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LEADING TOPIC

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Cannabis in Parkinson's Disease — the patient's perspective versus clinical trials: a systematic literature review

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ABSTRACT

Cannabis and cannabinoids are often considered in the treatment of Parkinson's Disease (PD). The purpose of this paper was to perform a systematic review of the available data on cannabis treatment. We aimed to assess randomised trials as well as surveys among patients. We identified 569 papers on PD and cannabinoid treatment. Of these, there were only seven papers featuring randomised trials on the effects of different cannabinoids on PD. The results of these trials did not support the efficacy of cannabinoids in the treatment of motor signs of PD. Based on the available data, we conclude that there is currently insufficient data to support the administration of cannabinoids to PD patients. Larger, randomised studies of cannabis use in PD should be conducted.

Key words: Parkinson's Disease, cannabis, CBD, marijuana, non-motor symptoms

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Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disease, after Alzheimer's Disease. With a lack of causative treatment, most interventions are directed at reducing motor and non-motor symptoms of the disease. Cannabis (marijuana) is obtained from the Cannabis plant. Tetrahydrocannabinol (THC) is the main psychoactive component of cannabis, while cannabidiol (CBD) is the most widely described component in the context of neurological treatment.

The first papers on the effect of cannabis in movement disorders came from observational studies. Consroe et al. [1] reported in 1986 that CBD exacerbated parkinsonian symptoms in patients with dystonia of various types (Meige's syndrome, torticollis). The study included a total of five patients, one with PD and dystonia induced by levodopa. Interestingly, doses of CBD applied in the study were quite high, reaching 600 mg/d. A paper by Frankel et al. [2] described five patients treated with marijuana cigarettes, along with diazepam, levodopa and apomorphine, each given on consecutive days. The authors reported no benefit of marijuana on PD tremor.

The current concept of the efficacy of cannabis in the treatment of PD is derived from the discovery of the endocannabinoid system (ECS). Endocannabinoid signalling is altered in most neurological disorders. Phytocannabinoids act via the cannabinoid receptors 1 (CB-1R) and 2 (CB-2R). Both types of receptor are expressed in the central nervous system, with a predominance of CB-1R. CB-1R is expressed in the basal ganglia, with especially high concentrations in the medial part of the internal pallidum [3]. CB-2R receptor expression is elevated in microglial cells within the substantia nigra (SN) of PD patients, and both the striatum and SN of lipopolysaccharide (LPS)-lesioned mice. The main endogenous ligands of CB-1R and CB-2R are anandamide and 2-arachidonoylglycerol [4, 5].

Slowing the progression of PD is the key target in its treatment. Evidence from in vitro studies on cell lines indicates that CBD may protect cells from MPP+ induced toxicity [6] or reduce amyloid-mediated neural toxicity [7]. The neuroprotective effects of CBD have been assessed in some studies using animal models of PD. Lastres-Becker et al. [8] showed both in vivo and in vitro that the administration of CBD counteracted neurodegeneration caused by the injection of

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6-hydroxydopamine in the medial prosencephalic bundle. The authors hypothesised that this effect could be related to anti-inflammatory and/or antioxidative effects of cannabinoids. Garcia-Arencibia et al. [9] tested many cannabinoid compounds following the lesion of dopaminergic neurons in the SN. They concluded that the acute administration of CBD seemed to have a neuroprotective action; however, the administration of CBD one week after the lesion had no significant effect. Some authors have also reported a reduction in the pro-inflammatory markers nuclear factor-κB, cyclooxygenase-2 activity, and phospho-ERK levels after CBD treatment [10]. Interestingly, it has been reported by some authors that the neuroprotective effect of CBD may be unrelated to a cannabinoid receptor, as CBD does not have a direct effect of CB-2R in physiological concentrations [11, 12]. Others have indicated that CB-2R should be the key target for studies on neuroprotective effects of cannabinoids because it is expressed in both reactive microglia and astrocytes, and thus may promote neuroinflammation [13].

The ability to modulate impaired basal ganglia activity by phytocannabinoids has been extensively investigated recently. This is postulated to be achieved by the ability of exogenous cannabinoids to: a) affect synaptic neurotransmission; b) influence corticostriatal plasticity; and c) have neuroprotective and anti-inflammatory properties [11, 14].

