

# Safety and Tolerability of Cannabidiol in Parkinson Disease: An Open Label, Dose-Escalation Study

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## Abstract

**Background:** Cannabis is increasingly used in Parkinson disease (PD), despite little information regarding benefits and risks.

**Objectives:** To investigate the safety and tolerability of a range of doses of cannabidiol (CBD), a nonintoxicating component of cannabis, and its effect on common parkinsonian symptoms.

**Methods:** In this open-label study Coloradans with PD, substantial rest tremor, not using cannabis received plant-derived highly purified CBD (Epidiolex<sup>®</sup>; 100 mg/mL). CBD was titrated from 5 to 20–25 mg/kg/day and maintained for 10–15 days.

**Results:** Fifteen participants enrolled, two were screen failures. All 13 participants (10 male), mean (SD) age 68.15 (6.05), with 6.1 (4.0) years of PD, reported adverse events, including diarrhea (85%), somnolence (69%), fatigue (62%), weight gain (31%), dizziness (23%), abdominal pain (23%), and headache, weight loss, nausea, anorexia, and increased appetite (each 5%). Adverse events were mostly mild; none serious. Elevated liver enzymes, mostly a cholestatic pattern, occurred in five (38.5%) participants on 20–25 mg/kg/day, only one symptomatic. Three (23%) dropped out due to intolerance. Ten (eight male) that completed the study had improvement in total and motor Movement Disorder Society Unified Parkinson Disease Rating Scale scores of 7.70 (9.39, mean decrease 17.8%,  $p=0.012$ ) and 6.10 (6.64, mean decrease 24.7%,  $p=0.004$ ), respectively. Nighttime sleep and emotional/behavioral dyscontrol scores also improved significantly.

**Conclusions:** CBD, in the form of Epidiolex, may be efficacious in PD, but the relatively high dose used in this study was associated with liver enzyme elevations. Randomized controlled trials are needed to investigate various forms of cannabis in PD.

**Keywords:** cannabidiol; parkinsonism; Parkinson's disease; cannabis; adverse events

## Introduction

Parkinson disease (PD) is a common neurodegenerative disorder characterized by motor symptoms of resting tremor, bradykinesia, rigidity, and impaired balance that often has nonmotor symptoms of cognitive dysfunction, anxiety, and psychosis. Since standard treatments may only partially relieve symptoms many patients are turning to complementary and alternative

medications. In many states across the United States, cannabis use has been permitted medicinally and recreationally, so increasing numbers of PD patients are using formulations with a myriad of cannabinoid components. In an anonymous web-based survey, 47.8% of PD patients reported that cannabis reduced their use of prescription medication.<sup>1</sup> Since the major component of the cannabis plant,  $\Delta$ -9 tetrahydrocannabinol

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(THC), is known to sometimes cause psychosis,<sup>2–4</sup> cognitive dysfunction,<sup>4–6</sup> anxiety,<sup>7–9</sup> and balance impairment,<sup>10,11</sup> it may be especially harmful in PD. Conversely, cannabidiol (CBD), the next largest cannabinoid plant constituent, may have neuroprotective, anxiolytic, and antipsychotic effects,<sup>12</sup> as well as relatively good tolerability; thus, it may have benefits in PD. The purpose of this study is to begin investigating the effects of cannabis in PD by focusing on the safety of a range of doses of a purified CBD formulation, Epidiolex<sup>®</sup>. In addition, the effect of CBD on common PD symptoms was studied.

Review of the literature shows that CBD is well tolerated at doses up to 1500 mg/day,<sup>13–15</sup> or ~13 mg/kg/day, and most definitively has a central nervous system effect, for example, reduction of seizures, at 25 mg/kg/day.<sup>16</sup> However, the literature is sparse and inconclusive, and most studies used much lower doses, usually in combination with THC, and have shown a range of effects. A study in Huntington's disease using purified CBD at 10 mg/kg/day showed no effect.<sup>17</sup> Thus, we designed this study to evaluate doses ranging from 5 to 25 mg/kg/day.

The U.S. governmental policies at the time this study was conducted required that human interventional cannabis research uses a study drug that is obtained from the National Institute on Drug Abuse (NIDA) or another Drug Enforcement Administration (DEA)-registered source. NIDA did not have a cannabis product with the desired dose of CBD that also had low enough THC content. Thus a highly purified form of CBD with minimal THC content was used for this study that was obtained from a DEA approved source.

## Methods

### Study participants

The trial was conducted at the University of Colorado Movement Disorders Center, an academic, tertiary referral center. Participants were eligible if they were 45–78 years old; lived in Colorado; met U.K. PD Society Brain Bank Clinical Diagnostic Criteria for idiopathic PD; and had resting tremor with at least an amplitude of  $\geq 1$  cm, that is, score of  $\geq 2$  on item 3.17 of the Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS), in any limb while taking their usual PD medication, that is, while in the ON state. Participants had to agree not to operate a motor vehicle while taking the study drug, as required by the FDA. Key exclusion criteria included the following: cannabis detectable at the screening visit or THC

detectable at the baseline visit; history of drug or alcohol dependence; use of dopamine antagonists within 180 days; and currently taking specified medications that are known to increase the risk of hepatotoxicity.

