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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Evidence for the use of cannabinoids in Parkinson's disease

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Abstract
Cannabis and synthetic cannabinoid formulations have now been legally approved in several countries for treatment of patients with Parkinson's disease (PD). Hence, PD patients consult physicians more frequently for prescription of cannabinoids to alleviate symptoms that might not respond well to dopaminergic treatment. Despite the increasing volume of research generated in the field of cannabinoids and their effect on Parkinson's disease, there is still paucity of sufficient clinical data about the efficacy and safety in PD patients. There is increasing understanding of the endocannabinoid system, and the distribution of cannabinoid receptors in basal ganglia structures might suggest potential benefit on parkinsonian symptoms. Concerning clinical research, only one of to date four conducted randomized placebo-controlled trials showed an effect on motor symptoms with alleviation of levodopa-induced dyskinesia. There are a growing number of uncontrolled trials and case reports that suggest beneficial effects of cannabinoids in PD patients. However, the variety of substances investigated, the varying routes of intake, differing doses and time courses make it difficult to compare data. We here provide an overview of the current literature in this field and discuss a pragmatic approach for the clinical use of cannabinoids in PD.

Keywords Cannabinoids · THC · Parkinson's disease · Therapy

Introduction

Due to a change in German law in March 2017, medical cannabis can be prescribed and is reimbursed by public and private health insurers for patients with severe symptoms of Parkinson's disease (PD), when previous therapies were unsuccessful or not tolerated, and a positive effect of cannabis on disabling symptoms is imaginable. Hereby, for the first time a substance has been approved without a specific indication and without any standard study demonstrating efficacy or safety. This led to an intense demand of patients for treatment with cannabinoids which is supported by a broad media interest and spectacular case reports on internet platforms showing tremendous improvement of parkinsonian symptoms such as dyskinesia or tremor after application of marijuana. Between June 2017 and April 2018, prescriptions of unprocessed marijuana leaves have increased more than fivefold up to 2.33 million Euro per month while prescriptions of standardized cannabinoid formulations are quite stable (Stellungnahme GKV-Spitzenverband Aug/2018).

The unusual approval of cannabinoids has led to a growing scientific interest in the potential therapeutic properties of cannabis for several, especially chronic diseases [for review see Mainka et al. (2018)]. In PD, high concentrations of cannabinoid receptors have been found in the basal ganglia (Giuffrida et al. 2005), and the influence of the endocannabinoid system on basal ganglia functioning and corticostriatal processing has recently been investigated intensively in parkinsonian models. However, there is still lack of clinical data on the use of cannabinoids in PD patients.

This article aims to provide an overview of the cannabinoid system, its potential impact for treatment of parkinsonian symptoms and the present experimental and clinical data in PD.

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Cannabinoids and the endocannabinoid system (ECS)

Cannabis sativa (marijuana) contains more than 100 phytocannabinoids (ElSohly and Gul 2014) with the psychotropic delta9-tetrahydrocannabinol (Δ^9-THC) being the most abundant, the non-psychotropic cannabidiol (CBD) being the second most abundant component. Similar to the endocannabinoids produced by the human body such as anandamide or 2-arachidonylglycerol (2-AG), these phytocannabinoids act via the cannabinoid receptors 1 (CB-1R) and 2 (CB-2R) which are the two most important receptors of the endocannabinoid system (ECS). In analogy to anandamide, Δ^9-THC in vitro activates both CB-1R and CB-2R. Due to CYP3A4 processing, some anandamide metabolites show higher affinity to CB-2R than CB-1R (Pratt-Hyatt et al. 2010). CBD in contrast does not elicit direct action on CB-R. Experimental evidence suggests agonism at, among others, 5-hydroxytryptamine receptors, transient receptor potential (TRP)-like channels and peroxisome proliferator-activated γ (PPARγ) receptors (Navarro et al. 2018). Moreover, recent data suggest a functional antagonism by modulating CB-R1 (Laprairie et al. 2015) and CB-R2 (Martinez-Pinilla et al. 2017) function. It might therefore lack detectable psychoactivity compared to Δ^9-THC.

