Thieme

Cannabinoids in the Treatment of Parkinson's Disease

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Key words
Parkinson's disease, THC, cannabinoids

Bibliography
DOI https://doi.org/10.1055/s-0043-115359
Published online: 2017
Neurology International Open 2017; 1: E307–E311

ISSN 2511-1795

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ABSTRACT

Due to the changing legal status of medical cannabis and derivatives in numerous countries, this therapeutic option has moved into the field of public debate. Neurologists treating patients with idiopathic Parkinson's disease are increasingly confronted with questions regarding cannabis as a treatment alternative, especially for levodopa-resistant Parkinson's symptoms. A number of single case reports and case series suggested improvement of Parkinsonian symptoms after cannabinoid intake, but the small number of available randomized clinical trials failed to reproduce the extent of these findings. Only one trial found a reduction of levodopa-induced dyskinesia with cannabinoid treatment, the remaining three trials showed no effect on Parkinsonian symptoms. This article gives an overview on the effects of cannabis, and reviews experimental and clinical trials studying the effects of cannabinoids in idiopathic Parkinson's disease.

Introduction

At the latest since the resolution of the German parliament on January 19, 2017 to ament the German Narcotic Drugs Act (Betäubungsmittelgesetz, BtMG) with regard to the treatment of severely ill patients with high-quality cannabis medications (documents 18/8965 and 18/10902 of the German parliament), there has been growing public interest in the therapeutic properties of cannabis. Until then, an exemption of the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) was required to allow for treating patients with cannabis products. Until 2016, such exemptions had been issued for about 1000 patients (www.bundestag.de). While so far patients had to pay for this treatment themselves, the new amendment now regulates the covering of treatment costs by health insurance companies.

Besides the change of the legal status, scientific interest in the potential therapeutic properties of cannabis has been growing, driven by advances in the understanding of the endocannabinoid system.

The isolation of cannabinoid receptors and endogenous cannabinoids in the nervous system by Raphael Mechoulam [1] and other groups and the discovery that the endocannabinoid system is capable of modulating numerous physiological processes, such as pain, eating behavior, memory, and mood [2, 3] have paved the way for systematic research into the effects of cannabis on a variety of chronic diseases [4–7]. Data from clinical studies supported a role of cannabis and endocannabinoids in the treatment of specific symptoms, such as spasticity and central or spasticity-associated pain in patients with multiple sclerosis, chemotherapy-induced nausea, and anorexia [7]. Until recently, the only medicines of this class approved in Germany were the combination drug Sativex® as an add-on therapy for adult multiple-sclerosis patients with moderate to severe spasticity, and the synthetically manufactured tetrahydrocannabinol analogue nabilone (Canemes®) for the treatment of adult cancer patients suffering from chemotherapy-induced nausea. Since March 10, 2017 cannabis flowers and

▲ **Table 1** Overview on the case series and randomized controlled trials evaluating the effects of cannabinoids or cannabinoid antagonists on symptoms of Parkinson's disease.

Author [reference]	Year	Study design	Sample size	Active substance evaluated	Results
Venderová et al. [40]	2004	open anonymous survey	85	asked about type of cannabis consumption: 84 patients with 1/2 teaspoon cannabis orally; 1 patient inhaled, 52.9 % daily.	improvement of cardinal PD symptoms in 45.9 % and LID in 14.1 %
Lotan et al. [41]	2014	case series	22	after baseline screening using motor and non-motor tests, smoked 0.5 g cannabis. After 30 min, testing repeated	improvement of tremor and bradykinesia
Frankel et al. [42]	1990	case series	5	1 g cannabis (with 2.9 % THC) smoked once	no improvement of tremor
Chagas et al. [43]	2014	randomized, double-blind, placebo-controlled	21	randomized to receive 75 mg, 300 mg daily dose of CBD or placebo for 6 weeks	improvement of PDQ-39 with 300 mg CBD; UPDRS unchanged
Sieradzan et al. [44]	2001	randomized, double-blind, placebo-controlled crossover design	7	randomized to receive single exposure to 0.03 mg/kg nabilone or placebo; half of dose administered 12 h and 1 h, respectively, before acute levodopa challenge test; crossover after 2 weeks	reduction in LID severity and duration
Carroll et al. [45]	2004	randomized, double-blind, placebo-controlled crossover design	17	randomized to receive standardized daily dose of Cannador (2.5 mg THC + 1.25 mg CBD) for 4 weeks, crossover after 2-week wash-out period	no improvement in LID severity duration, motor symptoms quality of life or sleep
Mesnage et al. [46]	2004	randomized, double-blind, placebo-controlled	4	randomized to receive daily dose of 20 mg rimonabant (CB-1R antagonist) or placebo for 16 days	no change in motor impairment or LID in neither On- nor Off-state

their extracts can be prescribed on a narcotic drug prescription form without limitation to specific indications [8].

