Original Paper

Effects of acute cannabidiol administration on anxiety and tremors induced by a Simulated Public Speaking Test in patients with Parkinson's disease

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Abstract

Background: Cannabidiol (CBD) is one of the main components of *Cannabis sativa* and has anxiolytic properties, but no study has been conducted to evaluate the effects of CBD on anxiety signs and symptoms in patients with Parkinson's disease (PD). This study aimed to evaluate the impacts of acute CBD administration at a dose of 300 mg on anxiety measures and tremors induced by a Simulated Public Speaking Test (SPST) in individuals with PD.
Methods: A randomised, double-blinded, placebo-controlled, crossover clinical trial was conducted. A total of 24 individuals with PD were included and underwent two experimental sessions within a 15-day interval. After taking CBD or a placebo, participants underwent the SPST. During the test, the following data were collected: heart rate, systemic blood pressure and tremor frequency and amplitude. In addition, the Visual Analog Mood Scales (VAMS) and Self-Statements during Public Speaking Scale were applied. Statistical analysis was performed by repeated-measures analysis of variance (ANOVA) while considering the drug, SPST phase and interactions between these variables.
Results: There were statistically significant differences in the VAMS anxiety factor for the drug; CBD attenuated the anxiety experimentally induced by the SPST. Repeated-measures ANOVA showed significant differences in the drug for the variable related to tremor amplitude as recorded by the accelerometer.
Conclusion: Acute CBD administration at a dose of 300 mg decreased anxiety in patients with PD, and there was also decreased tremor amplitude in an anxiogenic situation.

Keywords
Cannabidiol, Parkinson's disease, anxiety, tremor

Introduction

Cannabidiol (CBD) is one of the main components of *Cannabis sativa* and has a wide spectrum of effects due to its anxiolytic, antipsychotic, anti-inflammatory and neuro-protective properties (Campos et al., 2016; Pisanti et al., 2017). To date, the effects of this substance have been studied in several pathologies, including epilepsy, inflammatory diseases, cancer, psychiatric disorders and neurodegenerative diseases such as Parkinson's disease (PD; Campos et al., 2016; Pisanti et al., 2017).

PD affects 3.3% of the population older than 64 years of age and is characterised mainly by the presence of motor signs (Barbosa et al., 2006). The neurodegenerative process in the substantia nigra and consequent dysfunction of the nigrostriatal dopaminergic system explain the onset of motor signs in PD. However, PD is related to the presence of abnormal cytoplasmic inclusions of α-synuclein and neurodegeneration in other regions of the nervous system, which may explain the full range of non-motor signs and symptoms in PD (Braak and Del Tredici, 2008).

The presence of non-motor signs and symptoms is widespread in patients with PD and includes depression, anxiety, apathy, sleep disorders and psychosis, among others (Marinus et al., 2018). The signs and symptoms of anxiety can affect up to 67% of patients with PD (Chagas et al., 2009) and are related to the damage inherent to PD; dysfunctions in the serotonergic, dopaminergic and noradrenergic pathways; medications used to treat

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PD; and motor fluctuations throughout the day (Dissanayaka et al., 2014, 2016).

An important observation is that tremors may worsen when patients with PD experience anxiogenic situations. This increase may even be observed in experimental models of anxiety, such as the Simulated Public Speaking Test (SPST; Chagas et al., 2017). This model has already been used to test the effects of CBD in healthy populations and those with anxiety disorders and has always demonstrated an anxiolytic effect (Bergamaschi et al., 2011a; Zuardi et al., 1993).

We previously published a double-blinded study that evaluated the effects of CBD on PD (Chagas et al., 2014). In this study, the group that received CBD at a dose of 300 mg/day showed a significant improvement in the quality-of-life scores on the Parkinson's Disease Questionnaire-39 compared to the placebo group, mainly in emotional well-being and activities of daily living. However, no differences were observed between the groups regarding motor signs. One hypothesis is that the broad spectrum of action of CBD may improve non-motor symptoms, including anxiety, even when they are not yet clinically relevant. Also, the anxiolytic effect of CBD could attenuate tremors that may be exacerbated in anxiogenic situations.

