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Review

Effects of Cannabis in Parkinson's Disease: A Systematic Review and Meta-Analysis

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Abstract. The legalization of cannabis in many countries has allowed many Parkinson's disease (PD) patients to turn to cannabis as a treatment. As such there is a growing interest from the PD community to be properly guided by evidence regarding potential treatment benefits of cannabis. This systematic review and meta-analysis aims to compile the best available evidence to help guide patients and their family, clinicians and researchers make informed decisions. A systematic search of the literature was conducted in June 2021. Five randomized controlled studies and eighteen non-randomized studies investigated cannabis treatment in PD patients. No compelling evidence was found to recommend the use of cannabis in PD patients. However, a potential benefit was identified with respect to alleviation of PD related tremor, anxiety, pain, improvement of sleep quality and quality of life. Given the relative paucity of well-designed randomized studies, there is an identified need for further investigation, particularly in these areas.

Keywords: Cannabis, Parkinson's disease, efficacy of cannabis, tremor, UPDRS

INTRODUCTION

Parkinson disease (PD) is the second most common neurodegenerative disorder with a prevalence of 1% in populations over 60 years of age [1, 2]. It is a multisystem illness impacting a wide range of motor and non-motor functions.

While the underlying pathophysiology of this illness is yet to be fully defined, some histopathological features are well described, most notably, degeneration of the dopamine producing neurons in the substantia nigra pars compacta [3]. Approximately

5–10% of PD cases demonstrate Mendelian inheritance. At least four genes have been shown to predispose to PD and these may also interact with environmental risk factors [4–6].

Human and laboratory studies have also demonstrated that oxidative stress and the inflammatory cascade have important roles in the pathogenesis of PD [7, 8]. The endocannabinoid system has been shown to have a neuroprotective function and in particular, antioxidant and anti-inflammatory actions [9]. There are more than 100 cannabinoids that have been identified from the cannabis plant. The two most researched cannabinoids are cannabidiol (CBD) [10] and tetrahydrocannabinol (THC) [11, 12]. CBD has gained interest as a PD treatment due to its anticonvulsant, anxiolytic, and analgesic effects. Similarly,

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49 THC has desirable analgesic, muscle relaxant, and
50 antiemetic properties but also has problematic psy-
51 chotropic effects [11, 12].

52 There has been growing interest in cannabis as a
53 potential therapeutic agent for PD through counter-
54 acting oxidative cell damage and neuro-inflammation
55 [13]. Additionally, it has been hypothesized that
56 the antioxidant properties of cannabis could slow
57 PD progression and improve PD symptoms [7, 8].
58 Tremor is one of the common motor symptoms in PD.
59 There are studies demonstrating cannabinoid recep-
60 tor activation ameliorating tremor in animal models
61 [14, 15]. Cannabinoid 1 (CB1) receptor activation
62 inhibits glutamate release and regulates subthalam-
63 onigral neuronal overactivity which in return reduces
64 tremor [16, 17]. Dyskinesia resulting from levodopa
65 and dopaminergic therapy is another common motor
66 symptom in people with mid to late-stage PD [18].
67 Preclinical studies have shown that activation of
68 CB1 receptors reduced dyskinesia in PD animal
69 models [19, 20]. Cannabinoids have been shown to
70 block dopamine transporters consequently reducing
71 dopamine reuptake and dyskinesia [21]. There are
72 also PD patient reports [22] and large survey results
73 [37, 52] to suggest that cannabinoids can alleviate
74 both motor and non-motor symptoms of PD.

75 The aim of this review was to interrogate the
76 published and unpublished literature for evidence of
77 treatment effects of cannabis in PD. We have focused
78 on the potential effects on PD severity and progres-
79 sion, as well as effects on motor and non-motor
80 symptoms.

81 METHODS

82 *Search strategy*

83 Searches for published and unpublished studies
84 of cannabis treatment in people with PD were con-
85 ducted on 14 June 2021. A three-step approach was
86 utilized in searching for studies. First, an initial
87 search of MEDLINE and EMBASE was under-
88 taken using the following MeSH® terms: Parkinson
89 disease, cannabis, marijuana, medical marijuana to
90 develop a search strategy (Supplementary Tables 1
91 and 2). Second, the same search strategy was applied
92 to CINAHL, PsycINFO, Web of science, Scopus,
93 Proquest Dissertations, and CENTRAL databases
94 using all identified keywords and index terms
95 from the initial search. Public trial registers such
96 as ClinicalTrials.gov and World Health Organiza-
97 tion International Clinical Trials Registry Platform

(ICTRP) were also searched for ongoing and unpub- 98
99 lished studies. Lastly, bibliographies of all identified
100 relevant articles were hand searched for additional
101 studies.

102 *Inclusion and exclusion criteria*

103 Randomized controlled trials and non-randomized
104 studies such as open label studies, before and after,
105 case reports, chart reviews, surveys that evaluated
106 therapeutic effects of cannabis or cannabis-based
107 treatment in patients with PD were considered.
108 Review papers were excluded but were assessed for
109 additional relevant articles. Cannabis or cannabis-
110 based treatment included any agent considered a
111 cannabinoid whether used alone or combined with
112 other cannabinoids or other agents, whether synthetic
113 or a direct cannabis extract. Two commonly used
114 cannabinoids are tetrahydrocannabinol (THC) and
115 cannabidiol (CBD) [10]. The reported impact of any
116 dose or treatment duration upon any motor and/or
117 non-motor symptom of PD was included. The pro-
118 tocol for this review was registered in PROSPERO
119 under ID: CRD42019124256.