The purpose of this systematic review was to evaluate available studies for the clinical efficacy of the treatment of motor (tremor, bradykinesia, falls, dyskinesia) and non-motor (anxiety, pain, sleep disorders) symptoms with medical marijuana and cannabinoids in patients with PD.

Materials and method

Searches were performed according to the PRISMA guidelines 2020 [15]. The PubMed and Scopus databases were searched. The terms "Parkinson" plus "Marijuana", "Cannabis", "Nabilone", "Dronabinole" and "Nabiximols" were used. Reviews of the literature and case reports were excluded. We also included one paper assessing, among other drugs, the effect of rimonaband, a CB1 antagonist, on PD patients. Only full-text articles published in English from 2000 until 27 September 2021 were included in the final analysis.

Results

Searching with the terms "Parkinson" AND "marijuana" OR "Cannabis"; "nabilone"; "dronabinol"; "nabiximols" revealed 514 results in the Scopus database and 207 results in the PubMed database. After automatic (EndNote) and manual (M.F.) removal of duplicates, a total of 569 papers were identified that met the search criteria.

In the next step, available abstracts were read to identify the original research papers on the effect of treatment on patients with PD. We excluded original papers regarding the knowledge of medical personnel or their attitudes to treatment with cannabis. A PRISMA flow diagram of the search procedure is available as supplementary material 1. We identified a total of 18 original papers or case series on the effect of cannabis-based products on the symptoms of PD. Among those, there were seven double-blinded randomised trial results available. Three of the seven assessed the effect of pure CBD on PD symptoms [16–18], one study involved treatment with THC and CBD in combination [19], and two papers summarised the results of randomised clinical trials with nabilone [20, 21]. Table 1 summarises the findings from the randomised studies. There were five open-label studies/case series on the effect of treatment with CBD [22–24] or smoking/vaporisation of cannabis [25, 26] in PD. Finally, seven of the papers summarised findings from online or telephone surveys of patients with PD on the effects of marijuana (sometimes in addition to other treatments) on PD symptoms [27–33].

Motor signs of PD

There have been very few studies focusing on the effect of cannabis on motor signs of PD. For a summary of randomised papers on cannabis treatment in PD, please refer to Table 1. Different treatment regimens have been applied. Lotan et al. [26] reported in an unblinded trial a positive effect of smoking cannabis on such PD motor signs as tremor, rigidity and bradykinesia, reflected in a significant decrease in UPDRS part III scores (33.1 ± 13.8 at baseline to 23.2 ± 10.5; $p < 0.001$) after treatment. This is consistent with the findings of Shohet et al., where the authors focused on the sensation of pain, but also reported lower total UPDRS III scores during treatment (from 38.1 ± 18 to 30.4 ± 15.6; $p < 0.0001$) [25]. Both papers assessed direct effects 30 minutes after smoking a marijuana cigarette. The positive effects of marijuana consumption reported in open studies have not been confirmed in randomised double-blind trials. Chagas et al. [34] assessed patients in "ON" status on the UPDRS III scale before and after six weeks of treatment with CBD. They reported no improvement regarding motor signs of PD in groups receiving CBD 75 mg and 300 mg versus placebo. However, they reported significant improvements in total PDQ-39 scores in the group receiving 300 mg CBD vs a placebo group, as well as in a subset of questions regarding activities of daily living.

Levodopa-induced dyskinesia (LID) is a common motor complication of levodopa treatment. We have identified three clinical trials measuring the effects of cannabinoids on LID intensity. The study by Carroll et al. [19] was a randomised study with a crossover phase. It included 19 patients with PD and LID. Patients received a combination of THC 2.5 mg and CBD 1.25 mg tablets. The total dosage of THC was limited to 0.25 mg/kg/day, and the majority of patients did not reach that limit. The results showed a good safety profile, but no benefit. Although the authors did not provide detailed calculations of the total CBD dosage received by each patient, it was much lower than the dose administered in other studies on CBD (up to 25 mg/kg/day). A small (n = 7) double-blind crossover trial

Table 1. Summary of randomised, placebo-controlled trials on effect of cannabis in PD