Thus, the objective of this study was to evaluate the effects of acute CBD administration at a dose of 300 mg on anxiety measures (subjective and physiological) and tremor induced by the SPST in individuals with PD.

Methods

Design

The present study was a randomised, double-blinded, crossover clinical trial. The interval between the first and the second experiment was 15 days, and the medications used by the patients were not changed during this time.

Participants

Twenty-four volunteers with idiopathic PD were selected from those who responded to a public notice published in the press in the city of São Carlos, São Paulo state, Brazil, and some patients of neurology services in the same city and the surrounding region. The inclusion criteria were idiopathic PD, an absence of marked cognitive alterations according to a clinical evaluation, patients not on benzodiazepines or antidepressants, and those with clinical conditions that would permit maintenance of antiparkinsonian drug doses throughout the study. Patients with atypical Parkinsonism and dementia or current psychiatric disorders according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (5th edition; DSM-5) were excluded (American Psychiatric Association, 2013).

SPST

The SPST is an experimental model used to induce anxiety. The subject is asked to prepare a speech on a neutral theme that will supposedly be recorded and evaluated by a psychologist. During the speech, the volunteer remains seated in front of a TV screen that shows his/her own image captured by a video camera (McNair et al., 1982). In this study, the volunteer was asked to give a speech on the 'transportation system of his city' in the first experiment and on the 'water and sewage system' in the second experiment to minimise learning effects between the two tests.

Clinical evaluation

A baseline clinical evaluation of the patients was performed to characterise the signs, symptoms and severity of PD using the following scales: the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn and Elton, 1987), Hoehn and Yahr Scale (Hoehn and Yahr, 1967) and Schwab and England Scale (Schwab and England, 1969). The UPDRS is a 42-item scale that assesses symptoms, signs and activities of daily living through clinical observation and patient reports, with higher scores indicating greater severity. It is divided into four parts: behaviour and mood, activities of daily living, motor signs and complications. The Hoehn and Yahr Scale was used to assess the stage and severity of PD. This scale classifies the individual into five stages of evolution and impairment. The Schwab and England Scale evaluates the degree of independence of the volunteers to perform activities of daily living, with scores ranging from 0% to 100%.

Variables and outcomes

Visual Analog Mood Scales. The Visual Analog Mood Scales (VAMS; Norris, 1971) have been translated and adapted into Portuguese (Zuardi and Karniol, 1981) and are composed of 16 pairs of adjectives with opposite meanings, separated by a 10 cm line on which the subject indicates how he/she feels about the adjectives at the time of completion. The 16 items on the scale are grouped into four factors. In this study, the following factors were used: anxiety, sedation, cognitive impairment and discomfort (Zuardi et al., 1993).

Self-Statements during Public Speaking Scale. The Self-Statements during Public Speaking Scale (SSPS) includes items following with the cognitive model of social anxiety and consists of two subscales (positive self-assessment (SSPS-P) and negative self-assessment (SSPS-N)), each composed of five items. It is a Likert scale that the participant scores from 0 to 5 according to how much the statement matches his/her subjective state at the time, with 0 representing total disagreement with the sentence and 5 representing complete coherence with his/her feelings (Hofmann and Dibartolo, 2000; Osório et al., 2008).

Systemic blood pressure and heart rate. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were measured with an electronic pulse digital sphygmomanometer (model HEM-6124; Omron Healthcare, Kyoto, Japan), which was fixed to the volunteer's left wrist.

Tapping test. In this bradykinesia test, the subject is asked to tap two points separated by 30 cm. The subject must complete 10 cycles (one cycle corresponds to touching both sides of the segment) and the time to perform the task is measured for both sides (Ruiz et al., 2007).

Table 1. Flow chart of the procedures in the experimental session.