120 Study outcomes of particular interest for this
121 review were the Unified Parkinson's Disease Rating
122 Scale [23] and Movement Disorder Society UPDRS
123 (MDS-UPDRS) which measure the severity and pro-
124 gression of PD [24]. The UPDRS was developed in
125 1987 and has four parts: I) mentation, behavior, and
126 mood, II) activities of daily living, III) motor exam-
127 ination, and IV) complications of therapy. Parts I,
128 II, and IV require a PD medical specialist to eval-
129 uate the patient for each question according to a
130 scale provided. Part III requires the specialist to per-
131 form a series of prescribed physical examinations and
132 record the results according to the scales provided.
133 Higher UPDRS scores relate to higher PD severity.
134 The UPDRS was used in many of the reviewed studies
135 to measure possible therapeutic effects of cannabis in
136 PD. A reduction of between 4.1 and 4.5 on the total
137 UPDRS is generally considered a minimal clinically
138 important improvement [25]. The MDS-UPDRS is a
139 revision of UPDRS completed in 2007. It has four
140 parts: I) non-motor experiences of daily living, II)
141 motor experiences of daily living, III) motor examina-
142 tion, and IV) motor complications [26]. A reduction
143 of at least 7.1 on the total MDS-UPDRS score is
144 considered a minimal clinically important improve-
145 ment [27]. Other study outcomes included in this
146 review were any questionnaires, scales, or assess-
147 ments of PD motor and non-motor symptoms such

as tremor, levodopa-induced dyskinesia (LID), anxiety, pain and quality of sleep. Lastly, quality of life and safety data were also collected.

No language, publication date, or status restrictions were imposed. Non-English articles were translated using google translate. If articles were found to report the same or similar data and from the same study, it was ensured that only one copy of the data was included. The article that had more data or a fuller description of the same data was nominated as the included article (e.g., if a journal article and conference abstract from the same study were ascertained, the former was included in this review). Two authors (BU and JC) independently screened and evaluated all articles. Any disagreements were resolved through a discussion with another author (MAO).

Data extraction and quality assessment

Quantitative data from included studies were extracted using a data extraction and assessment tool that was adapted from The Cochrane Public Health Group [28]. The extracted data included specific details on the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

We assessed the quality of all randomized studies using the criteria outlined in the Cochrane's risk of bias (RoB) tool for conducting a systematic review [29]. Biases assessed for each study were: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other (other sources of bias).

Statistical analysis

Where available, for randomized studies, treatment effects were measured as differences (treatment-control) in mean total UPDRS scores and meta-analyzed as weighted mean differences (WMD) utilizing a range of random effects models. The MDS-UPDRS was used in one RCT and is reported separately as it was determined that UPDRs and MDS-UPDRS scores could not be meaningfully combined.

Treatment effects reported in cross-over and parallel randomized studies were combined using the methods described in Curtain et al. 2002 [30] and Elbourne et al. 2002 [31]. Stata 15 (College Station,

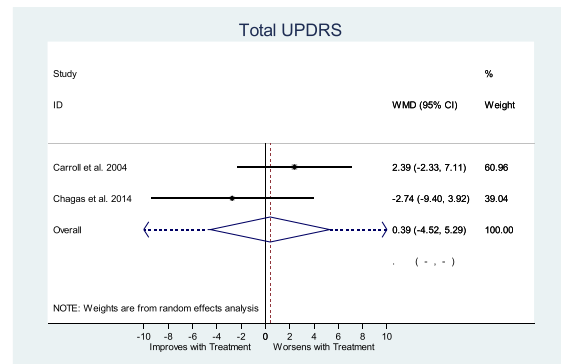


Fig. 1. Meta-analysis of Total UPDRS Score ($p=0.877$).

TX, US) packages metan, metaan and mvmeta were used to perform random effects meta-analyses. Data that could not be meta-analyzed due to heterogeneity in outcome measures and study designs have been presented in descriptive terms.

RESULTS

Search results and study selection

Electronic and hand searches returned 2,555 journal articles. After screening the titles and abstracts, 33 articles were found to be eligible for full-text screening. There were 26 randomized and non-randomized studies that met all inclusion and exclusion criteria.

Six included articles were randomized studies [32–37] and twenty were non-randomized studies (NRS) and case reports [34, 38–56]. Two were published as both journal articles and conference abstracts [47, 48] and four journal articles presented essentially similar (or the same) results [33, 34, 53, 54]. Duplicates were identified during data extraction and only the most complete dataset included. Therefore, a total of 23 unique studies (5 randomized and 18 non-randomized studies) were included in this review. Figure 1 presents the PRISMA Flow diagram of the search, screening and selection process of studies. The reasons for excluding each article during the full-text review are also presented.

Population characteristics

All studies (randomized and non-randomized) investigated the effects of cannabis in people diagnosed with PD.