Written informed consent was obtained from all participants. This study is registered with ClinicalTrials.gov, NCT02818777, and approved by the Colorado Multiple Institutional Review Board. Study progress and safety were monitored by its Colorado Clinical & Translational Sciences Institute Drug Safety and Monitoring Board.

### Study design and procedures

Participants in this open label, dose escalation study had a screening visit, a baseline visit within 3 weeks, a final assessment visit on their maximal dose, and a safety visit 2 weeks later. From the baseline visit, qualified study participants took a pharmaceutical formulation of highly purified CBD derived from *Cannabis sativa* L. plant in oral sesame oil solution (100 mg/mL, Epidiolex in the United States; GW Research Ltd., Cambridge, United Kingdom) with  $\leq 0.15\%$  THC twice daily. CBD was started at 5 mg/kg/day and was titrated by adjusting the dose every  $\geq 4$ th day, by up to 5 mg/kg/day, until the maximum targeted (20–25 mg/kg/day) or tolerated dose was achieved. Participants maintained their maximal dose, as tolerated, for 10–15 days, and then stopped it the next day. A registered nurse or nurse practitioner interviewed participants using a standardized phone script at each dose regarding study drug effects and at 3 days after stopping CBD to check for signs of withdrawal. At study visits, efficacy assessments were conducted when the participants' PD medications were in optimal effect, that is, when participants were in their ON state. To monitor study drug compliance, participants filled out home diaries and study drug bottles were weighed. Participants maintained the same PD medications throughout the study period.

Dopaminergic medications were converted into levodopa equivalents (LE), according to the accepted formula<sup>18</sup> (LE = immediate-release levodopa  $\times$  1 + controlled-release levodopa  $\times$  0.75 + pramipexole  $\times$  100 + ropinirole  $\times$  20 + rotigotine  $\times$  30 + selegiline  $\times$  10).

**CBD analysis.** Cannabinoid concentrations were measured in plasma samples collected during the screening visit, baseline visit (before the first dose was administered), at final assessment visit (3 h after the maximal

dose was administered), and at the safety follow-up visit. A previously validated high-performance liquid chromatography atmospheric pressure chemical ionization mass spectrometry-based assay determined cannabinoid levels.<sup>19</sup>

### Outcomes

The primary outcome was safety and tolerability of CBD and was measured in four ways: (1) the frequency and severity of adverse effects, using Common Terminology Criteria for Adverse Events terminology and grading, at each dose level; (2) vital signs, orthostatic blood pressures, physical examinations, electrocardiograms, and laboratory values (hematology, complete metabolic liver function tests, and urinalysis); (3) standardized assessment tools on relevant symptoms of PD; and (4) the proportion of participants that dropped out of the study due to study drug intolerance.

The prespecified major secondary outcome was the effect of CBD on severity and duration of tremor: the change from baseline to the maximal dose in the total of scores on items 3.17 and 3.18 in part III of the MDS-UPDRS in the ON state if the participant was taking anti-PD medication. Item 3.17 measures rest tremor amplitude, ranging from 0 (no tremor) to 4 (> 10 cm in maximal amplitude) for each extremity and ranging from 0 (no tremor) to 4 (> 3 cm in maximal amplitude) for lips/jaw. Item 3.18 measures constancy of rest tremor, ranging from 0 (no tremor) to 4 (present > 75% of the examination). Other secondary outcomes were other motor signs and the common nonmotor symptoms of PD. The other motor signs were evaluated with the MDS-UPDRS parts II, III, and IV, as well as the Unified Dyskinesia Rating Scale (UDysRS). The effect of CBD on common nonmotor symptoms was measured using the following tools: MDS-UPDRS part I, Montreal Cognitive Assessment (MoCA), parts of Quality of Life in Neurological Disorders (NeuroL-QOL) short forms for anxiety, depression, and emotional and behavioral dyscontrol, the Neuropsychiatric Inventory Questionnaire (NPI, © JL Cummings, 1994), Scales for Outcomes in PD-Sleep Scale (SCOPA-Sleep),<sup>20</sup> Fatigue Severity Scale (FSS, © Lauren B. Knupps), the Patient Reported Outcome Measurement Information System (PROMIS) pain intensity and pain interference short forms, Impulsive-Compulsive disorders in Parkinson's disease Rating Scale (QUIP-RS), the Columbia-Suicide Severity Rating Scale (C-SSRS),<sup>21</sup> International Restless

Legs Syndrome Study Group Rating Scale (IRLS),<sup>22</sup> and REM (rapid eye movement) sleep behavior disorder screening questionnaire (RBDSQ).<sup>23</sup>

### Statistical analysis

Proportions presented for each adverse event type are the number of patients with any instance of the event divided by the total number of patients. Mean severity and standard deviation were calculated by averaging all the severity scores for each adverse event type across all the occurrences of the event within each patient and then taking the mean and standard deviation of the patient means, weighted by number of events. The same procedure was performed on any event type and by dose for any event type and several of the most common adverse event types. Generalized estimating equations (GEE) logistic regression models and Cochran-Mantel-Haenszel statistics were used to investigate the effect of dosage on the odds of adverse events.

Pre-Post changes in the motor and nonmotor scores were analyzed by performing permutation paired *t*-tests, with a univariate alpha = 0.05 considered statistically significant. The Benjamini-Hochberg procedure was considered to control the false discovery rate (FDR) at alpha = 0.05.