CB-1R is primarily located in the nervous system. High concentrations have been found in the hippocampus, the association cortex, cerebellum, basal ganglia [especially in the medial part of the internal pallidum (GPi)], the dorsal roots of the spinal cord, and peripheral nerves, with almost no traceability in the thalamus and brain stem. CB-2R is mainly expressed in the gastrointestinal tract, in lymphatic tissue and peripheral nervous system but also in the CNS, primarily in neurons of the dorsal nucleus of the vagus nerve, the nucleus ambiguus, the spinal trigeminal nucleus, and on microglia. CB-1R and CB-2R are G protein-coupled receptors, which inhibit the activity of the adenyl-cyclase via the G_0/G_i unit, thereby influencing the release of neurotransmitters such as glutamate, dopamine and acetylcholine. Other transmitter pathways including serotonergic, GABAergic (γ-aminobutyric acid), NMDA (*N*-methyl-D-aspartate) and opioid systems are also modulated via indirect mechanisms. Amongst the other G protein-coupled receptors of the ECS, it was recently shown that the TRPV1-receptor (transient receptor potential cation channel subfamily V member 1) is also expressed in the basal ganglia (Stampanoni et al. 2017). Overall, the ECS regulates synaptic transmission via feedback mechanisms to avoid excitatory and inhibitory excesses. Furthermore, the ECS activates the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway via the $G_{\beta\gamma}$ complex, a pathway that has regulatory properties regarding cell development, cell differentiation and apoptosis. 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 (for reviews see Gandor and Ebersbach 2017; Mainka et al. 2018).

Experimental studies suggesting potential implications of cannabinoids for treatment of motor complications and neuroprotection in experimental models of Parkinson's disease

Cannabinoids modulate basal ganglia function on two levels which are especially relevant for levodopa-induced dyskinesia (LID), i.e. the glutamatergic/dopaminergic synaptic neurotransmission and the cortico-striatal plasticity. Furthermore, activation of the ECS might induce neuroprotective effects related to direct receptor-independent mechanisms (Carroll et al. 2012), activation of anti-inflammatory cascades in glial cells via CB-2R (Klein 2005; Lastres-Becker et al. 2005), and anti-glutamatergic anti-excitotoxic properties (Fernandez-Ruiz et al. 2010a).

Effect of cannabinoids on synaptic neurotransmission

Early animal studies demonstrated an effect of cannabinoids on the catecholaminergic and dopaminergic systems (Garriott et al. 1967; Howes and Osgood 1974). CB-1R and the endocannabinoid agonists anandamide and 2-AG occur in high concentrations in the dopaminergic system, including the striatum (Herkenham et al. 1991), where they modulate dopaminergic transmission as a retrograde feedback system on presynaptic glutamatergic and GABAergic nerve endings (Pertwee and Ross 2002). Cannabinoid agonists are thought to enhance GABA-induced signal transduction in the basal ganglia's indirect loop by inhibiting GABA uptake into the lateral part of the GPi. Activation of CB-1R at glutamatergic synapses suppresses the excitatory drive onto NMDA and AMPA receptors on dopaminergic neurons resulting in suppression of excitation. Both mechanisms may contribute to an anti-dyskinetic effect (for review see Covey et al. 2017). Especially the medial part of the GPi, the main thalamocortical output region within the basal ganglia expresses high concentration of CB-1R (Sierra et al. 2015).

CB-2R have been found on human nigrostriatal dopaminergic neurons (Garcia et al. 2015), which suggests direct modulating properties of the ECS on dopaminergic transmission (Stampanoni et al. 2017). Nigrostriatal neurons, however, do not express CB-1R (Julian et al. 2003), but are

influenced by the endocannabinoid system (Fernandez-Ruiz 2009; Fernandez-Ruiz et al. 2010b) via CB-1R expressing GABAergic, glutamatergic, and opioidergic neurons (Gubellini et al. 2002; van der Stelt and Di Vincenzo 2003; Centonze et al. 2007). In addition, some endocannabinoids have been found to interact with TRP channels (Starowicz et al. 2007), which are expressed on dopaminergic neurons (Mezey et al. 2000).