Session (min)	Phase	Procedure
−1:30	Baseline (B)	Drug or placebo intake and BP, HR, TT, VAMS, SSPS and accelerometer measurements
0	Pre-stress (P)	Accelerometer, BP, HR, TT, VAMS and SSPS measurements
+0:10	Instruction on television	Orientation for the preparation of the speech on a neutral theme
+0:12		Preparation of the speech
+0:14	Anticipatory (A)	Accelerometer, BP, HR, TT, VAMS and SSPS measurements
+0:24	Start of the speech (S1)	Start of the speech, accelerometer measurements
+0:26	Performance (S)	BP, HR, TT, VAMS and SSPS measurements
+0:33	Continuation of the speech (S2)	Continuation of the speech and accelerometer measurements
+0:35		End of the speech
+0:45	Post-stress 1 (F1)	Accelerometer, BP, HR, TT, VAMS and SSPS measurements
+1:00	Post-stress 2 (F2)	Accelerometer, BP, HR, TT, VAMS and SSPS measurements

BP: blood pressure; HR: heart rate; SSPS: Self-Statements during Public Speaking Scale; TT: tapping test; VAMS: Visual Analog Mood Scales.

Tremors measured by an accelerometer

Studies have indicated that frequency and amplitude data from accelerometers have strong correlations with tremors measured by clinical evaluation (Dai et al., 2015; Jang et al., 2013; Wile et al., 2014). In this study, the MPU-6050 sensor (InvenSense Inc., San Jose, CA) was used, which is small in size, with dimensions of 4 mm×4 mm×0.9 mm. The sensor was connected to an Arduino Uno R3 board that transmitted data to a computer via an USB cable using 32 Hz sampling. The sensor was unilaterally fixed to the index finger of the hand that had greater tremor according to the previous clinical evaluation. As outputs, the sensor generates three signals or time series. These series correspond to the acceleration in the three spatial directions (the *x*-, *y*- and *z*-axes). In this study, fusion between the axes was performed based on the Euclidean distance to generate a single time series by measurement. This fusion is based on the sum of the squares, which allows determination of the instantaneous acceleration independent of the axis. In fact, in this study, we were mainly interested in measuring the amplitudes along all axes. So, the equation that calculates the time series used to perform the computational experiments is: $s(t) = \sqrt{x(t)^2 + y(t)^2 + z(t)^2}$.

This independent fusion is essential because the sensor can be positioned in different ways and rotate during the test, which causes a crossing of the axes; this could be misinterpreted by the programme that performs the data extraction for the time series. The time and frequency analyses were performed from the signal $s(t)$. Since these are time series, tools were used to extract information from the amplitudes of $s(t)$ over time.

All techniques received the signal $s(t)$ as input and produced features that explain the original signal. More than merely using an algorithm that generates outputs, the research focused on finding patterns in the data that allow tremor evaluation using acceleration data alone.

To find those patterns for the whole series, we employed a frequency analysis using the fast Fourier transform algorithm. Due to theoretical limits for sampling observations along time, the signals were filtered for the frequency of 32 Hz to avoid misinterpreting the analysis (Gibson, 1994). The following variables were extracted from the signal: the power spectrum entropy (PSE), which is a measure of information complexity computed along all frequency amplitudes; the power spectrum peak frequency (PSPF), which concerns the main frequencies (in terms of cycles per second – Hz) that represent the tremor; and the power spectrum peak (PSP), which codifies the amplitudes of the fundamental frequencies of movement. The characteristics were computed as described in Ponti et al. (2017). To normalise the data (signals) captured by the accelerometer, the *z*-score was used, such that the signals had a mean of 0 and a standard deviation close to 1.

Procedures

This study was approved by the Research Ethics Committee of the Federal University of São Carlos (number 1.631.701), and all participants signed the informed consent form before taking part. After the public notice for interested volunteers was posted, a form with the selection criteria was completed online or by telephone. The included volunteers were contacted sequentially by phone or email and scheduled according to their availability to undergo experiments in the Gerontology Department of the Federal University of São Carlos.