### Findings

#### Participant characteristics

Between October 17, 2016 and June 19, 2017, 15 participants were enrolled, one was a screen failure due to electrocardiogram changes, one withdrew consent before starting treatment, thus 13 started study drug. Safety data are presented on these 13 participants. Three dropped out due to treatment related adverse events, thus 10 completed the study. Efficacy data are presented on these 10 participants. Note that these 10 participants are also in the Safety Group. Baseline characteristics of the 13 participants that took at least 1 dose of study drug, the Safety Group, and of the 10 participants, the Efficacy Group, that finished the study are described in Table 1.

#### Safety and tolerability

Due to adverse events experienced by the first five enrolled participants, the maximal targeted dose was reduced from 25 to 20 mg/kg/day. The mean maximum CBD dose was 19.4 (SD 5.2) mg/kg/day, that is, 1623.0 mg/day (range 552.5–3458.8 mg/day) in the safety analysis group and 20.3 (3.4) mg/kg/day in the efficacy analysis group, that is, 1731.4 mg/day (range 1014.0–3458.8 mg/day). The mean maximum volume of sesame oil taken per participant per day was 16 mL (range 5.5–34.5 mL) in the safety analysis group. The average length

**Table 1. Characteristics of the Participants at Baseline**

	Safety analysis group (n = 13)	Efficacy analysis group <sup>a</sup> (n = 10)
Age, years, mean (SD)	68.1 (6.05)	68.7 (6.65)
Male, n (%)	10 (77)	8 (80)
Total MDS-UPDRS score, mean (SD)	39.2 (13.3)	43.2 (12.2)
Motor MDS-UPDRS score, mean (SD)	22.9 (9.3)	24.7 (8.9)
Disease duration, years, mean (SD)	6.1 (4.0)	6.3 (4.5)
H&Y, mean (SD)	1.73 (0.56)	1.75 (0.59)
MoCA, mean (SD)	28.2 (1.6)	27.9 (1.6)
Levodopa daily dose equivalent, <sup>b</sup> mean (SD)	398.3 (331.0)	443.8 (349.0)

<sup>a</sup>The 10 participants in the Efficacy Analysis Group are a subgroup of the 13 in the Safety Analysis Group. These are the 10 participants that completed the study.

<sup>b</sup>Levodopa Daily Dose Equivalent (LE) = immediate release levodopa × 1 + controlled release levodopa × 0.75 + Pramipexole × 100 + Ropinirole × 20 + Rotigotine × 30 + Selegiline × 10.

H&Y, Hoehn and Yahr scale; MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale; MoCA, Montreal Cognitive Assessment.

of time on study drug was 26.8 (8.0) days in safety group and 28.5 (3.4) days in efficacy group.

Adverse events, shown in Table 2, reported in all participants, were transient and mild ( $1.17 \pm 0.49$ ) on average. The adverse events reported at each dose are shown in Figure 1. There were no serious adverse events and no withdrawal symptoms. The percentage of participants reporting diarrhea directly correlated with dosage, as shown in Figure 1. A GEE logistic regression model found that each 5 mg increase in the dosage increased the odds of diarrhea by an estimated factor of 2.32 (95% CI: 1.46–3.69,  $p=0.01$ ).

There were no clinically significant adverse changes in other outcome safety assessments, except for in-

**Table 2. Adverse Effects Reported in Safety Group Analysis (n = 13)**

Adverse effects <sup>a</sup>	Frequency, n (%)	Severity, mean (SD)
Any	13 (100)	1.17 (0.49)
Diarrhea	11 (84.6)	1.24 (0.68)
Somnolence	9 (69.2)	1.10 (0.31)
Fatigue	8 (61.5)	1.17 (0.22)
Weight gain	4 (30.8)	1.17 (0.33)
Abdominal pain	3 (23.1)	1 (0)
Dizziness	3 (23.1)	1 (0)
Weight loss, nausea, anorexia, increased appetite, headache <sup>b</sup>	2 (15.4)	N = 6 (46.2%) 1.29 (0.37)
Vomiting, flatulence, gastroesophageal reflux disease, allergic reaction, spasm, fever, weakness <sup>b</sup>	1 (7.7)	N = 6 (46.2%) 1.13 (0.27)

<sup>a</sup>Adverse effects terminology and severity is as per the Common Terminology Criteria for Adverse Events. Regarding severity, 1 = mild, 2 = moderate, 3 = severe.

<sup>b</sup>Individually each of the miscellaneous conditions occurs in only one or two patients, but when pooled for calculating the severity, 6 patients experience at least one.

creases in liver enzymes, especially alkaline phosphatase. Liver enzymes were measured at baseline and not again until the final assessment visit when participants were on their highest tolerated or the targeted dose. Elevations, shown in Table 3, occurred in five (38.5%) participants, one symptomatic and four asymptomatic, all on 20–25 mg/kg/day. The symptomatic participant, ID 02, developed moderate anorexia, diarrhea, somnolence, mild abdominal pain, dizziness, fatigue, fever, headache, and weight loss; had a cholestatic pattern of liver enzyme changes; and his liver ultrasound was normal. All symptoms and laboratory changes resolved after discontinuation of study drug.