Activation of CB-1R in mesencephalic brain areas has furthermore been described to increase acetylcholine release and thereby reduce the local cholinergic deficit in PD (Chagas et al. 2014a). In addition, interaction of cannabinoids with the serotonergic system might also influence LID: striatal dopaminergic denervation leads to a shift of levodopa conversion into dopamine from dopaminergic into serotonergic neurons, which results in a non-physiologic pulsatile dopamine release (false transmitter) (Espay et al. 2018).

The activating properties of a ligand with low CB-receptor affinity, such as Δ^9-THC depend mainly on the CB-receptor concentration on a target structure. Since CB-receptor concentration varies widely between different brain areas, this might explain the different properties CB-ligands have on the brain. Furthermore, the relative sensitivity of GABAergic and glutamatergic neurons to CB1-R ligands differ between species (Pertwee 2008).

Effect of cannabinoids on cortico-striatal plasticity

Experimental in vivo PD studies indicate that the ECS modulates cortico-striatal synaptic plasticity. In conditions with LID, CB-1R agonists induce an anti-dyskinetic effect by reducing abnormal dopamine induced cortico-striatal long-term potentiation (LTP) and promoting long-term depression (LTD), which makes glutamatergic synapses less excitable to future stimulation. Inhibition of CB-1R reverses this anti-dyskinetic effect [for review see Stampanoni et al. (2017)].

An increase in ECS activity was detected both in a PD animal model and in human tissue analyses from PD patients (Fernandez-Ruiz et al. 2011), showing an upregulation of cannabinoid receptors (Gomez-Galvez et al. 2016; Lastres-Becker et al. 2001), an accumulation of cannabinoid receptor agonists (Di Marzo et al. 2000; van der Stelt et al. 2005) and a reduction in their degradation (Gubellini et al. 2002). This adaptation of the ECS was reversed by chronic levodopa substitution in an animal model (Maccarrone et al. 2003).

Effect of cannabinoids on neuroprotection

Cannabinoids have been reported to provide neuroprotection not only in cell tissue, but also in rodent PD models. One study provided evidence that Δ^9-THC acted as a neuroprotective substance in rats with hemiparkinsonism. Chronic administration of this cannabinoid after they were subjected to unilateral lesions of the nigrostriatal dopaminergic neurons with 6-hydroxydopamine produced a significant recovery in the impairment of dopaminergic transmission caused by the toxin, suggesting a reduction of dopaminergic cell death (Lastres-Becker et al. 2005). In another study, the CB-2R agonist HU-308 and the inhibitor of the endocannabinoid inactivation (IoEI) AM404, but not the CB-1R agonist ACEA or the IoEI UCM707 reversed 6-OHDA-induced dopamine (DA) depletion or tyrosine hydroxylase deficit (Garcia-Arencibia et al. 2007). Both study groups suggested potential receptor-independent antioxidant or anti-inflammatory properties of those cannabinoids that provide neuroprotection against the progressive degeneration of nigrostriatal dopaminergic neurons. The activation of CB-2R, but not CB-1R, might exhibit some neuroprotective potential in PD which is potentially based on an anti-inflammatory effect (Garcia-Arencibia et al. 2007; Gomez-Galvez et al. 2016). This assumption is supported by a rodent PD model study, where CB-2R agonism protected against MPTP-induced nigrostriatal degeneration by inhibiting microglial activation/infiltration (Price et al. 2009).