No.	Authors	Number of patients randomised	Primary outcome	Active treatment	Dosage	Result
1.	Chagas et al. 2014 [10]	21	Change in UPDRS and PDQ-39 score	CBD	300 mg	No change in "ON" UPDRS. Significant improvement in PDQ-39 ($p = 0.05$)
2.	Carroll et al. 2004 [12]	19	Change in LID, measured by UPDRS IV questions 32–34 score	THC + CBD	THC 2.5 mg and 1.25 mg CBD tablets – to a total dose limit of 0.25 mg/kg/day THC	No change in LID intensity
3.	De Faria et al. 2020 [11]	24	Change in scales: – VAMS – Self-Statements during Public Speaking Scale – Systemic blood pressure and heart rate – Bradykinesia measured by tapping test – Tremors measured by accelerometer	CBD	300 mg	Significant differences in VAMS anxiety factor for drug, $p < 0.001$)
4.	De Almeida et al. 2021 [9]	33	Change of RBS occurrence in sleep diary. Change on CGI scale	CBD	75–300 mg	No change
5.	Peball et al. 2020 [30]	38	Change in UPDRS-MDS I	Nabilone	0.91 ±0.4 mg/day	Significant reduction in UPDRS-MDS I score of 2.63 points ($p = 0.002$)
6.	Sieradzan et al. 2001 [13]	7	Total dyskinesia disability using Rush Dyskinesia Disability Scale	Nabilone	0.03 mg/kg	Significant reduction in dyskinesia score: nabilone 17 (11–25), placebo 22 (16–26) $p < 0.05$
7,	Mesnage et al. 2004 [28]	24	UPDRS III and IV	1) Neurotensin antagonist (SR 48692) 2) Cannabinoid CB1 antagonist (SR 141716) 3) NK3 antagonist (SR 142801)	1) 180 mg 2) 20 mg 3) 200 mg	No effect of LID intensity or "ON" onset or duration

LID — Levodopa-Induced Dyskinesia; PDQ-39 — Parkinson's Disease Questionnaire; UPDRS — Unified Parkinson's Disease Rating Scale; VAMS — Visual Analogue Mood Scales

by Sieradzan et al. [20] demonstrated the efficacy of nabilone in LID reduction. A paper by Mesnage et al. [35] assessed the efficacy of three substances — neuropeptides neurokinin B, neurotensin, and anandamide. Of these, anandamide acted as a CB receptor antagonist. Patients were randomly assigned to one of the three substances or to a placebo. The authors reported a lack of improvement in delay of the "ON" period, duration of the "ON" period, the percentage of parkinsonian motor improvement (UPDRS III), or the severity of the LID.

Non-motor symptoms of PD

Sleep

Cannabis-based products have been frequently investigated regarding sleep problems in different disorders. Most PD patients (c.80% at late stages) complain of sleep disorders. Their treatment is challenging as they are multifactorial and, in the majority, no defined causes are identified. A case series by Chagas et al. [36] reported positive initial observation of four patients with REM sleep behaviour disorder (RBD)

treated with CBD. On the other hand, a randomised study on 33 patients (conducted in the same centre) showed no advantage of CBD over placebo regarding the reduction of RBD. The authors reported better sleep satisfaction at the 4th and 8th weeks in the CBD versus a placebo group with $p = 0.049$ and $p = 0.038$ respectively. This effect was, however, transient [16]. Leehey et al. [22] also reported improvements in sleep, reflected by SCOPA-sleep change, but no effect of treatment with CBD on RBD. A study by Lotan et al. [26] reported, among others, improvement in quality of sleep, but no specific questionnaire or test was applied to measure it.

Pain

Pain is a common problem in PD of heterogeneous origin and with only a partial response to dopaminergic treatment. The reduction of pain, reflected by improvements on the Visual Analogue Scale (VAS), was reported in the study by Lotan et al. [26]. The paper by Shohet et al. [25] examined pain sensation in a very elaborate manner, with similar conclusions. The authors reported a decrease in the cold and hot pain thresholds in patients smoking cannabis using the Quantitative Sensory Testing method. In both papers, assessments were performed before, and 30 minutes after, smoking cannabis, and the patients were not blinded regarding the received treatment.