All volunteers underwent two experimental sessions lasting approximately three hours and were evaluated during the *on* state. The participants were instructed to take their antiparkinsonian and clinical medications as usual. On the first day of the experiment, in addition to the SPST, a clinical evaluation of PD was performed using the instruments mentioned above. The CBD or placebo was administered before to begin the experimental sessions. During these sessions, anxiety induced by the SPST was evaluated by VAMS, SSPS and HR and blood pressure measurements. Motor signs were assessed by the tapping test (TT), and tremor data were captured by the accelerometer for one minute in each phase of both experiments. The procedures adopted on the day of the experiments are summarised in Table 1. In each experimental session, a single dose of oral CBD or placebo was administered in a double-blind procedure, followed by baseline measurements (B). Pretest measurements (P) were made 90 minutes after drug ingestion. The subjects then received instructions and had two minutes to prepare a four-minute speech on a neutral topic. Each participant was also told that the speech would be recorded on videotape and subsequently analysed by a psychologist. Anticipatory speech measurements (A) were taken before the subject started speaking. The subject then spoke in front of the camera while viewing his/her own image on the TV screen. Accelerometry data were collected

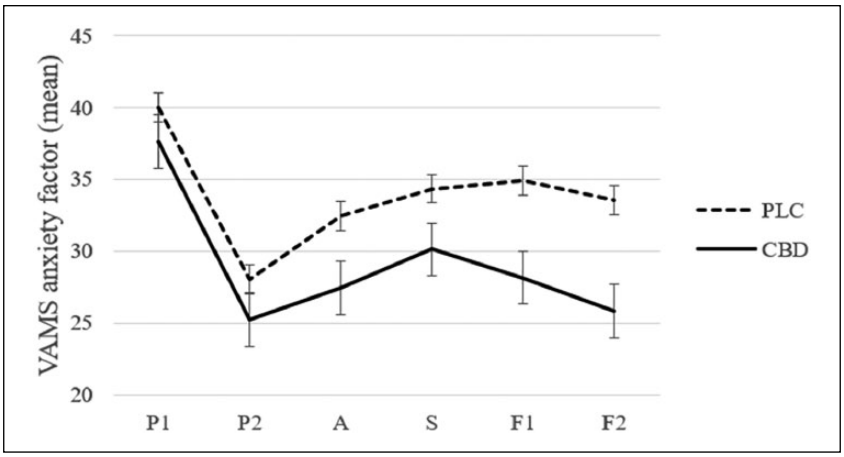

Figure 1. Comparison of CBD versus PLC administration for VAMS anxiety factor. Points in the curves indicate the positive and negative measures of the standard error. There was a significant difference between drug treatments (n=23). A: anticipatory; B: baseline; CBD: cannabidiol; F1: post-stress 1; F2: post-stress 2; P: pre-stress; PLC: placebo; S: performance.

during the first minute of the speech (S1). The speech was interrupted in the middle, and performance measurements (S) were taken. The speech was then continued for an additional two minutes, with accelerometry data collected in the first minute (S2). Post-test measurements F1 and F2 were made 10 and 25 minutes after the end of the speech, respectively.

CBD and placebo capsules were prepared in the Psychopharmacology Laboratory of the Department of Neurosciences and Behavioural Sciences of the Ribeirão Preto Medical School, University of São Paulo. The 300 mg dose of 99.9% pure CBD powder (BSPG-Pharm, Sandwich, UK) was dissolved in corn oil and packaged in gelatine capsules, which were prepared and conditioned in a dark vial. The CBD and placebo were distributed in identical capsules. The dose of 300 mg was chosen based on a study by Chagas et al. (2014), in which significant improvements were found regarding the emotional well-being dimension of the Parkinson's Disease Questionnaire-39 when using this dose.