The discovery of high concentrations of cannabinoid receptors in the basal ganglia triggered an increasing interest in the therapeutic potential of cannabinoids for the treatment of Parkinson's disease (PD) and other movement disorders. Public awareness of this topic was raised by anecdotal reports of considerable improvement of PD symptoms after cannabis consumption that were shared via social networks and published in the general press. For example, Larry Smith, a US-American PD patient claiming improvement of his dyskinesia with cannabis consumption, attracted broader public attention via YouTube™ [9]. In Germany, cannabis consumption to alleviate PD symptoms gained attention when the topic was raised in the German TV drama series "Lindenstrasse" (the German equivalent to the British TV drama series "Coronation Street") [10].

Cannabis and the Endocannabinoid System

Cannabis is a mixture of more than 60 substances, referred to as phytocannabinoids due to their plant origin (as opposed to endocannabinoids produced by the human body). The main active constituents of cannabis are the psychotropic cannabinoid delta9-tetrahydrocannabinol (THC) and the non-psychotropic cannabinoid cannabidiol (CBD). These substances were isolated in the 1960s and proven to be active components of cannabis [1, 11]. In the 1990s, the two most important receptors — the cannabinoid receptor 1 (CB-1R) [12] and the cannabinoid receptor 2 (CB-2R) [13] — and their endogenous ligands, such as anandamide and 2-arachidonylglycerol (2-AG), and hence the endocannabinoid system (ECS) were discovered.

CB-1R is primarily located in the nervous system (except for the thalamus and brain stem), with high concentrations in the hippocampus, the association cortex, cerebellum, basal ganglia, and spinal cord (here with high concentration in the dorsal roots), and peripheral nerves [7]. CB-2R is expressed in the gastrointestinal tract, in lymphatic tissue and peripheral nervous system. However, in 2014 it was shown that CB-2R is also expressed in the CNS, primarily in neurons of the dorsal nucleus of the vagus nerve, the nucleus ambiguus, in the spinal trigeminal nucleus, and on microglia [14–16].

CB-1R and CB-2R are G protein-coupled receptors and via the G_0/G_i unit inhibit the activity of the adenyl cyclase, thereby influencing the release of excitatory neurotransmitters, such as glutamate, dopamine and acetylcholine. In addition, other transmitter systems, such as the NMDA (N-methyl-D-aspartate) and the serotonin, the opioid and GABA (γ-aminobutyric acid) systems are also modulated via indirect mechanisms [7]. Furthermore, the mitogen-activated protein kinase/extracellular signal–regulated kinase (MAPK/ERK) pathway is activated via the $G_{\beta\gamma}$ complex [17–19], a pathway that has regulatory properties regarding cell development, cell differentiation and apoptosis [20].

The structural analysis of cannabinoid receptors ultimately paved the way for the development of synthetic cannabinoids. Today, several cannabinoid-based preparations are available for medicinal use (▶ **Table 1**).

Parkinson's Disease and Neuroprotection in Experimental Studies

In the late 1960s and early 1970s, early animal studies demonstrated an effect of cannabinoids on the catecholaminergic and dopaminergic systems [21, 22]. CB-1R and the endocannabinoid ligands anandamide and 2-AG occur in high concentrations in the dopaminergic system, including the striatum [23], where they modulate dopaminergic transmission as a retrograde feedback system on presynaptic glutamatergic and GABAergic nerve endings. In-vitro studies in the late 1970s generated conflicting evidence, demonstrating both an increase [24] and a dose-dependent decrease of dopamine synthesis [25] and release [22]. In-vivo studies showed an increase in dopamine release in the prefrontal cortex, striatum, but also in the nucleus accumbens. Thus, an increased firing rate of dopaminergic neurons after acute THC exposure can be assumed, resulting in augmented dopamine synthesis and release. Interestingly, acute and chronic THC exposure seems to result in different effects on neuronal firing rate, transmitter synthesis, transmitter release and reuptake within the dopaminergic system [26].