Three participants (23%) stopped study drug due to intolerability, one due to rash at 5 mg/kg/day, one to abdominal pain and gas at 17.5 mg/kg/day, and one, described above, to fatigue, diarrhea, and elevated liver enzymes, that is, hepatitis, at 25 mg/kg/day.

### Efficacy

The mean decreases in the total and motor MDS-UPDRS scores at the maximal dose compared with baseline were a 17.8% ( $p=0.012$ ) and 24.7% ( $p=0.004$ ) improvement, respectively. Two nonmotor assessments also showed significant improvement, the SCOPA-Sleep nighttime and the emotional and behavioral dyscontrol short form. At 2 weeks follow-up, the total MDS-UPDRS and nighttime sleep assessments remained improved; the other two assessments did not. Enrolled subjects had minimal levodopa induced dyskinesia, cognitive dysfunction, restless leg syndrome symptoms, REM sleep behavior disorder, and impulsivity at baseline, and these assessments did not change on study drug. Table 4 shows the data for all assessments.

Applying the Benjamini–Hochberg procedure to control the FDR at  $\alpha=0.05$  found none of the tests to be statistically significant. The small sample size severely limits power for multiple testing adjustment.

### CBD plasma levels

Three hours after the final dose was administered, the participant on 12.5 mg/kg/day had a CBD plasma level of 181 ng/mL, while those on 20 mg/kg/day,  $n=7$ , showed plasma levels of  $376 \pm 78$  ng/mL (mean  $\pm$  SEM) and those on 25 mg/kg/day,  $n=2$ , showed plasma levels of  $340 \pm 4$  ng/mL. Fourteen days after discontinuation of CBD, the values were 13,  $24 \pm 5$ , and  $39 \pm 14$  ng/mL for the 12.5, 20, and 25 mg/kg/day treatment groups, respectively.

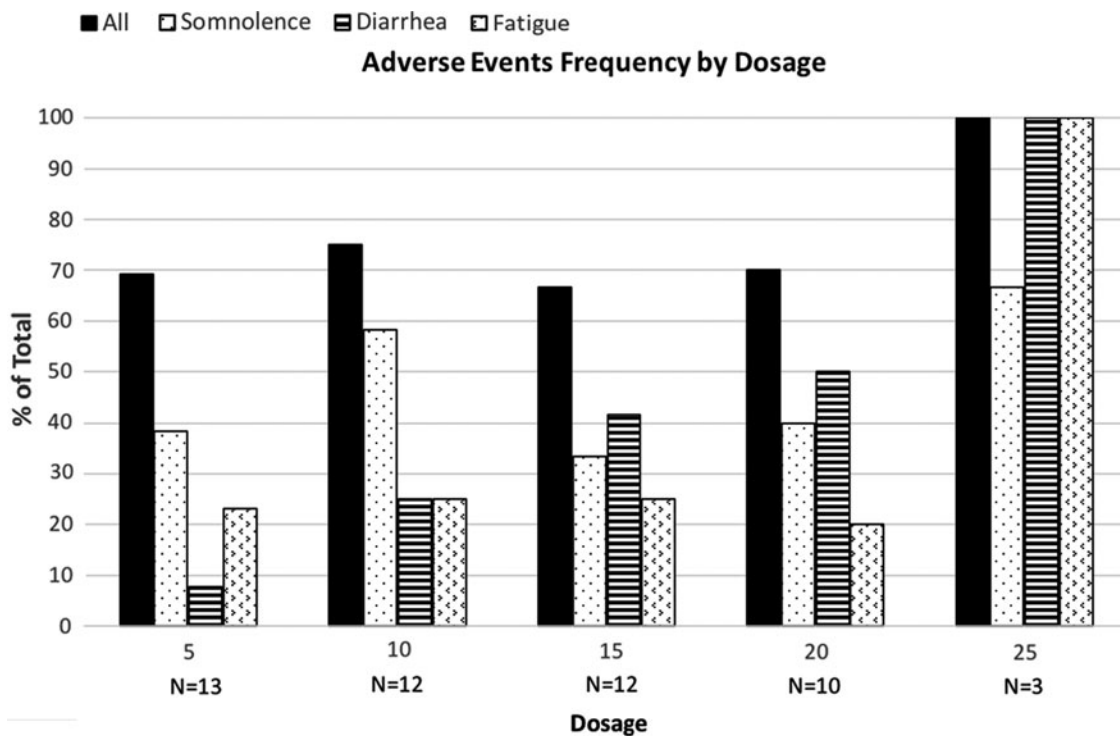


FIG. 1. Adverse event frequency by dosage.

## Discussion

This is the first study of the effects of relatively high dose, ~20 mg/kg/day, purified CBD in humans with PD. The purpose of the study was to determine tolerability of a range of doses in the PD population and explore efficacy. The study found that relatively high dose CBD, ~1600 mg/day, with <0.15% THC, that is, Epidiolex, taken orally, is associated with mild adverse effects, especially somnolence, fatigue, and diarrhea, and perhaps hepatotoxicity in persons with PD. In this dose ranging study somnolence occurred early in dose titration, but improved, diarrhea was common and increased with higher doses, and the 25 mg/kg/day dose was poorly tolerated. These adverse effects were similar to those reported in prior studies in pediatric epilepsy at this dose.<sup>16,24</sup> However, they were more frequent in our population, perhaps due to different characteristics of the PD population or the smaller sample size in the present study. The only dose-related adverse event was diarrhea, which could be related to sesame oil. In three controlled trials conducted by GW Pharmaceuticals, manufacturer of Epidiolex, diarrhea was reported in 9% of participants on placebo, 9% on 10 mg/kg/day,

and 20% on 20 mg/kg/day.<sup>a</sup> This suggests that the diarrhea is related to the CBD rather than sesame oil.