Neuropsychiatric symptoms

Neuropsychiatric symptoms of PD are among the most researched in terms of cannabis treatment. De Faria et al. [18] performed a double-blind, placebo-controlled study on the efficacy of CBD 300 mg on PD-related anxiety. The authors proved that anxiety and anxiety-induced tremor in PD, measured during a Simulated Public Speaking Test, was significantly reduced. Interestingly, while psychosis was an exclusion criterion in the majority of trials on cannabis and CBD, a paper by Zuardi et al. [24] reported improvements of psychosis in six PD patients treated with CBD 150–300 mg, and no additional antipsychotic treatment, reflected by score reductions in the Parkinson Psychosis Questionnaire and on the Brief Psychiatric Rating Scale. On the other hand, in a study by Sieradzan et al. [20], focused on intensity of LID, 5/7 patients experienced sedation, hallucinations of varying intensities, dizziness or disorientation.

A paper by Peball et al. [37] assessed the safety and efficacy of nabilone, a synthetic analogue of tetrahydrocannabinol, in the treatment of non-motor symptoms of PD. In phase I of the study, nabilone was titrated, while in phase II subjects were randomly assigned to a previously established dose of nabilone or a placebo. The authors reported a significant reduction in UPDRS-MDS I, in particular the 'anxious mood' and 'night time sleeping problems' items of the scale. Interestingly, although pain-related endpoints (King's Parkinson Pain Scale and VAS of pain) improved significantly during the open-label trial phase, this was not confirmed in the randomised phase.

Patient's perspective

In contrast to the modest effect found in randomised, double-blinded clinical trials, patients' subjective perception of cannabis treatment is good. Table 2 summarises papers detailing surveys among patients. Such surveys have taken various forms (i.e. performed by a physician in person, over the phone, by email, or by the patient accessing a website), and some papers have also included patients with other diseases (multiple sclerosis [31], atypical parkinsonism [28]), or have focused only on one symptom (e.g. pain). While different approaches and presentations of the results make direct comparisons difficult, improvements in such non-motor symptoms as pain or anxiety have been reported most frequently. Patients have also reported improvements in motor signs of PD, with tremor and rigidity mentioned in the majority of studies. This is in line with the findings of non-blinded clinical trials. The results of the surveys are also difficult to interpret, because we might have expected patients to give different answers to anonymous internet-based questionnaires rather than those collected by physicians.

Discussion

In our paper, we have aimed to summarise the current knowledge regarding different cannabis-based products in PD treatment. Strikingly, there is a high total number of papers on the treatment of PD with cannabis, compared to a low number of actual original clinical trials. This reflects the great interest in these types of medication expressed by both patients and clinicians. While advanced therapies such as vector-based treatment of PD are appearing on the horizon [38], many patients turn instinctively to the methods they consider 'traditional' or 'natural'. The upshot is that studies in randomised controlled trials have included motor signs assessed mainly in UPDRS scale part III, such as resting tremor, rigidity and bradykinesia. Some non-motor symptoms, such as RBD and anxiety, have also been assessed in randomised trials. Other authors have used an open-label approach to assess motor symptoms, dyskinesia, pain etc.

The chief limitations of the currently available studies on cannabis-based products in PD are small sample sizes and differing schedules of administration of the products. There are many differences in the method of intake of cannabis and/or the dosage of CBD. Smoking marijuana cigarettes seems to make an objective measurement of the dose difficult. This leads to difficulties in comparing the studies. There are also some cultural differences between investigated groups. Some authors have suggested that cannabis and cannabis products may require very individual dosing and that large randomised studies may fail to show their efficacy for that reason. Progress in genetic testing and identification of subtypes of PD may also lead to the development of more individualised approaches [39, 40]. Open label studies with positive results carry an

Table 2. Summary of surveys performed in different countries on effects of cannabis and/or other treatments on intensity of different Parkinson's Disease (PD) symptoms