Statistical analysis

A descriptive analysis of the demographic and clinical data was carried out to determine percentages and average frequencies. Differences between the VAMS, SSPS, BP, HR, TT and variables recorded by the accelerometer were verified by repeated-measures analysis of variance (ANOVA) by analysing the phases, drug, order and interactions among them. In cases in which the sphericity condition was violated, the degrees of freedom were corrected with the Greenhouse–Geisser test. The Bonferroni post hoc test was used when a difference was found in the ANOVA. Data were analysed using IBM SPSS Statistics for Windows v23 (IBM Corp., Armonk, NY), and the level of significance adopted was 0.05.

Results

Characterisation of the sample

Regarding the sociodemographic characteristics of the sample, most participants were men (n=22), married (n=22) and retired (n=19). The mean age of the participants was 64.13 years (standard deviation (SD) ±9.72) with 12.79 years of schooling (SD ±6.46).

Regarding the clinical data, all patients reported the onset of symptoms after 50 years of age, with a mean duration of 6.5 years (SD ±5.03). All participants were classified between stage 1 and stage 2.5 according to the Hoehn and Yahr scale. Scores on the Schwab and England functional scale ranged from 70% to 90%, with a mean of 85% (SD ±7.79%). The mean score on the motor section of the UPDRS was 21.71 (SD ±9.38). Most patients were taking levodopa (n=19). Other medications used were pramipexole (n=11), amantadine (n=8), selegiline (n=3), biperiden (n=2) and entacapone (n=1). In addition to antiparkinsonian medications, the participants were taking simvastatin (n=4), omeprazole (n=3), atenolol (n=2), losartan (n=2), propranolol (n=1), nifedipine (n=1), amiodarone (n=1), melatonin (n=1), fenofibrate (n=1), levothyroxine (n=1), acetylsalicylic acid (n=1) and finasteride (n=1). There were no reports of side effects during or after the experiments.

Anxiety measures

There were statistically significant differences in the VAMS anxiety factor for the drug (F(1, 21)=6.27; p=0.021) and phase (F(2.75, 57.66)=5.26; p<0.001). In the Bonferroni post hoc analysis, the mean values for the anxiety factor were lower when the participants received CBD (Figure 1). Regarding the SPST phases, there were statistically significant differences between the B phase and all other phases, with higher scores in the baseline. In addition, the P phase had lower scores than the A, S and F1 phases. There were no statistically significant differences between the other phases of the SPST. There were no significant differences in the drug–phase interaction or order effect.

The VAMS cognitive impairment (F(1, 21)=0.75; p=0.396), sedation (F(1, 21)=2.647; p=0.119) and discomfort (F(1, 21)=0.04; p=0.838) factors did not show significant differences in relation to the drug. The repeated-measures ANOVA showed differences in relation to the phase for the mental sedation (F(2.80, 58.77)=5.78; p<0.001) and physical sedation (F(21.94,