Effect of cannabinoids on motor function in animal studies and humans

With regard to the effect of cannabinoids on motor function, studies in animal models of PD yielded heterogeneous and partially conflicting results. CB-1R agonists have been found to reduce akinesia, motor impairment (Fernandez-Espejo et al. 2004; Kreitzer and Malenka 2007; van Vliet et al. 2008) and tremor (Sanudo-Pena and Walker 1997), potentially due to a receptor-independent mechanism (Kreitzer and Malenka 2007; Fernandez-Espejo et al. 2004). In contrast, another group reported an increase in bradykinesia after administration of Δ^9-THC or the cannabinoid agonist levonantradol in primates (Meschler et al. 2001). During the same study, a CB-1R antagonist failed to alleviate MPTP-induced parkinsonian symptoms. Another study in rodents, however, found reduced akinesia in 6-hydroxydopamine lesioned rats after administration of the CB-1R antagonist rimonabant (Kelsey et al. 2009). Furthermore, antidyskinetic effects have been described after administration of both CB-1R agonists (Fox et al. 2002; Kelsey et al. 2009) and antagonists (van der Stelt et al. 2005; van Vliet et al. 2008).

Clinical studies in patients with Parkinson's disease

Numerous case series and single case reports concluded that cannabinoids might have potential beneficial effects on PD motor symptoms such as akinesia, tremor or dyskinesia. In contrast, data from randomized placebo-controlled trials

(RCTs) on effects on PD motor symptoms are rare and less encouraging. So far, 4 RCTs evaluating the effects of CBD, THC/CBD, nabilone, and rimonabant with altogether 49 PD patients have been published. Of those, 3 RCTs failed to show a significant effect of cannabinoids on parkinsonian motor symptoms or LID when applied as add-on therapy. Overall, CB-1R antagonists did not reduce bradykinesia (Mesnage et al. 2004), and the effect on tremor is not clear (Consroe 1998; Sieradzan et al. 2001; Carroll et al. 2004). However, one RCT reports reduced LID after administration of the CB-1R agonist nabilone (Sieradzan et al. 2001). Several case series and reports suggest improvement of non-motor symptoms with cannabinoids, but there is lack of RCTs addressing these effects.

Uncontrolled studies: surveys and prospective observational studies ("case series")

In an anonymous survey of 339 Czech PD patients, 25% reported to take cannabis buds orally ("half a teaspoon of fresh or dried leaves" with a meal). Of these 85 patients, 46% reported general improvement of their PD symptoms with reduction of resting tremor (31%), decrease in bradykinesia (45%), reduction of muscle rigidity (38%) and improvement of LID (14%). 5% of patients experienced worsening of symptoms (Venderova et al. 2004).

In a Web-based self-reported assessment of PD and MS patients with a high recruitment rate (96.1%), 454 of 595 (76.3%) subjects were PD patients. 36.6% of them either inhaled or, to a least extent, consumed cannabis orally, mainly for medicinal use (73.7%) and for longer than 12 months (72.3%). The cannabis using PD patients reported high efficacy of cannabis (6.2 [SD 1.8] on a scale from 0 to 7) with lower levels of disability, specifically in domains of mood, memory, and fatigue. Furthermore, 47.8% reported reducing prescription medication since beginning cannabis use (Kindred et al. 2017).

An observational study in 22 Israeli patients showed a significant motor improvement (UPDRS III) in 30% of subjects after smoking cannabis (0.5 g, unspecified composition) with improvement of the UPDRS subitems resting tremor, rigidity, and bradykinesia, and the non-motor aspects sleep and pain (Lotan et al. 2014).

In contrast, tremor did not improve in a case series with 5 PD patients smoking a single cigarette with a comparatively high (first) dose of 1 g marijuana (2.9% THC) (Frankel et al. 1990).

In an open-label study in 6 patients with PD-associated psychosis, CBD powder dissolved in oil and administered orally in a capsule (mean dose of 400 mg/day) significantly reduced psychiatric positive symptoms, such as illusions and hallucinations, and negative symptoms, such as withdrawal and depression, assessed with the Brief Psychiatric Rating Scale (BPRS). Furthermore, the total UPDRS score assessed as secondary outcome measurement significantly improved at a 4-week follow-up (Zuardi et al. 2009).