In this study five participants (38%) had transient elevated liver enzymes, one symptomatic and four asymptomatic, resolving after discontinuation of the study drug. In this study, the pattern of enzyme changes, particularly in the symptomatic patient, was consistent with a cholestatic rather than hepatocellular process. The drug may have caused idiopathic or bland cholestasis and, much less likely, granulomatous hepatitis or vanishing bile duct syndrome, since all liver tests normalized. Liver biopsy was not performed. None of these participants had significant elevated bilirubin or internalized normalized ratio, suggesting no change in liver function.

While liver enzyme elevations in a hepatocellular pattern have been reported with Epidiolex<sup>16</sup> on doses similar to those taken by the present study participants, the cholestatic pattern has not. Single or multiple factors, such as older age, having PD, concomitant medications, and relatively high CBD dosage, may

<sup>a</sup>Epidiolex [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc; 2020. Available at: [https://www.epidiolex.com/sites/default/files/EPIDIOLEX\\_Full\\_Prescribing\\_Information.pdf](https://www.epidiolex.com/sites/default/files/EPIDIOLEX_Full_Prescribing_Information.pdf)\_ga=2.42410341.1764361511.1577819316-2124301189.1577819316

**Table 3. Liver Function Test, Final Dose, and Medications**

ID	Age	Sex	ALT (normal 7-52 U/L) BL, final, SF	AST (normal 12-39 U/L) BL, final, SF	GGT (normal 9-64 U/L) BL, final, SF	ALP (normal 39-117 U/L) BL, final, SF, FU	T. Bilirubin (normal 0.1-1.3 mg/dL) BL, final, SF	Final dose, mg/kg/day	Medications known to cause ANY hepatotoxicity <sup>a</sup>	Other medications
02 <sup>b</sup>	70	M	11, 150, 49	16, 58, 23	9, 206, 116	99, 503, 247, 103	0.9, 1.4, 1.0	25	Aspirin, celecoxib, rasagiline	None
06 <sup>b</sup>	71	M	36, 64, 34	27, 46, 25	49, 101, 75	54, 81, 60	1.3, 1.8, 1.2	25	Acetaminophen, fish oil, lisinopril, rasagiline, <b>sildenafil</b> , vitamin B6	Biofreeze, glucosamine chondroitin, loperamide, magnesium, potassium citrate, vitamin B12, vitamin D3
08 <sup>b</sup>	70	M	12, 41, 9	17, 80, 29	29, 229, 229	12, 317, 182, 94	0.7, 0.9, 0.4	20	Acetaminophen, aspirin, <b>atorvastatin</b> , doxazosin, esomeprazole, meloxicam	Carbidopa/levodopa, finasteride
09 <sup>b</sup>	68	M	13, 29, 11	19, 22, 16	46, 129, 68	108, 137, 107	0.7, 0.7, 0.4	20	Aspirin, ibuprofen, lisinopril, methylphenidate, ropinirole, selegiline, trazodone	Melatonin, vitamin D3
10 <sup>b</sup>	68	M	16, 20, 12	15, 30, 18	20, 162, 62	75, 134, 84	0.6, 0.6, 0.6	20	Amantadine, aspirin, <b>atorvastatin</b> , citalopram, ibuprofen, omeprazole, Ropinirole	Carbidopa/levodopa, coQ10, folic acid, melatonin, vitamin C
01	68	F	4, 8, N/A	17, 20, N/A	N/A, 13, N/A	62, 53, N/A	0.4, 0.4, N/A	17.5	Escitalopram, fish oil, gabapentin, lansoprazole, lorazepam, ropinirole, prasterone	Carbidopa/levodopa, CoQ10, garlic, magnesium, melatonin, MiraLAX <sup>®</sup> , nystatin, senna, turmeric, vitamin B complex, vitamin D2
03	75	M	13, 14, N/A	15, 19, N/A	17, 16, N/A	33, 31, N/A	0.8, 1, N/A	25	Amlodipine, aspirin, hydrochlorothiazide, metoprolol, telmisartan	Docusate, calcium, etanercept, magnesium, vitamin B12
04	74	M	3, 8, N/A	17, 25, N/A	20, 24, N/A	38, 38, N/A	0.4, 0.5, N/A	25	Diclofenac, hydrochlorothiazide, docusahexaenoic acid, propranolol, selegiline	Carbidopa/levodopa, coQ 10, Heart Burn Relief <sup>®</sup> , multivitamin, stool softener.
05	62	M	25, 25, N/A	21, 29, N/A	54, 51, N/A	53, 49, N/A	1, 0.8, N/A	5	Fish oil, ibuprofen (Advil <sup>®</sup> ), meloxicam, olmesartan, rasagiline	Albuterol, coQ10, fluticasone, melatonin.
07	74	M	3, 4, N/A	19, 17, N/A	13, 11, N/A	54, 49, N/A	0.5, 0.7, N/A	20	Aspirin, clonazepam, entacapone, loratadine, omeprazole, <b>simvastatin</b> , tramadol	Carbidopa/levodopa, Centrum <sup>®</sup> , ocuvite, omega 3, pramipexole, vitamin D3
11	58	F	20, 26, N/A	18, 18, N/A	15, 20, N/A	57, 63, N/A	0.5, 0.4, N/A	20	Estradiol, lisinopril, prasterone, progesterone, rasagiline	CoQ10, magnesium, melatonin, pramipexole
13	73	M	25, 37, N/A	26, 42, N/A	24, 56, N/A	52, 64, N/A	0.7, 0.7, N/A	12.5	Acetaminophen, gabapentin, ibuprofen, niacin/chromium	Carbidopa/levodopa, coQ10, ferrous sulfate
14	56	F	4, 6, N/A	19, 20, N/A	11, 14, N/A	80, 84, N/A	0.4, 0.4, N/A	20	Conjugated estrogens, naproxen, nortriptyline, sumatriptan	Bone Nutrient <sup>®</sup> , carbidopa/levodopa, cellular vitality, diphenhydramine, essential oil, Food Nutrient <sup>®</sup>