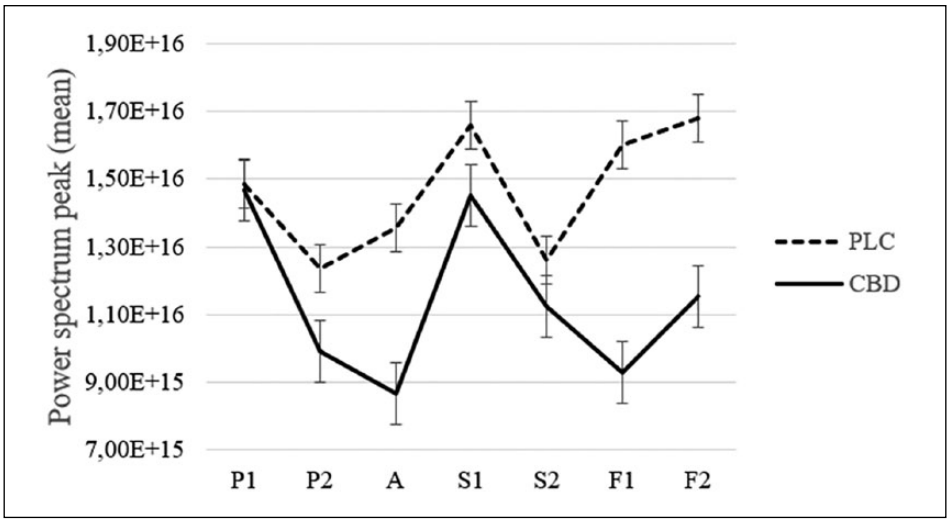

Figure 2. Comparison of the CBD versus PLC administration for the PSP characteristic measured by the accelerometer. Points in the curves indicate the positive and negative measures of the standard error. There was a significant difference between drug treatments (n=23). S1: start of the speech; S2: continuation of the speech.

40.69)=4.68; p=0.016) factors; there were no differences in the other feelings factor or in the three drug–phase interaction factors. One participant did not complete the VAMS adequately and was excluded from the analysis. Regarding the SSPS, there were no statistically significant differences in the SSPS-P or SSPS-N subscales for the drug, phase, or drug–phase interaction. Likewise, the repeated-measures ANOVA did not show significant differences in the SBP, DBP or HR.

Tremor and bradykinesia measures

Regarding the variables captured by the accelerometer, the repeated-measures ANOVA showed significant differences for the drug only in the PSP variable (F(1, 20)=6.19; p=0.022). There were no significant differences in the PSE (F(1, 20)=1.63; p=0.216) or PSPF (F(1, 20)=0.02; p=0.899) variables for the drug. Moreover, there were no differences in the phase or the drug–phase interaction for all variables captured by the acceleration sensor. The variables were not evaluated in two participants because the signal was not captured adequately. Figure 2 shows the PSP values throughout the SPST.

Regarding the TT for the evaluation of bradykinesia, no effect was observed from the drug (F(1, 21)=0.15; p=0.701). There were significant differences in the phase (F(3.14, 65.87)=10.22; p<0.001) and drug–order interaction (F(1, 21)=4.39; p=0.049). Therefore, the time spent on the TT was lower throughout the SPST and lower in the second experimental session, which was expected after repeating the bradykinesia test.

Discussion

The role of the endocannabinoid system in anxiety and PD has been investigated in both animal and clinical models but in isolated manners. The novelty of this study was to study the effects of CBD on the interaction between anxiety and motor signs in patients with PD while considering that increased anxiety may worsen tremor (Chagas et al., 2017). Our findings show that CBD administration attenuated SPST-induced anxiety and decreased tremor amplitude in patients with PD during the experimental test. This observation is in accordance with anxiolytic effects of CBD observed in studies using the SPST as an experimental model of anxiety in individuals with social anxiety (Bergamaschi et al., 2011b) and healthy volunteers (Linares et al., 2019; Zuardi et al., 1993), as well as during the Public Speaking in Real Life model (Zuardi et al., 2017).

CBD has shown to modulate brain regions related to stress and anxiety. Fusar-Poli et al. (2010) conducted a neuroimaging study on healthy subjects and showed that CBD reduces the effectiveness of the connection between the anterior cingulate cortex and the amygdala during the processing of stimuli comprising facial expressions showing fear (Fusar-Poli et al., 2010). The amygdala is a structure directly related to conditioned fear and to fight-or-flight behaviour (Duvarci and Pare, 2014) and has already been implicated in anxiety in patients with PD (Vriend et al., 2016). The volumetric reduction of the left amygdala seems to be related to increased anxiety symptoms in patients with PD (Vriend et al., 2016). These observations suggest that CBD may be an alternative treatment for patients with PD and anxiety. Thus, the chronic administration of CBD could be tested in future studies.