In an open-label study, Zuardi et al. treated six PD patients with psychiatric plus symptoms, such as illusions and hallucinations, and minus symptoms, such as withdrawal and depression, with CBD over a period of 4 weeks and reported a significant reduction in psychotic symptoms, as measured with the Parkinson Psychosis Questionnaire (PPQ) and the Brief Psychiatric Rating Scale (BPRS) (Zuardi et al. 2009).

In a small uncontrolled study, 4 PD patients with REM sleep behaviour disorder received 75 or 300 mg 99.9% purified CBD orally per day (dissolved in corn oil and placed in gelatin capsules) and reported reduced or completely eliminated agitation, beating, kicking and nightmares (Chagas et al. 2014a).

Randomized, double-blind, placebo-controlled trials

In a randomized, double-blind, placebo-controlled crossover trial, Caroll et al. studied the potential effect of a standardized whole-plant extract with a defined THC content, a THC-to-CBD ratio of about 2:1 and body-weight adapted dosage on dyskinesia in 17 PD patients. Despite the double-blind design, 71% of patients correctly identified their respective treatment arm. Cannabis was applied as oral cannabis extract and well tolerated, but showed no alleviation or worsening of parkinsonian symptoms. There was no evidence for a treatment effect on LID as assessed by the UPDRS and Rush Dyskinesia Rating Scale, or on any of the secondary outcome measures such as other UPDRS motor scores, PDQ-39, pain or sleep quality (Carroll et al. 2004).

Chagas et al. randomized 21 PD patients to receive CBD daily in doses of either 75 mg, 300 mg, or placebo, with each group containing 7 patients. CBD was provided in powdered form, dissolved in corn oil and placed in gelatin capsules. After 6 weeks, motor function (UPDRS motor score) and quality of life (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 (Chagas et al. 2014b).

Sieradzan et al. evaluated the effect of the CB-1R and CB-2R agonist nabilone (administered orally as capsule of same colour and taste compared to placebo) on levodopa-induced dyskinesia in 7 patients in a crossover design. A total dose of 0.03 mg/kg body weight was administered in 2 portions 12 h and 1 h before an acute levodopa challenge, which then was repeated 14 days later when groups had been crossed over. Severity, but not duration of dyskinesia improved significantly 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 (Sieradzan et al. 2001).

In an exploratory, randomized, double-blind, placebo-controlled study, Mesnage et al. evaluated among others the effects of the CB-1R antagonist rimonabant on the severity of motor symptoms and LID after administration of a single dose of levodopa in 4 PD patients. Rimonabant was well tolerated, but did not improve UPDRS motor scores or the UPDRS dyskinesia score (Mesnage et al. 2004).

Table 1 gives an overview of surveys, case series, open-label studies and randomized controlled trials evaluating the effects of cannabinoids or cannabinoid antagonists in Parkinson's disease.

Table 2 gives an overview on single motor- and non-motor symptoms assessed in trials evaluating the effects of cannabinoids or cannabinoid antagonists in Parkinson's disease.

Tolerability, medical risks and contraindications of prescribing cannabinoids in PD patients

Medical cannabinoids containing THC can cause central, gastro-intestinal and cardiovascular unwanted effects, such as somnolence, dizziness, nausea, vomiting, tachycardia, hypotension, dry mouth, diarrhoea, loss of balance or fatigue, as well as psychiatric symptoms such as disorientation, confusion, hallucinations, and altered mood. Tolerance to these side effects usually develops within a short time. Withdrawal symptoms of therapeutically used cannabis have hardly ever been a problem (Grotenhermen and Muller-Vahl 2012; Whiting et al. 2015). While THC is responsible for the psychotropic effects of cannabis, clinical studies did not reveal psychotic side effects for CBD (Chagas et al. 2014b). CBD does not seem to induce psychiatric symptoms, but may have some anti-psychotic effects in PD patients (Zuardi et al. 2009).