Various cannabis formulations were investigated in the five randomized studies. Two studies [32, 37]

investigated the effect of cannabis treatment on LID in PD patients.

On the eighteen non-randomized studies (NRS), both prescribed and unprescribed cannabis treatments were investigated [39–41, 43, 44, 48–52, 54, 55]. Some studies investigated cannabis treatment in PD patients in relation to specific PD related disorders; namely, rapid eye movement [57] sleep behavior disorder [58], severe tremor [42], intractable tremor [46], and psychosis [56]. One study [45] explored dose escalation and safety of cannabidiol [10].

Cannabis intervention

The cannabis formulations used in the randomized studies were cannabis extract (~11.5 mg THC and 5.75 mg CBD) [32], pure CBD capsules [34, 35] and synthetic THC [36, 37].

Of the NRS, four investigated pure CBD with specified doses [45, 46, 56, 58] whilst the remainder assessed unspecified cannabinoid formulations and doses [38, 39, 41–44, 48–50, 52, 54, 55, 59].

Study outcome measures

Only three of the five randomized studies measured UPDRS or MDS-UPDRS as an outcome [32, 34, 36], whilst of the eighteen NRS, six studies reported some information of cannabis effects in terms of UPDRS or MDS-UPDRS [38, 45, 46, 48, 52, 56]. All NRS assessed outcomes related to PD symptoms such as LID, tremor, pain, improvement in sleep and quality of life. Some studies also provided safety data [38, 39, 43, 46, 48, 51, 56] which were included in this review. Detailed study characteristics are presented in Table 1.

Reported study quality

The overall quality of the five randomized studies was considered high due to low risk of bias. The Cochrane's risk of bias assessment revealed 88.57% and 11.43% measures of low and unclear risk of bias respectively for all randomized studies (Supplementary Figure 2). Reviewers' evaluation for risk of bias is available on Supplementary Tables 3 and 4.

One study did not provide detail regarding the treatment allocation process [37] and for three studies, it was unclear if independent blinded assessors were utilized [34–36]. The detailed risk of bias and reviewers' judgments across studies can be found in Supplementary Table 3.

The quality of non-randomized studies was considered as low due to a high for risk of bias. They were included in this review only in a narrative context and not used in meta-analysis.

Meta-analysis of total UPDRS score

Only two out of five randomized studies reported total UPDRS [32, 34]. Carroll et al. (2004) [32] provided their UPDRS raw data to us while for Chagas et al. (2014) [34], the UPDRS data were available in the article. Meta-analysis of these two studies using a random effects model is shown in Fig. 1. The overall estimate of the treatment effect was a marginal worsening of total UPDRS with a weighted mean difference of 0.39 (95% CI -4.52, 5.29; $p=0.877$).

Of the eighteen non-randomized studies (NRS), only three presented data on total UPDRS or MDS-UPDRS. One open label study using 150–400 mg/day of pure oral CBD reported an improved total UPDRS score [56] while two other open-label studies of ~1600 mg/day of pure oral CBD reported an improvement in total MDS-UPDRS scores [45, 46].

Meta-analysis of all UPDRS Parts were also undertaken. There was no evidence of an effect with regards to UPDRS Parts I, II, III, and IV (Fig. 2). Peball et al. (2020) [36] presented MDS-UPDRS Part I and reported significantly less deterioration in non-motor symptoms (MDS-UPDRS Part I) for THC treated patients compared to placebo [36], whilst MDS-UPDRS Parts II-IV did not show significant differences between groups.

The three randomized studies that presented UPDRS and MDS-UPDRS data [32, 34, 36] differ in their study design (cross-over vs. parallel RCT), cannabis products investigated (THC alone, CBD alone, THC: CBD), the cannabis dose used (~11.5 mg THC and 5.75 mg CBD, 75 or 300 mg CBD, or 0.75 mg THC), and study population (early-stage to mid-late stage PD).

No single study in this review investigated the long-term effects of cannabis including that on PD progression.

Effects of cannabis on tremor

One randomized study demonstrated a decrease of tremor amplitude after administering a single CBD 300 mg dose compared to placebo ($p=0.022$) [35].

Eleven out of the eighteen NRS that measured tremor reported an improvement following cannabis treatment [38–40, 43, 46, 48–51, 54].