An increase in ECS activity was detected both in a PD animal model and in human tissue analyses from PD patients [27], including an upregulation of cannabinoid receptors [28, 29], an accumulation of cannabinoid receptor agonists [30, 31] and a reduction in their degradation [32]. This adaptation of the ECS was reversed by chronic levodopa substitution in an animal model [33].

With regards to the effect of CB-1R on motor function, experimental studies yielded heterogeneous and partially conflicting results. Direct activation of CB-1R reduced dopamine release and resulted in an increase in bradykinesia, shown in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) animal model of PD [34]. Others reported improvement of motor impairment with cannabinoid receptor agonists, possibly due to receptor-independent mechanism of action [35, 36]. Furthermore, alleviation of levodopa-induced dyskinesia has been reported for cannabinoid receptor agonists and antagonists [31, 37].

In addition, ECS activation may confer neuroprotective such as direct receptor-independent mechanisms [38], activation of anti-inflammatory cascades in glial cells via CB-2R [39, 40], and anti-glutamatergic and thus anti-excitotoxic properties [41].

Clinical Research

Numerous case series and single case reports concluded that cannabinoids might have potential beneficial effects on PD symptoms.

In a large survey with 339 Czech PD patients, about 25 % of the respondents stated to regularly consume cannabis as an add-on therapy. Of these 85 patients, 39 (46 %) reported general improvement of their PD symptoms. 26 patients (31 %) reported a reduction of resting tremor, 38 patients (45 %) an improvement of bradykinesia, 32 patients (38 %) a decrease in muscle rigidity, and 12 patients (14 %) reduction of levodopa-induced dyskinesia [42].

An observational study from Israel involving 22 PD patients showed a reduction of the Unified Parkinson's Disease Rating Scale (UPDRS) motor score of 30 % thirty minutes after patients smoked cannabis. In addition, pain and sleep quality improved under long-term therapy with cannabis [43]. A very early and small case series from London with 5 PD patients evaluated the effect of cannabis smoking on resting tremor but found no improvement [44].

In contrast to the clearly positive effects described in single case reports and case series, data from randomized placebo-controlled trials (RCTs) on effects on PD motor symptoms are less encouraging. So far, 4 RCTs evaluating the effects of cannabinoids on altogether 49 PD patients have been published.

In a study by Chagas et al., PD patients were randomized to receive CBD daily in doses of either 75 mg, 300 mg, or placebo, with 7 patients randomized into each group. After 6 weeks, motor function (UPDRS motor score) and quality of life (Parkinson's Disease Questionnaire - PDQ-39) were assessed and compared to baseline. The improvement in PDQ-39 sum score was significantly higher in patients treated with 300 mg/day of CBD, while UPDRS scores did not differ between groups [45].

A study from Manchester evaluated the effect of nabilone, a CB-1R and CB-2R agonist, on levodopa-induced dyskinesia in 7 patients in a crossover design. A total dose of 0.03 mg/kg body weight was administered with half the dose 12 h before the remainder 1 h before an acute levodopa challenge, which then was repeated 14 days later when groups had been crossed over. Dyskinesia duration and severity were significantly reduced in the nabilone group. However, no change in the severity of PD symptoms and no difference in motor improvement after the acute levodopa challenge were observed. In the nabilone group, 5 of 7 patients experienced mild sedation, dizziness, hyperacusis, disorientation, and scenic visual hallucinations [46].

Caroll et al. studied the effect of Cannador®, a whole-plant extract with defined THC content and a THC to CBD ratio of about 2:1, on 17 PD patients. Over a period of 4 weeks, increasing doses of Cannador®, were administered b.i.d., up to a maximum THC daily dose of 0.25 mg/kg. Despite the double-blind design, 71 % of patients correctly identified their respective treatment arm. Neither levodopa-induced dyskinesia (assessed with UPDRS dyskinesia score and Rush Dyskinesia Rating Scale) nor UPDRS motor scores, PDQ-39 or sleep quality improved. In contrast, a (non-significant) trend towards an increase of dyskinesia severity with Cannador® treatment was observed [47].