<sup>a</sup>Hepatotoxicity is generally rare, unless the medication is in bold.

<sup>b</sup>02 had symptomatic hepatitis. 06, 08, 09, and 10 had asymptomatic liver enzyme changes.

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BL, baseline visit; final, final visit; FU, follow-up visit; participants had ALP checked until it was in the normal range; GGT, gamma-glutamyl transferase; M, male; mg/dL, milligrams per deciliter; SF, safety follow-up visit 2 weeks after final visit; T. Bilirubin, total bilirubin; U/L, units per liter.

**Table 4. Change in Motor and Nonmotor Scores Among Efficacy Analysis Group (n = 10)**

	Baseline, mean (SD)	Final, mean (SD)	Change from baseline to final, mean (SD)	<i>p</i> <sup>a</sup>	Follow-up, mean (SD)	Change from baseline to follow-up, mean (SD)	<i>p</i> <sup>a</sup>
Rest Tremor <sup>b</sup>	3.10 (2.23)	2.70 (2.31)	-0.40 (1.26)	0.471	4.20 (2.10)	1.10 (2.56)	0.109
Total MDS-UPDRS	43.20 (12.21)	35.50 (14.31)	-7.70 (9.39)	0.012 <sup>a</sup>	35.70 (14.97)	-7.50 (6.74)	0.008 <sup>a</sup>
Motor MDS-UPDRS	24.70 (8.93)	18.60 (9.66)	-6.10 (6.64)	0.004 <sup>a</sup>	27.40 (10.51)	2.70 (4.74)	0.188
H&Y	1.75 (0.59)	1.80 (0.89)	0.05 (0.76)	1.000	1.95 (0.685)	N/A	N/A
SCOPA-Sleep NS	5.70 (2.95)	2.90 (2.60)	-2.80 (3.91)	0.040 <sup>a</sup>	3.30 (2.36)	-2.40 (3.66)	0.023 <sup>a</sup>
SCOPA-Sleep DS	2.60 (2.27)	2.20 (1.69)	-0.40 (1.65)	0.575	2.10 (2.42)	-0.50 (1.84)	0.453
Emotional and behavioral dyscontrol SF	44.39 (7.91)	39.70 (6.75)	-4.69 (6.14)	0.047 <sup>a</sup>	40.17 (7.08)	-4.22 (7.24)	0.125
NPI	0.78 (1.20)	0.75 (1.39)	-0.13 (1.55)	1.000	N/A	N/A	N/A
Anxiety SF	46.24 (6.35)	46.57 (7.27)	0.33 (3.57)	0.783	45.99 (7.05)	-0.25 (4.11)	0.945
Depression SF	43.09 (6.03)	42.24 (7.04)	-0.85 (3.13)	0.440	41.1 (5.85)	-1.99 (4.55)	0.500
Fatigue Severity Scale	28.50 (15.54)	28.00 (14.49)	-0.50 (11.46)	0.907	27.4 (14.91)	-1.10 (9.85)	0.648
Pain interference SF	52.25 (8.63)	49.93 (8.99)	-2.320 (6.008)	0.253	49.94 (9.16)	-2.31 (6.99)	0.438
Pain intensity SF	44.64 (7.36)	42.78 (9.20)	-1.860 (4.711)	0.311	42.96 (9.78)	-1.68 (5.20)	0.469

<sup>a</sup>Paired *t*-test, permutation distribution; *p*-values of less than 0.05 were considered to indicate statistical significance.

<sup>b</sup>Rest tremor score was the prespecified major secondary outcome: total of the severity (MDS-UPDRS item 3.17) and duration (MDS-UPDRS item 3.18) of rest tremor.