Table 1
Characteristics of included studies

Article	Study Design	Intervention	Dose (per day)	Population	Sample Size	Duration of Treatment (Tx)	Frequency of Tx	Delivery of Tx	OUTCOMES										CONCLUSION
									Total UPDRS	Motor UPDRS	PDQ-39	Dyskinesia	Tremor	Rigidity	Sleep quality	Pain	Safety		
RANDOMIZED CONTROLLED STUDIES																			
Carroll et al. 2004 [32]	RDBC	Canador capsule (THC + CBD)	~11.5mg THC + ~5.75mg CBD	PD w/ LID	17	4wks per tx arm	OD	po	✗	✗	✗	✗			✗	✗	No significant safety issues described. Higher incidence of AEs with higher doses of Canador. Similar spectrum of AE for both canador and placebo.	Canador did not improve dyskinesia and quality of life of PD patients. Canador was well tolerated by PD patients. There was an improvement of MMSE in cannabis group, most likely due to practice effect.	
Chagas et al. 2014 [32]	RCT	CBD capsule	75mg or 300mg	PD	21	6 wks	OD	po	✗	✗	✓						No significant safety issues described.	CBD improved functioning and wellbeing of PD patients.	
de Faria et al. 2020 [35]	RDBC	CBD capsule	300mg	PD	23	Single dose per tx arm	Once	po					✓				No significant safety issues described.	CBD attenuated SPST-induced anxiety and tremors in PD patients.	
Peball et al. 2020 [36]	RCT	Nabilone capsule (THC)	0.75mg	PD	38	4 weeks	OD	po		✗						✗	No significant safety issues described. Similar spectrum of AE for both nabilone and placebo.	Nabilone improved non-motor symptoms of PD (UPDRS Part I) but not significant in reducing pain.	
Sieradzan et al. 2001 [37]	RDBC	Nabilone capsule (THC)	0.3mg/kg	PD w/ LID	9	12 hrs and 2 hrs before levodopa per tx arm	Two times (split doses)	po				✓					No significant safety issues described. Similar spectrum of AEs for both nabilone and placebo. Drop in sBP similar between groups. Most AEs are mild and transient.	Nabilone reduced total levodopa-induced dyskinesia but not the antiparkinsonian effects of levodopa in PD patients.	
NON-RANDOMIZED STUDIES																			

(Continued)

Table 1
(Continued)

Balash et al. 2011 [38]	XS (prospective survey)	Cannabis ¹	1-4 cannabis cigars	PD	6	1-12 wks	OD	smoking		✗				✗	✗	✓	✓	Smoking cannabis caused psychosis (50%)	Cannabis smoking as adjuvant treatment appears to improve sleep, relieve pain, but no motor improvement.
Balash et al. 2017 [39]	XS (retrospective survey)	Pres cannabis	0.9g (+/-0.5g)	PD taking pres cannabis	40	≥ 3 months	!	smoking						✓	✓	✓	✓	Cannabis caused cough mainly from smoking (34.9%), confusion (17%) and hallucination (17%)	Cannabis may lessen pain, tremor and rigidity, and may improve mood, and quality of sleep.
Chagas et al. 2014 [58]	CS	CBD	75mg-300mg	PD with RBD	4	6 wks	OD	po								✓			CBD may control symptoms of RBD in PD.
Feeney et al. 2021 [40]	XS	Cannabis ¹	nd	PD	261	nd	!	~						✓	✓	✓	✓		Cannabis may lessen pain, tremor, rigidity, anxiety and improve sleep.
Finseth et al. 2015 [41]	XS	Cannabis ¹	nd	PD	9	nd	nd									✓			Cannabis may improve mood, sleep, motor symptoms and quality of life in PD patients.
Frankel et al. 1990 [42]	CS	Cannabis ¹	1 g	PD with severe tremor	5	1 day	once	smoking						✗					Cannabis did not alleviate tremor and other parkinsonian symptoms.
Gurevich et al. 2015 [43]	XS	Pres cannabis	1.1 g (+/-0.9g)	PD	39	2 months	OD	smoking						✓	✓	✓	✓	Cannabis caused coughing due to smoking (23%), hallucinations (15%), restlessness (15%) and confusion (13%)	Cannabis may help to relieve pain, rigidity, tremor, and improve general condition, mood and quality of sleep.
Kindred et al. 2017 [44]	XS w/control	Cannabis ¹	nd	PD cannabis vs. non-cannabis users	454	nd	nd	varies											Cannabis may improve memory and mood in PD patients.
Leehey et al. 2017 [46]	OL	CBD	5-25 mg/kg	PD with intractable tremor	6	27 days	OD	po	✓					✓		✓	✓	Cannabis caused rash, abdominal pain and flatulence, fatigue, diarrhea and elevated liver enzymes. No serious AE. Higher incidence of AE with higher doses.	Cannabis may improve UPDRS, sleep, tremor, reduce pain and anxiety.
Leehey et al. 2020 [45]	OL	CBD	5-25 mg/kg/d	IPD	10	10-15 days	BD	po	✓	✓						✓		No significant safety issues except for increased liver enzymes	Cannabis significantly improved total and motor UPDRS scores, sleep, and attenuated emotional lability.

Table 1
(Continued)