A recent meta-analysis showed that 31% of patients with PD present anxiety disorders (Broen et al., 2016). Also, clinically relevant anxiety symptoms are commonly present even in the absence of a specific anxiety disorder and may be associated with the severity of the motor signs, motor fluctuations and disease duration (Chagas et al., 2009; Sagna et al., 2014). However, very few studies have been conducted to evaluate the treatment of anxiety in patients with PD. The available therapeutic options are selective inhibitors of the serotonin and benzodiazepines, which generally have side effects such as increased tremor, increased risk of falls and worsened cognition (Pontone et al., 2013), especially in the elderly. These observations reinforce the need to provide alternatives for the treatment of signs and

symptoms of anxiety in PD. CBD could be an alternative therapeutic option, considering that this compound is safe and has very few side effects (Bergamaschi et al., 2011a). However, recent literature reviews report the need for more systematic evaluations of the side effects of CBD, especially with regards to interactions with other drugs (Brown, 2019; Iffland and Grotenhermen, 2017).

CBD has multiple pharmacological actions and acts on several neuroreceptors, such as CB_1, CB_2, transient receptor potential vanilloid 1 ($TRPV_1$) and 5-HT_{1A} (Campos et al., 2012). The 5-HT_{1A} receptor plays an essential role in the control of anxiety; the effects of CBD on anxiety may be related to its agonist action on this receptor (Campos and Guimarães, 2008; Gomes et al., 2011). In an animal model of PD, a decrease in the density of serotonergic neurons in the dorsal raphe nucleus and the expression of 5-HT_{1A} receptors were observed in the pre-limbic region of the ventromedial prefrontal cortex, which could be responsible for the increase in anxiogenic responses (Hui et al., 2015). Furthermore, administration of the 5-HT_{1A} receptor agonist 8-OH-DPAT in the ventromedial prefrontal cortex (Hui et al., 2015) and amygdala (Sun et al., 2015) showed anxiolytic action in PD rat models. It is interesting to note that Zuardi et al. (1993) used ipsapirone, a 5-HT_{1A} receptor partial agonist, which attenuated the anxiety symptoms induced by the SPST in healthy volunteers. This mechanism of action may be suggested considering the anxiolytic effects observed in our study.

The CB_1 neuroreceptor has also been implicated in emotional regulation, including anxiolytic effects. The activation of these receptors seems to diminish unconditioned fear and may also assist in the extinction of conditioned fear (Blessing et al., 2015; Ruehle et al., 2012). CBD inhibits fatty acid amide hydrolase (FAAH), which leads to an increase in anandamide, an endocannabinoid agonist of CB_1 receptors. This may explain the anxiolytic effects of CBD. Nevertheless, the agonists of the CB_1 receptor seem to have a biphasic effect, such that high doses may be ineffective or even anxiogenic (Blessing et al., 2015; Ruehle et al., 2012). In the present study, we used a dose of 300 mg based on a previous study involving patients with PD (Chagas et al., 2014).

We observed that CBD attenuated the anxiety induced by the SPST and also reduced the amplitude of tremors measured by the accelerometer, in particular at the dominant frequency (peak). A hypothesis is that increased anxiety is likely to increase the amplitude of tremors, considering that the presence of tremors can occur even in healthy individuals in anxiogenic situations. In addition, the individual's own negative evaluation of tremor presence and severity may reinforce anxiety symptoms, as observed in the social anxiety that is more prevalent in PD (Moriyama et al., 2016). Despite this positive finding regarding the amplitude of tremors, it should be pointed out that there were no differences in the variables measured by the acceleration sensor, particularly with regards to the frequency of tremors. In addition, the administration of CBD did not alter negative self-evaluations during the act of public speaking (measured using the SSPS-N). In contrast, Bergasmarchi et al. showed that the increase of the SSPS-N scores was almost abolished by CBD in a study involving volunteers with social anxiety disorder.

