliet et al., 2008).

The mechanism of action of CBD, in general and particularly in PD, remains unknown despite increasing efforts to explain it. CBD acts in a number of sites and its action as a neuroprotective agent is based on the following effects: local anti-inflammatory properties, reduction of oxidative stress, attenuation of glial cell activation and normalization of glutamate homeostasis (Fernandez-Ruiz et al., 2013). It is noteworthy that the neuroprotective effect of CBD seems to be independent from its action on the CB_1 and CB_2 receptors (Garcia-Arencibia et al., 2007; Lastres-Becker et al., 2005).

Despite the possible neuroprotective action of CBD, we found no statistically significant differences across groups in respect to UPDRS scores. Unfortunately the sample enrolled in the study was too small, which restricts the reach of our analyses and does not allow for definitive conclusions. Also, most participants were in the early stages of the disease, which hampers the observation of broad variations, as these patients tend to have low baseline scores. On the other hand, the inclusion of patients with longer disease duration could also pose a problem to the evaluation and the observation of positive effects due to increased damage in the substantia nigra in the later phases of the disease. Finally, although all UPDRS measures were made during the *on* stage and in the morning, some items measured by the scale may vary during the day and from day to day, which does not necessarily mean improvement or worsening of the disease (Siderowf et al., 2002).

The neuroprotective effects of CBD are not easily measured in humans and, although they have been reported in animal models, we failed to find such effects with the measures used here. We hypothesized that the administration of CBD could increase BDNF levels and the ratios of metabolites NAA and Cr as measured with H^1-MRS, which are related to neuronal viability. Some

limitations should also be noted including those related to H^1-MRS and BDNF measures: the 6-week period might have been insufficient for the occurrence of detectable changes in spectroscopy measures linked to neuronal viability, added to the fact that this measure has not been explored in depth in PD. Probably, a longer treatment period should be tested before definitive conclusions are drawn. Also, BDNF levels have large inter-individual variations, which increases standard deviations and may hinder the occurrence of differences in small samples.

Nowadays, most drugs used in the treatment of PD act in the dopaminergic system and little is known about the role of other neurotransmitter systems in the disease. The endocannabinoid system seems to be an important target of investigation, mostly because of its action in those considered as the non-motor symptoms of PD and of reports of its possible neuroprotective effects.

Conclusions

This study points to a possible effect of CBD in improving measures related to the quality of life of PD patients without psychiatric comorbidities. We found no statistically significant differences concerning the motor symptoms of PD; however, studies involving larger samples and with systematic assessment of specific symptoms of PD are necessary in order to provide stronger conclusions regarding the action of CBD in PD.

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Conflict of interest

The authors declare that there is no conflict of interest.

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