Lotan et al. 2014 [48]	BA	Pres cannabis	0.5 g	PD with pres cannabis at least 2 months	22	Pre/post	OD	Smoking		✓		✓	✓	✓	✓	No significant safety issues described. Common AE were drowsiness and bad taste.	Cannabis significantly improved motor UPDRS, tremor, rigidity, bradykinesia and pain scores.
Mischley et al. 2017 [50]	XS	Pres cannabis	n.d.	PD with pres cannabis	10	14 days	nd	nd				✓					Cannabis may reduce tremor for PD patients.
Micheli et al. 2020 [49]	XS	Cannabis ¹	n.d.	PD	121	nd	nd					✓	✓	✓	✓	No significant safety issues described.	Cannabis may lessen pain, tremor, and rigidity, and improve sleep.
Myers et al. 2020 [51]	RCR	Pres cannabis	nd	PD	69	nd	nd	nd			✓	✓	✓	✓	✓	Common AEs were somnolence, fatigue, confusion, dizziness.	Cannabis may improve tremor, pain, rigidity, dyskinesia, sleep, mood, anxiety, gait instability, and nausea and vomiting.
Shohet et al. 2017 [52]	BA	Pres cannabis	1 g	PD with pres cannabis	20	Pre/post	OD	smoking ¹		✓					✓		Cannabis improved motor scores and alleviated pain symptoms in PD patients.
Venderova et al. 2004 [54]	XS	Cannabis ¹	nd	PD	85	n.d.	nd					✓	✓	✓			Cannabis alleviated rest tremor, bradykinesia, muscle rigidity, LID
Yenilmez et al. 2021 [55]	XS	Cannabis ¹	nd	PD	113	nd	nd	~				✓	✓	✓			Cannabis may alleviate pain, tremor, and rigidity
Zuardi et al. 2009 [56]	OL	CBD	150-400 mg	PD with psychosis for at least 3 months that cannot be controlled by PD meds	6	4 wks	OD	po	✓	✓						No observed AE during the experiment.	CBD may be effective, safe and well tolerated for the treatment of psychosis in PD. CBD did not improve cognitive and motor symptoms, however total UPDRS scores were significant.

AE, adverse event; BA, before and after study; BD, twice a day; CBD, cannabidiol; CS, case study; LID, levodopa-induced dyskinesia; MMSE, Mini-Mental State Examination; nd, no data; OD, once a day; OL, open label (non-randomized) study; PD, Parkinson's disease patients; po, oral; Pres, prescribed; RBD, REM sleep behavior disorder; RCR, retrospective chart review; RCT, randomized controlled trial; RDBC, randomized double blinded crossover; SPST, simulated public speaking test; Unpres, Unprescribed; XS, Cross-sectional study; ~, varied methods/delivery/route but mostly smoking; 1, varied cannabinoid contents, doses & dosing frequencies; ✓, statistically significant improvement for RCTs or reports of improvement for NRS; ✗, not statistically significant improvement

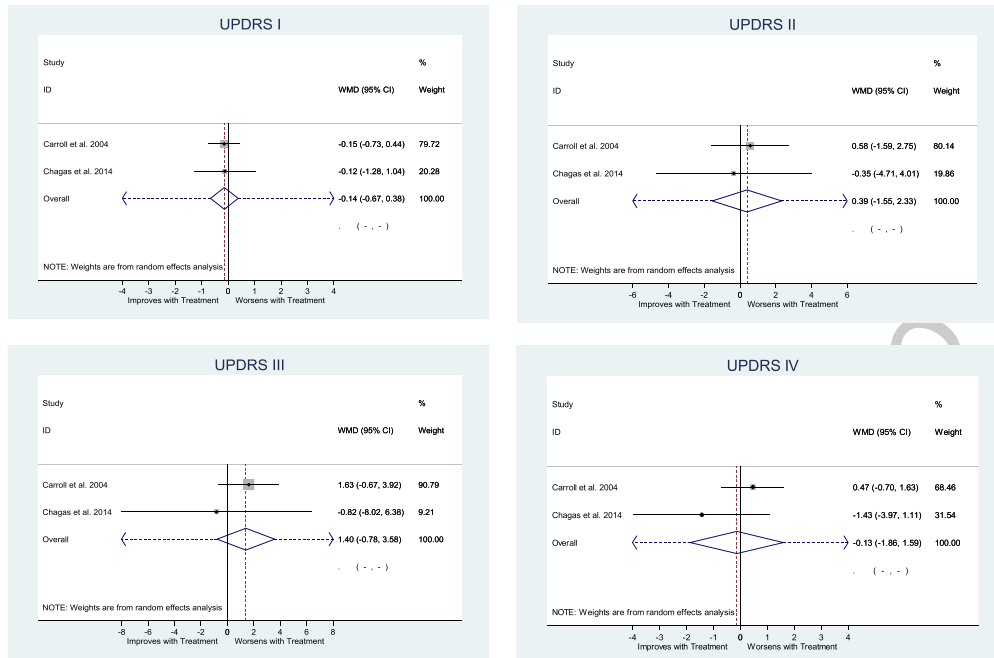


Fig. 2. Meta-analysis of UPDRS Part I ($p=0.596$), Part II ($p=0.692$), Part III ($p=0.209$), Part IV ($p=0.880$).

Twenty-two PD patients in Israel reported reduction of their tremor after smoking medical cannabis measured by UPDRS Items 20 and 21 [48]. Also in Israel, another study similarly reported that smoking prescribed medical cannabis for at least 3 months showed improvements in tremor following telephone interviews [39]. Another study also showed that inhalation of cannabis by PD patients suffering tremor alleviated in their symptom as detected by a movement monitor wore by participants for 14 days during treatment [50].

An electronic survey in the US of 261 respondents with PD who were cannabis users in the past six months and taking various forms of cannabis be it THC, CBD or mixed taken orally found that 25% of these respondents reported considerable improvement in tremor, while 38% reported moderate improvement, 24% reported slight improvement and only 13% reported no improvement [40]. Also, from a telephone survey of 39 PD patients taking medicinal cannabis approved by the Ministry of Health in Israel, 59% reported decrease in tremor symptoms [43]. A survey sent via mail to PD patients in Prague revealed 85 out of 339 respondents (25.1%) were already taking cannabis for PD [54]. Of these cannabis users, 31% reported improvement of rest tremor and that a minimum of 3 months of cannabis treatment provided more constant and consistent benefits compared to

short term treatment. Finally, a survey of cannabis users with PD in Germany revealed that 25% of respondents felt significant relief in tremor from taking cannabis mostly via oral route [55].