In 2004, Mesnage et al. studied the CB-1R antagonist rimonabant, among others, and its effect on PD symptoms. Over a period of 16 days, 4 patients received 20 mg/day of rimonabant. At the end of period, neither UPDRS motor scores nor UPDRS dyskinesia scores changed significantly [48].

To date, only one other study investigating the effect of CBD on PD tremor has been registered (NCT02818777), aiming at recruiting 60 patients.

Psychotropic and Cardiovascular Side Effects

Considering the increased prevalence of psychotic symptoms in patients with idiopathic Parkinson's disease, psychotropic effects of cannabis and cannabinoids are of special interest (Chang and Fox 2016). In a study by Sieradzan and colleagues, 5 of 7 PD patients treated with the THC analog nabilone experienced psychotropic

side effects such as scenic visual hallucinations [46]. In the study of Lotan et al., 6 of the initially included 28 patients (21 %) with an average age of 65 years dropped out due to psychotic symptoms following cannabis consumption [43].

The primary active component responsible for the psychotropic effect of cannabis is THC. In clinical studies investigating the effects of CBD, no psychotic side effects were observed [45]. In an open-label study, 6 PD patients with psychiatric plus symptoms, such as illusions and hallucinations, and minus symptoms, such as withdrawal and depression, received CBD over a period of 4 weeks. Treatment was started with an initial daily dose of 150 mg and gradually increase over a period of 1 month up to a maximum daily dose of 400 mg [49]. The authors reported a significant reduction in psychotic symptoms, as measured with the Parkinson Psychosis Questionnaire (PPQ) and the Brief Psychiatric Rating Scale (BPRS).

Apart from psychotropic effects, cannabinoids are associated with adverse cardiovascular events. Non-motor PD symptoms include orthostatic hypotension caused by sympathetic cardiac denervation, among others [50]. Similarly, cannabis consumption can also lead to an orthostatic drop in blood pressure and even orthostatic syncope [51]. Due to sympathetic cardiac denervation, the ability to counteract a drop in blood pressure by increasing the heart rate is limited in PD patients. This, in turn, may intensify the impact of cannabinoids on orthostatic dysregulation. The study of Sieradzan et al. detected an orthostatic drop in systolic blood pressure in all patients. One patient in the nabilone group was unable to continue the study due to symptomatic orthostatic hypotension [46]. Furthermore, the increased sympathetic activity with cannabis consumption results in an increased myocardial oxygen demand. In patients with preexisting angina pectoris, exercise symptoms of myocardial hypoxia occur earlier with cannabis consumption [52, 53]. In addition, the risk of myocardial infarction is increased by 1 to 4.8 fold in cannabis users [54, 55]. With the possibility of cardiac comorbidities in PD patients, these adverse events should receive additional attention.

Conclusion

In summary, the positive effects of cannabinoid consumption on motor symptoms in patients with Parkinson's disease described in single case reports and case series have not been confirmed by the few placebo-controlled studies available as yet. Results of studies on cannabinoids for the treatment levodopa-induced dyskinesia have been inconsistent. The postulated beneficial effects of cannabinoids are opposed by potential side effects, such as hallucinations and orthostatic hypotension, which require special attention in PD patients.

Therefore, the clinical use of cannabinoids in patients with Parkinson's disease should be preceded by careful individual risk-benefit assessments. Currently, it should be limited to symptoms for which positive effects can be expected from other indications for cannabinoids, such as refractory pain or sleep disorders. In view of the extended approval of cannabinoids, further controlled studies are urgently needed to provide data that support evidence-based treatment recommendations, and to increase confidence in the safety of prescribing cannabinoid therapies.

Conflict of Interest

Dr. Florin Gandor, MD: Fees for advisory board participation: AbbVie Pharma. Lecture fees: MERZ Pharma, Prof. Georg Ebersbach, MD: Consultancy fees: AOK Nordost. Fees for advisory board participation: AbbVie Pharma, Grünenthal Pharma, Neuroderm Inc., GE Healthcare GmbH. Lecture fees: AbbVie Pharma, BIAL Pharma, Desitin Pharma, Licher GmbH, TEVA Pharma, UCB Pharma, Zambon Pharma, Medtronic, Royalties: Kohlhammer Verlag

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