Because of the high prevalence of psychotic symptoms in PD patients, the psychotropic effects of THC are of special interest (Chang and Fox 2016). Sieradzan et al. reported psychotropic side effects such as scenic visual hallucinations in 5 of 7 PD patients treated with the synthetic THC analogue nabilone (Sieradzan et al. 2001). In a study by Lotan et al. 6 of included 28 patients (21%) dropped out due to side effects including psychotic symptoms following cannabis application (Lotan et al. 2014). Furthermore, PD patients often show an insufficient adherence to the prescribed medication with a drop-out rate of 10–67%, depending on the study (Malek and Grosset 2015). Prevalence of dopaminergic dysregulation syndrome consisting of an addictive use of dopaminergic substances is 3.4–4.1% in PD patients (Giovannoni et al. 2000; Pezzella et al. 2005). Since abuse mostly occurs with fast-acting substances such as soluble levodopa or apomorphine s.c. (Roland et al. 2016), inhalative cannabis should be handled with special care in PD patients because they provide a significantly faster onset of action compared to manufactured drugs or extracts. However, long-term data for safety and tolerability of medically used inhalative cannabinoids are lacking. It must furthermore be emphasized that in THC-based preparations similar to those available for non-medical use, the psychotropic adverse effects outweigh potential therapeutic effects.

Considering the cardiovascular side effects, cannabinoids can lead to an orthostatic drop in blood pressure and even orthostatic syncopes (Sidney 2002). This might have a special impact on PD patients, since orthostatic hypotension caused by sympathetic cardiac denervation is a frequent non-motor-symptom in PD (Barone et al. 2009). In accordance, Sieradzan et al. described an orthostatic drop in systolic blood pressure in all seven PD patients after nabilone intake with one drop-out due to symptomatic orthostatic hypotension (Sieradzan et al. 2001).

Although medical guidelines defining contraindications for using cannabis are missing, there is consensus that cannabinoids should not be prescribed in patients with severe personality disorders, schizophrenia and other psychotic disorders, or in patients with a history of substance abuse (Izzo et al. 2009; Ablin et al. 2016). Cannabis consumption goes along with increased sympathetic activity resulting in an increased myocardial oxygen demand. In accordance, symptoms of myocardial hypoxia occur earlier in patients with pre-existing angina pectoris (Prakash et al. 1975; Aronow and Cassidy 1974), and the risk of myocardial infarction is increased by 1- to 4.8-fold in cannabis users (Jouanjus et al. 2014; Mittleman et al. 2001). Therefore, a strict indication is recommended in patients with cardiovascular disease (Health Canada 2017). Cannabinoids may promote fatty liver disease and should be avoided in patients with chronic hepatitis C (Hezode et al. 2008). In patients with impaired liver or kidney function, the effect of THC and CBD may be increased or prolonged. Pregnant women and those considering becoming pregnant should be advised to avoid using marijuana or other cannabinoids; nursing mothers should not be prescribed cannabinoids because Δ^9-THC accumulates in breast milk and metabolites have been found in infant faeces, indicating that THC is absorbed and metabolized by the infant (The American College of Obstetricians and Gynecologists Committee 2015; Health Canada 2017).

Table 1 Overview of surveys, case series, open-label studies and randomized controlled trials evaluating the effects of cannabinoids or cannabinoid antagonists in Parkinson's disease