Effects of cannabis on levodopa induced dyskinesia

One randomized study shown that THC at a dose of 0.3 mg/kg alleviated dyskinesia ($p=0.05$) [37] while another randomized study using ~ 11.5 mg THC and ~ 5.75 mg CBD total dose reported no significant difference between cannabis and placebo groups ($p=0.09$) [32]. The former study used only one outcome measure, i.e., total dyskinesia score while the latter used a range of dyskinesia assessments. The sample sizes for both randomized studies were small ($n=26$) and both used a crossover design in which THC psychoactive effects may have made it difficult to blind patients and to some extent, investigators and outcome assessors.

A survey of 85 PD patients who were cannabis users found 14.1% reported an improvement in dyskinesia after taking cannabis of unspecified cannabinoid content [54]. A retrospective chart review of PD patients in a single center found that 69 PD patients were already using medical cannabis for their condition and were reporting dyskinesia

improvement after taking unspecified cannabis formulations [51].

Effects of cannabis on anxiety

Data from a randomized study indicated that a single CBD administration reduced anxiety in PD patients who underwent the simulated public speaking test (SPST) compared to control as evaluated by the visual analog mood scales anxiety factor ($p=0.021$) [35]. As this study used only a single CBD administration and induced anxiety experimentally, its results are not easily generalizable. Also, in another RCT [36], participants from a THC treated group reported reduction of their anxiety levels compared to placebo as measured by MDS-UPDRS Item 1.4 ($p=0.044$).

In an open label study of CBD, 3 out of 6 PD patients who were treated for 2 weeks reported less anxiety symptoms after taking CBD [46]. Also, in an electronic survey in the US accumulated 261 respondents with PD reporting improvement of anxiety after taking cannabis [40]. 35%, 43% and 15% respondents reported considerable, moderate and slight improvement in anxiety, respectively and only 6% did not.

Effect of cannabis on sleep quality

A randomized double-blind trial [36] of nabilone (THC) reported fewer sleep problems in the treated group compared to placebo ($p<0.001$). The placebo group in this RCT experienced difficulties getting a full night's sleep (Item 1.7 total score: 2.30) compared to nabilone (THC) treated group who suffered some sleep problems but these did not lead to difficulties getting a full night of sleep (Item 1.7 total score: 1.00)

In an open label study, CBD treatment for 2 weeks in PD patients was reported to improve participants' quality of sleep [45, 46]. Other NRS also reported cannabis of unspecified cannabinoid content to improve sleep quality [38–41, 43, 49].

A case series of 4 PD patients treated with oral CBD (3 patients 75 mg CBD and one patient 300 mg CBD) for 6 weeks had prompt, significant and persistent reduction of rapid eye movement [57] sleep behavior disorder (RBD) [58]. In fact, 3 out of 4 participants had elimination of RBD symptoms after CBD treatment such as yelling, talking, pushing kicking, or punching during sleep.

An electronic survey of PD patient in the US of 261 respondents reported substantial improvement

in sleep disorders after taking cannabis. 46%, 31%, and 15% respondents reported considerable, moderate, and slight improvement in sleep disorders with only 9% who did not [40].

In a telephone survey of 39 PD patients taking medical cannabis in Israel, 59% reported improvement of sleep quality after taking cannabis [43] while in a German survey, 27% of PD cannabis users reported significant improvement of sleep quality [55]

An open label study of purified CBD taken for between 10 and 15 days reported an improvement of sleep quality in PD patients [45]. Twenty-two PD patients who received medical permission to smoke cannabis and were additionally treated with 0.5 g of cannabis (unspecified cannabinoids) showed 12 of these 22 PD patients reported significantly less sleep problems while 8 also had mild relief [48].

Effects of cannabis on pain

In an open label study of oral CBD, three of six PD patients reported significant reduction of pain levels [46]. NRS reporting the use of prescribed cannabis of unspecified cannabinoids also noted immediate pain reduction [48, 49, 52, 55].

In a telephonic survey in Israel of PD patients granted medicinal cannabis prescriptions, 64% reported improvement in pain [43]. Also, an electronic survey in the US of 261 respondents with PD reported substantial alleviation of pain after taking cannabis [40]. 35%, 36%, and 15% of respondents reported considerable, moderate, and slight reduction of pain with only 14% experienced no effect in reducing pain.

Moreover, twenty-two PD patients who inhaled 500 mg of medical cannabis (unspecified cannabinoids) reported a significant reduction of pain [48]. The same outcome was achieved when fourteen PD patients who smoked cannabis were assessed on their pain threshold using thermal quantitative sensory testing revealing a significant reduction of subjective perception of pain after inhaling cannabis [52]. In a survey of PD patients using cannabis in Germany, 50% of responders reported significant reduction of pain after taking cannabis [55].