Despite this natural relation between motor signs and anxiety, it is possible to state a hypothesis regarding the direct action of CBD in areas related to motor signs. The 5-HT_{1A} receptor also plays a vital role in the regulation of motor signs and is present in several brain regions associated with motor control (Huot and Fox, 2013); tremor severity seems to be related to a reduction in this receptor (Doder et al., 2003). Therefore, it is possible that the action of CBD at the level of this receptor reduces tremor amplitude. These data may be supported by a study that showed that mirtazapine decreased parkinsonian tremors (Gordon et al., 2002). Mirtazapine is an antagonist of the alpha-2 adrenergic receptors that leads to an increase in serotoninergic neurotransmission and an indirect agonist effect on the 5-HT_{1A} receptor.

Furthermore, CB_1 receptors are present in the central nervous system in regions that are essential for motor coordination and are located predominantly in the presynaptic terminals (Svíženská et al., 2008). However, the expression of CB_1 receptors may be different throughout PD, with downregulation in the early stages of the disease and upregulation in the late stages (García-Arencibia et al., 2009). This observation is important because CBD could lead to different responses regarding motor signs. Besides, CBD has a broad spectrum of action, and its ability to antagonise the activity of CB_1 agonists and inhibit the FAAH enzyme, which leads to increased levels of the CB_1 agonist anandamide as previously reported, is fundamental to understanding its role in motor function (Peres et al., 2018). Thus, these aspects should be considered in future research on CBD and may partly explain the inconsistent findings found in the endocannabinoid system and motor signs of PD (Arjmand et al., 2015). In the present study, it was not possible to conclude whether CBD had a direct effect on the amplitude of the tremors or whether the reduction in anxiety levels led to the differences observed, as no significant differences were found in the drug–phase interaction. Future studies should evaluate motor signs without the SPST to gain a better understanding of this relation. Similarly, there were no statistically significant differences in drug–phase interaction in the VAMS anxiety factor, which points to a nonspecific anxiolytic effect, which may have been independent of SPST.

The present study has limitations that should be considered. The small sample size and the selection method impede the generalisation of the data. The time between the administration of CBD or the placebo and the onset of the SPST should have been longer, as T_{max} (time to the maximum measured plasma concentration) can be as much as four hours (Millar et al., 2018). Another limitation was the non-inclusion of an active drug (such as a benzodiazepine) and other doses of CBD for the purposes of comparison. Moreover, the anxiolytic effects observed cannot be generalised directly to any symptom of anxiety that may occur in daily living, since anxiety was induced experimentally in this study.

Despite these limitations, this is the first study that shows the anxiolytic effects of CBD in patients with PD and its ability in attenuation of the tremor amplitude in anxiogenic situations. Future double-blind controlled trials could assess the impact of chronic CBD administration on signs and symptoms of anxiety as well as anxiety disorders in patients with PD. It is also important to evaluate the effects of different doses of CBD in this population. Finally, the use of devices, such as acceleration sensors, could be useful to assess motor symptoms more reliably by avoiding motor fluctuations that may occur throughout the day.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: J.A.C., A.W.Z. and J.E.C.H. are co-inventors (Mechoulam R, Zuardi AW, Kapczinski F, Hallak JEC, Guimarães FS, Crippa JA, Breuer A) of the patent 'Fluorinated CBD compounds, compositions and uses thereof. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023', Def. US no. Reg. 62193296; 29/07/2015; INPI on 19/08/2015 (BR1120150164927). The University of São Paulo has licensed the patent to Phytecs Pharm (USP Resolution No. 15.1.130002.1.1). The University of São Paulo has an agreement with Prati-Donaduzzi (Toledo, Brazil) to 'develop a pharmaceutical product containing synthetic cannabidiol and prove its safety and therapeutic efficacy in the treatment of epilepsy, schizophrenia, Parkinson's disease, and anxiety disorders'. J.A.C. has received travel support from BSPG-Pharm and is a medical advisor of SCBD Centre. J.A.C. has a grant from University Global Partnership Network (UGPN)–Global priorities in cannabinoid research excellence. J.A.C., A.W.Z. and J.E.C.H. are recipient of CNPq productivity fellowships (1A), and M.A.P. is a recipient of CNPq productivity fellowships (level 2).

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