NPI, Neuropsychiatric Inventory Questionnaire; SCOPA-Sleep DS, Scales for Outcomes in Parkinson's Disease-Sleep, Daytime Sleep; SCOPA-Sleep NS, Scales for Outcomes in Parkinson's Disease-Sleep, Nighttime Sleep; SD, standard deviation; SF, Short Form.

contribute to this. To date Epidiolex has been used primarily in pediatric populations. Perhaps older age and/or pathologic mechanisms that underlie PD, for example, mitochondrial dysfunction, are relevant factors. Regarding concomitant medications, most of the participants in prior epilepsy studies on Epidiolex were also on valproate; and while none in this PD study was, they were taking concomitant medications with potential hepatotoxicity, as shown in Table 3. Generally medications specific for PD have little potential for hepatotoxicity, with the exception of tolcapone, which none of the study participants was taking. There was no apparent difference in the overall hepatotoxic potential of concomitant medications being taken by those that did and did not develop liver enzyme changes. Table 3 also shows the final CBD dose of participants, and again there was no apparent difference between those that did and did not have liver enzyme changes. Thus, it is unlikely that the liver enzyme elevations were solely due to hepatotoxicity of concomitant medications or CBD dose. Regarding dose, in this study liver enzymes were tested at the final, that is, highest dose, and not at lower doses, so the dose at which liver enzymes started to change is unknown. Perhaps persons with PD would have better tolerability of lower doses. Taken in whole, it is likely that multiple factors contributed to the liver enzyme changes that occurred in this study, with older age and relatively high CBD dosage being particularly relevant.

This was an open label study so no conclusions can be drawn regarding efficacy. However, assessments were done to check for hints of efficacy to inform future

studies. The results suggest that CBD has a beneficial effect on total and motor MDS-UPDRS scores, nighttime sleep, and emotional and behavioral dyscontrol. Interestingly, the *p*-values on these assessments were still significantly or close to significantly improved 2 weeks after stopping CBD, compared to baseline. It is possible that CBD was still having some effect, since participants still had low plasma levels at that time.

A review of the literature of clinical studies of cannabinoids in PD shows that four randomized, blinded controlled studies have been reported, one Class 1<sup>25</sup> (according to the American Academy of Neurology Classification of Evidence for Rating of a Therapeutic Article, © 2014 American Academy of Neurology, AAN.com/guidelines), one Class 2,<sup>26</sup> and two Class 3.<sup>27,28</sup> Other studies were open label,<sup>29-31</sup> case reports,<sup>32,33</sup> or surveys.<sup>34-36</sup> These other studies mostly evaluated cannabis; one included CBD,<sup>25</sup> and three studied 99% pure CBD.<sup>26,29,32</sup>

The presented study is the first study of the effects of relatively high dose, ~20 mg/kg/day, purified CBD in humans with PD. There were three prior studies of purified oral CBD, with reports of effects of lower doses. A double-blind study in 21 participants using ~4.5 mg/kg/day found no change in UPDRS and other outcomes, except improved scores on the PD Questionnaire-39, which assessed functioning and well-being.<sup>26</sup> An open label study in six patients found an improvement in total UPDRS scores and psychotic symptoms on ~5 mg/kg/day of pure oral CBD.<sup>29</sup> The third study was open label and reported that four participants taking ~1-4 mg/kg/day had improvement in REM sleep behavior disorder, that is, reduction in

acting out dreams.<sup>32</sup> These three studies reported no adverse events. Other studies in PD examined the use of cannabis: two measuring the acute effects of smoked cannabis, total  $n=42$ , reported significantly improved motor UPDRS scores and reduced pain,<sup>30,31</sup> another administered a medium dose of oral THC (0.25 mg/kg/day) and very low dose of CBD (0.125 mg/kg/day),  $n=17$ , and showed no significant change on all measured outcomes.<sup>25</sup> Adverse effects of cannabis included somnolence, dizziness, decreased concentration, palpitations, and altered taste. Accumulating literature suggests that CBD may reduce psychosis,<sup>29,37</sup> which is a frequent debilitating symptom in PD.

Most previous pre-clinical studies using animal models of PD have focused on cannabinoid receptor 1 (CB1) agonists and antagonists, rather than pure CBD. The studies show evidence of therapeutic effects, improving motor symptoms, and levodopa induced involuntary movements, that is, dyskinesia. However, these effects were found with both CB1 agonists and antagonists. Furthermore, there is a dose dependent effect: low doses of CB1 antagonists have been reported to improve motor function and dyskinesia more consistently than CB1 agonists, while high doses of both CB1 agonists and antagonists have no effects or impair motor function.<sup>38–47</sup> Regarding CBD, a study using the 6-hydroxydopamine rat model of PD found that CBD, and also THC, attenuated neurodegeneration from the toxin, perhaps through antioxidant or anti-inflammatory mechanisms.<sup>48</sup> Another study with the same toxin inducing PD, but in mice, studied pain thresholds and suggested that CBD modulated analgesic effects by increasing anandamide, a major endocannabinoid, levels and acting on CB1 and the transient receptor potential vanilloid receptor 1 (TRPV1) and that lower doses are more effective than intermediate doses.<sup>49</sup> Evidence from pre-clinical studies to date suggests that there is more to learn about the effects of different types of cannabinoids on the motor signs of PD.<sup>38–47,50–54</sup>