Effects of cannabis on quality of life

Quality of life has been explored in a randomized study using the Parkinson's Disease Questionnaire-39 (PDQ-39) scale [34]. Treatment with CBD, 300 mg/day for 6 weeks, reduced feelings of stigma

472 associated with PD ($p = 0.038$) and improved overall
473 activity of daily living ($p = 0.022$) positively affecting
474 overall quality of life [34]. No effect was noted at a
475 dose of 75 mg/day for 6 weeks. Carroll et al. (2004)
476 [32] reported no improvement in QoL (~ 11.5 mg
477 THC+ ~ 5.75 mg CBD/day). Participants who took
478 higher CBD and THC doses experienced psychotic
479 events.

480 *Safety*

481 There were no significant safety events or concerns
482 reported in the five randomized trials [32, 34–37].
483 Mild severity adverse events [60] were detected
484 across both cannabis treatment and control groups in
485 all randomized studies. However, a higher incidence
486 of AEs was associated with higher cannabis dosing
487 especially products with THC [32]. For cannabis
488 products with THC, psychological side effects were
489 common such as drowsiness, forgetfulness, insomnia
490 and nightmares [32, 36]. These AEs resolved when
491 the cannabis doses were reduced or when treatment
492 was stopped.

493 *Common cannabis products and routes of* 494 *administration*

495 Both inhalation and oral routes of cannabis
496 administration have reportedly provided significant
497 improvement in some PD related motor and non-
498 motor symptoms. More numerous studies have
499 investigated the safety of oral CBD products.

500 For example, an open label safety analysis of pure
501 CBD taken orally in 10 PD patients demonstrated that
502 high dose of CBD, ~ 1600 mg/day (or 20 mg/kg/day),
503 is associated with mild adverse reactions such as liver
504 enzymes elevation, diarrhea, fatigue and somnolence
505 [45] and resolved when the dose was reduced, or
506 treatment was stopped. A double-blind trial of 21 PD
507 patients using 75 mg CBD, 300 mg CBD and placebo
508 taken orally demonstrated similar side effects in all
509 groups [34]. An open label study of 6 PD patients
510 suffering psychosis for 6 months were treated with
511 150–400 mg of CBD for 4 weeks demonstrating sig-
512 nificant reduction of psychotic symptoms [56]. CBD
513 also decreased UPDRS total scores signifying poten-
514 tial benefit in PD symptoms overall. Lastly, case
515 series presentation of 4 PD patients suffering with
516 RBD were treated with CBD (3 patients 75 mg/day
517 and 1 patient 300 mg/day) demonstrated substantial
518 reduction of their RBD symptoms [58].

519 However, there are also evidence supporting the
520 use of pure THC, or mixed THC and CBD suggesting
521 some benefits. However, most of cannabis products
522 (unspecified cannabinoids) used in various NRS were
523 taken orally with less than half of respondents were
524 inhaled cannabis.

525 An electronic survey of PD patients in the US
526 accumulated 261 respondents who reported improve-
527 ments in tremor, stiffness, pain and sleep disorders.
528 40% of these respondents were taking cannabis via
529 inhalation, and at least 50% were taking cannabis
530 orally either by drinking, eating, or spray. 32% of
531 respondents were using THC (high or low), 36% CBD
532 (pure, high or low), and 12% mixed cannabinoids
533 [40].

534 A questionnaire web-based survey of 113 PD-
535 related cannabis users in Germany take medicinal
536 cannabis mostly via oral route ($\sim 70\%$), and few took
537 via inhalation ($\sim 30\%$) [55]. 40% take CBD only, 10%
538 THC only, 20% both THC and CBD, while the rest
539 did not know the cannabinoid contents. Inhaling THC
540 compared to oral CBD was reported to produce more
541 significant efficacy and improvement of motor symp-
542 toms such as freezing (80% of inhalation THC versus
543 24% of oral CBD users). However, there were only
544 4 of 5 responders reported improvement of inhaled
545 THC.

546 **DISCUSSION**

547 This review revealed no strong evidence suggest-
548 ing clinical benefits of cannabis in treating patients
549 with PD. Treatment duration in the two random-
550 ized studies included in meta-analysis was, however,
551 short; 4 and 6 weeks [32, 34], respectively. Treatment
552 of at least 3 months would seem a more appropriate
553 period especially in trials investigating PD with motor
554 symptoms uncontrolled by levodopa [61]. Also, some
555 participants did not attain the target treatment dose
556 due to cannabis related AEs particularly psycholog-
557 ical side effects associated with THC [32]. The use
558 of an optimization phase prior to a double-blind trial
559 may assist in ensuring each participant attains the
560 maximal beneficial dose without or with minimal
561 undesired side effects. Finally, there were relatively
562 few randomized studies, all of small sample size for
563 which there was heterogeneity in the cannabis prod-
564 ucts used (THC alone, CBD alone, and combination),
565 dose, study design, and participants' stage of PD.

566 Some potential areas of benefit requiring further
567 investigation were identified; however, reduction of

568 tremor, alleviation of some non-motor symptoms
569 particularly anxiety, pain, sleep quality, and improve-
570 ment of QoL.