No.	Author	Survey conduction mode	Number of cannabis users with PD in survey	Symptoms reported to be affected by cannabis
1.	Balash et al. 2017 [25]	Telephone survey	47	• Improvement (r^2) for falls (0.89, pain relief (0.73), depression (0.64), tremor (0.64), muscle stiffness (0.62), sleep (0.60)
2.	Yenilmez et al. 2020 [20]	Self-developed paper questionnaire, anonymous	113	• 54% of users reported benefit • Improvement in pain (43.9%), muscle cramps (41.4%), depression (28.1%), stiffness/immobility/akinesia (27.3%), sleep disorders (27.1%), tremor (25%), fear (24%), RLS (21.4%)
3.	Micheli et al. 2020 [31]	Semi-structured questionnaire performed by physician	121	• 44.6% — improvement — 25.6% in motor symptoms: 12.4% stiffness (n = 15); 9.1% gait (n =11); 6.6% tremor (n = 8); 5% motor slowness (n = 6) — 28.1% in non-motor symptoms: 12.4% anxiety (n = 15); 9.1%, pain (n = 11); 9.1% sleep (n = 11); 6.6%, depression (n = 8) — 9.1% in both
4.	Kindred et al. 2017 [24]	Web-based survey Multiple sclerosis and PD patients	Exact numbers not provided	• Improvement in Guy's Neurological Status Scale (F = 7.481, p = 0.006): Memory (F = 4.717, p = 0.030), Mood (F = 9.328, p = 0.002), and Fatigue (F = 6.870, p = 0.009) subscales
5.	Yust-Katz 2017 [21]	Structured survey-telephone/clinic visit	31 patients	• Improvement of pain 77%
6.	Feeney 2021 [26]	Anonymous, electronic survey by e-mail	261	• Improvement in severity of anxiety (78.0%, 71/91), pain (71.6%, 63/88), sleep disorders (76.1%, 67/88), stiffness (64.0%, 55/86), and tremor (63.1%, 53/84)
7.	Venderova 2001 [32]	E-mail survey	85 patients	• 39 patients (45.9%) reported mild or substantial alleviation of PD symptoms in general — 26 (30.6%) improvement of rest tremor — 38 (44.7%) alleviation of bradykinesia — 32 (37.7%) alleviation of muscle rigidity — 12 (14.1%) improvement of L-dopa-induced dyskinesias. • 4 patients (4.7%) reported that cannabis worsened their symptoms

additional bias because cannabis intake according to popular understanding leads to a high expectation of a positive effect.

Treatment with marijuana and its compounds can lead to complications. Fear of addiction and psychotic side effects can be among the most important issues discouraging patients from cannabis treatment. Some symptoms of cannabinoid treatment may be unpleasant for patients. These include somnolence, dizziness, nausea, vomiting, tachycardia, hypotension, dry mouth, diarrhoea, loss of balance and fatigue, as well as psychiatric symptoms such as disorientation, confusion, hallucinations, and altered mood [14]. These are usually most pronounced at the beginning of treatment. All of these symptoms are undesirable in the older PD population, and can also exacerbate preexisting symptoms frequent among PD patients, such as hypotension or visual disturbances [41, 42]. Importantly, CBD, in contrast to THC, is considered not to cause psychotic symptoms [34]. It has been proven that psychotic symptoms are a result of CB-1 receptor activation, which is not achieved when CBD is administered in physiological concentrations [43]. A study by Zuardi et al. [24] may encourage the belief that CBD actually relieves psychotic symptoms. On the other hand, nabilone seems to cause such complications fairly frequently (5/7 patients) [20]. Treatment is mostly associated with long term use and may lead to withdrawal symptoms. Cognitive dysfunction can also appear as a long-term effect of cannabis consumption [44]. Dependency and a lack of official licence in many countries may also be contributory factors.

One potentially positive aspect of marijuana treatment may be an increase in weight [31]. Although generally seen as a drawback, this may actually benefit advanced PD patients with malnutrition, something which is observed in 50% of PD patients [45].

We conclude that currently there is insufficient evidence to routinely recommend the addition of cannabis or CBD-based products to PD treatment regimes.

While subjective reports claim positive results of cannabinoids on a range of symptoms, randomised placebocontrolled trials in the literature currently do not demonstrate improvements in motor signs, and show inconsistent impacts on LID, anxiety, and psychosis. Legal limitations, lack of social

acceptance, and troubling side effects may be obstacles in the administration of cannabis.

Large, randomised, double-blind, long-term studies with a representative number of patients and dose standardisation are needed to assess the real efficacy of these treatments. In particular, placebo control is needed to provide adequate assessment of the efficacy of cannabinoids in PD therapy. This should include placebo substitutes of both CBD and cannabis administered by inhalation, with careful monitoring of the doses administered to patients.

Based on our literature review, we conclude that non-motor symptoms of PD such as pain, anxiety and sleep seem to respond better to cannabis treatment than do motor signs. Therefore future studies should perhaps focus on non-motor symptoms, especially as these frequently place a higher burden on PD patients' quality of life than do motor symptoms.

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