How CBD influences PD is unclear, as its effect in humans is complex. CBD has low affinity for the endogenous cannabinoid receptors, but it can upregulate the levels of anandamide, by inactivation of fatty acid amide hydrolase, which metabolizes anandamide. Equally important, CBD interacts with many noncannabinoid signaling systems, and these functions may vary depending on its concentration.<sup>55</sup> Activation of the serotonin 5-HT<sub>1A</sub> receptor may underlie improvement of motor signs.<sup>56</sup> Other theories involve actions at G-protein coupled receptor 55,<sup>57,58</sup> TRPV1,<sup>59,60</sup> and

GRP6 receptors. For example, the G-coupled protein receptor GPR6 is highly expressed in the basal ganglia. Depletion of GPR6 causes an increase of dopamine. By acting as an inverse agonist at the GPR6 receptor, CBD boosts dopamine levels in pre-clinical studies.<sup>61</sup> A neuroprotective effect has been proposed due to studies showing anti-oxidant activity, for example, upregulating superoxide dismutase mRNA levels in the substantia nigra,<sup>62–65</sup> and through anti-inflammatory activity, for example, activating peroxisome proliferator-activated receptor gamma.<sup>62,66–69</sup>

The plasma concentrations of CBD in our participants were consistent with prior pharmacokinetic studies of Epidiolex. Taylor et al.<sup>70</sup> showed in a multiple ascending dose study of Epidiolex at 750 mg and 1500 mg twice daily (21.4 and 42.8 mg/kg/day for a 70 kg person) a  $t_{max}$  of ~3–5 h after administration, depending on fasting versus nonfasting state. The  $C_{max}$  was also dependent on the fasting state: 335 ng/mL when subjects were fasting versus 1628 ng/mL when subjects received a high-fat breakfast. In our study CBD plasma peak concentrations 3 h after the last administration of study drug of the treatment period (10–15 days) were  $376 \pm 78$  ng/mL (mean  $\pm$  SEM) for the 20 mg/kg/day ( $n=7$ ). This is consistent with the Epidiolex PK study<sup>70</sup> where 290 ng/mL (in the morning, fasting) and 732 ng/mL (in the afternoon, not fasting) were reported in the 750 mg (~21 mg/kg/day) twice daily group. However, relatively high interindividual variabilities were observed in our study, likely because we did not control for food intake.

This study has some limitations. First, conclusions about adverse effects, but especially efficacy, are limited by the absence of a placebo arm. Also rater bias can occur in an open label design, both with regard to noting adverse effects, as well as rating scale assessments. Note, however, that the data that showed improved sleep and emotional and behavior dyscontrol were collected from participant questionnaires, rather than a rater. Furthermore, the number of participants was small and those included had minimal dyskinesia, cognitive dysfunction, restless leg syndrome, REM sleep behavior disorder, and impulse control disorder. These important problems may be altered by CBD treatment, but they were not addressed in this study. Furthermore, efficacy did not achieve significance when adjusted for multiple testing.

There was not a significant change in the major secondary outcome, tremor. Tremor was chosen because of the author's clinical experience: persons with PD



in clinic frequently reported reduction in tremor with CBD, but rarely reported changes in other motor symptoms. Participants had to have a tremor amplitude in the ON state of at least 2 cm to be in the study, but tremor is variable from time to time and thus may be a less reliable motor symptom to measure. Quantifying tremor at home with a device may yield a more accurate measurement.

Further study of the effects of cannabinoids in PD is greatly needed, since presently these persons are trying products with various cannabinoid compositions despite little data regarding safety and efficacy. The usual dose of CBD in dispensary products is quite variable, for example, 2–200 mg/day, is much lower than that used in this study, and the CBD is often combined with clinically relevant doses of THC. Besides dosage, routes of administration might alter outcomes, for example, smoking or vaping would likely cause more immediate intense and shorter lasting effects. As increasing numbers of persons with PD visit cannabis dispensaries, they are presented with a wide range of choices. Randomized controlled studies are needed to confirm this study's findings and to investigate lower doses of CBD, CBD in combination with THC at varying compositions, and the effects of routes of administration.

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### Abbreviations Used

CB1 = cannabinoid receptor 1  
 CBD = cannabidiol  
 C-SSRS = Columbia-Suicide Severity Rating Scale  
 DEA = Drug Enforcement Administration  
 FDR = false discovery rate  
 FSS = Fatigue Severity Scale  
 H&Y = Hoehn and Yahr scale  
 IRLS = International Restless Legs Syndrome Study Group Rating Scale  
 LE = levodopa equivalents  
 MDS-UPDRS = Movement Disorder Society Unified Parkinson Disease Rating Scale  
 MoCA = Montreal Cognitive Assessment  
 Neurol-QOL = Quality of Life in Neurological Disorders  
 NIDA = National Institute on Drug Abuse  
 NPI = Neuropsychiatric Inventory Questionnaire  
 PD = Parkinson disease  
 PROMIS = Patient Reported Outcome Measurement Information System  
 QUIP-RS = Impulsive-Compulsive disorders in Parkinson's disease Rating Scale  
 RBDSQ = REM sleep behavior disorder screening questionnaire  
 REM = rapid eye movement  
 SCOPA-Sleep = Scales for Outcomes in PD-Sleep Scale  
 THC = Δ-9 tetrahydrocannabinol  
 TRPV1 = transient receptor potential vanilloid receptor 1  
 UDysRS = Unified Dyskinesia Rating Scale