571 This review suggested a potential benefit of
572 cannabis in controlling tremor, a common PD motor
573 symptom. The one randomized study [35] to investi-
574 gate this effect demonstrated that the administration
575 of a single CBD 300 mg dose effectively reduced
576 tremor amplitude compared to placebo. Other NRS
577 [48, 54] supported this outcome where cannabis
578 notably reduced tremor. However, the measured
579 outcomes were subjective experience rather than
580 quantitative measurements. These results suggest fur-
581 ther research is warranted, especially the effect of
582 CBD over a longer treatment period.

583 Another area that cannabis may have a benefit is
584 on the alleviation of non-motor symptoms. One ran-
585 domized study [36] demonstrated less deterioration
586 of non-motor symptoms, measured by MDS-UPDRS
587 Part I, for a THC (nabilone) treated group compared
588 to placebo. A survey of PD patients in Germany
589 reported benefits from cannabis in relieving non-
590 motor symptoms such as pain, muscle cramps,
591 depression, and sleep disorders [55]. Most of the
592 113 PD cannabis users in this survey reported taking
593 cannabis orally while some via smoking, using either
594 THC or CBD only, or combination cannabis products.
595 A similar outcome was observed in a US survey [40].
596 Around 44% of respondents reported cannabis (THC,
597 CBD, or mixed) effectiveness in treating anxiety, pain
598 and sleep issues [40].

599 Possible beneficial effects in relation to anxiety,
600 sleep, and pain reported from NRS and surveys
601 should be investigated using more robust experi-
602 mental designs. This is particularly warranted given
603 results of cannabis efficacy in other medical con-
604 ditions. In a double blind randomized trial [62]
605 and a retrospective case series [63] of participants
606 with social anxiety disorder and healthy volunteers,
607 cannabis was reported to reduce anxiety levels in par-
608 ticipants. Preclinical and clinical studies have also
609 consistently shown cannabis to possess analgesic
610 properties [64–66]. A systematic review of clinical
611 studies demonstrated cannabis as an effective pain
612 control in chronic, non-cancer, pain populations [67].
613 Lastly, a systematic review of clinical studies aiming
614 to find patient reported reasons for taking medical
615 cannabis revealed that cannabis was mainly sought
616 to treat pain, depression, and anxiety [68].

617 Another promising area of benefit for PD patients is
618 the effect of cannabis, especially, CBD in improving
619 QoL. Many PD patients experience stigma because

620 of their condition. Experienced stigma is an impor-
621 tant key determinant of QoL in PD [69]. Shame arises
622 from increased physical dependence, need for help,
623 and deteriorated body image [70]. It is also impor-
624 tant to note that difficulty in performing activities
625 of daily living [70] is independently associated with
626 a higher perception of stigma towards self. CBD
627 may improve the overall ability to carry out activ-
628 ities of daily living which as a result may reduce
629 negative perception of self [71]. This could explain
630 why CBD showed significant outcomes in both carry-
631 ing out ADLs and stigma experience domains of
632 PDQ-39 [34]. This outcome has also been observed
633 in treatment-resistant epilepsy treated with CBD [72].
634 It should be noted, however, that the meta-analysis
635 in this review of UPDRS Part II [70] showed no
636 treatment effect (Fig. 2). Again, while there is a
637 considerable amount of observational evidence with
638 respect to the QoL effects of cannabis treatment, until
639 definitive RCTs are performed its benefits remain
640 suggestive.

641 CONCLUSION

642 This review did not find strong evidence for
643 the beneficial use of cannabis in PD patients. No
644 clinically significant improvement in the overall
645 symptoms of PD was detected from robust studies
646 though NRS and surveys suggested potential bene-
647 fits. Relatively few RCTs were identified. These had
648 small sample sizes and were highly heterogeneous in
649 the cannabinoids investigated, their methods of mea-
650 surement, and study design. Only three studies used
651 the UPDRS/MDS-UPDRS.

652 Conversely, there are some number of non-ran-
653 domized studies, case series, and surveys identi-
654 fied in the cannabis literature. These, generally,
655 reported favorable therapeutic effects, which when
656 compared to the equivocal or absence of effect seen
657 from the few RCTs would suggest bias. However,
658 notable improvements were seen for THC and CBD
659 in treating non-motor symptoms of PD particularly
660 in reducing anxiety, pain, and improving quality of
661 sleep. There are also potential benefits of CBD in
662 improving QoL and attenuating tremor. There were
663 no major safety adverse events described.

664 Although this review revealed possible areas of
665 clinical significance, robust and sufficiently powered
666 randomized controlled studies are lacking. Well-
667 designed studies are needed to accurately estimate the
668 treatment effects of specific cannabis formulations

669 for each potential therapeutic application as well as
670 to identify therapeutic doses.

671 *Implications for clinical practice and future*
672 *research*

673 This review provides some evidence that cannabis
674 may improve quality of life of PD patients and allevi-
675 ate tremor and some non-motor symptoms but better
676 designed RCTs are needed to confirm these observa-
677 tions. A more focused study objective may provide
678 more meaningful and positive outcomes such as
679 evaluating CBD/THC effects in tremor or pain. Addi-
680 tionally, a longer treatment period and supporting
681 MDS-UPDRS scale with specific motor and non-
682 motor scales would be beneficial for future studies.

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689 **CONFLICT OF INTEREST**

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SUPPLEMENTARY MATERIAL

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