Author [References]	Year	Study design	Sample size	Active substance evaluated	Results
Venderova et al. (2004)	2004	Open anonymous survey	85	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%
Kindred et al. (2017)	2017	Open anonymous survey	454	73.7% reported medicinal cannabis use	High efficacy with cannabis, improvement of non-motor symptoms, reduction of prescribed medication
Lotan et al. (2014)	2014	Case series	22	After baseline screening using motor and non-motor tests, 0.5 g cannabis smoked, reassessment after 30 min	Improvement of tremor and bradykinesia
Frankel et al. (1990)	1990	Case series	5	1 g cannabis (with 2.9% THC) smoked once	No improvement of tremor
Chagas et al. (2014a)	2014	Case series	4	3 patients 75 mg, 1 patient 300 mg daily dose of CBD	Improvement of parasomnia
Zuardi et al. (2009)	2009	Open-label study	6	400 mg/day CBD powder dissolved in oil administered as capsule	Improvement of psychiatric plus and minus symptoms, mild improvement
Sieradzan et al. (2001)	2001	Randomized, double-blind, placebo-controlled crossover design	7	Randomized to single exposure of 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. (2004)	2004	Randomized, double-blind, placebo-controlled crossover design	17	Randomized to 2.5 mg THC + 1.25 mg CBD daily for 4 weeks or placebo, crossover after 2-week wash-out period	No improvement in LID severity duration, motor symptoms quality of life or sleep
Chagas et al. (2014b)	2014	Randomized, double-blind, placebo-controlled	21	Randomized to 75 mg, 300 mg daily dose of CBD or placebo for 6 weeks	Improvement of PDQ-39 with 300 mg CBD; UPDRS unchanged
Mesnage et al. (2004)	2004	Randomized, double-blind, placebo-controlled	4	Randomized to 20 mg rimonabant daily or placebo for 16 days	No change in motor impairment or LID in neither On- nor Off-state

Table 2 Studies with cannabinoids or cannabinoid antagonists addressing single motor- and non-motor symptoms in Parkinson's disease

Symptom	Design	Sample size	Duration	Primary outcome	Application form	Dosage	Outcome	References
Rigor, tremor, bradykinesia	Open-label observational study in patients at least 2 months on cannabis medication	22	Single evaluation, 30 min after inhalation of cannabis	Improvement of UPDRS motor score	Smoking of cannabis	0.5 g (THC/CBD content unknown)	Significant improvement of UPDRS III from 33.1 ± 13.8 to 23.2 ± 10.5 with significant improvement of subitems resting tremor, rigidity and bradykinesia, but not posture	Lotan et al. (2014)
	Open-observational case series	5	Single dose	Parkinsonian disability, particularly tremor	Smoking of cannabis	1 g shredded leaves (2.9% THC)	No improvement of tremor	Frankel et al. (1990)
	Questionnaire survey	85	Once	% of cannabis use, improvement of parkinsonian symptoms	"Fresh or dried leaves orally"	"Half a teaspoon"	Cannabis use by 25% of patients; 45.9% with mild to substantial alleviation of general PD symptoms, 30.6% improvement of resting tremor, 44.7% improvement of bradykinesia, 37.7% improvement of rigidity, 4% worsening of symptoms	Venderova et al. (2004)
	Double-blind, randomized, placebo-controlled crossover study	17	2×4 weeks, 2 weeks wash-out phase	UPDRS III	Orally	2.5 mg THC + 1.25 mg CBD (Cannador) or placebo	No positive effect	Carroll et al. (2004)
	3-Arm, explorative, randomized, double-blind, placebo-controlled	21	6 weeks	UPDRS III	Orally	75 or 300 mg CBD	No positive effect	Chagas et al. (2014b)
	Exploratory, randomized, double-blind, placebo-controlled	4	16 days	UPDRS III after suprathreshold dose of levodopa	Unknown	20 mg rimonabant	No improvement of UPDRS III	Mesnage et al. (2004)

Table 2 (continued)

Symptom	Design	Sample size	Duration	Primary outcome	Application form	Dosage	Outcome	References
Levodopa-induced dyskinesia (LID)	Double-blind, randomized, placebo-controlled crossover study	7	Levodopa challenges 2 weeks apart	Intensity (Rush Dyskinesia Disability Scale) and duration of dyskinesia after a standardized levodopa challenge	Orally	Nabilone 0.03 mg/kg body weight 12 h and 1 h before levodopa administration or placebo	Nabilone significantly reduced total LID compared with placebo (17 vs. 22), no difference in duration of dyskinesia (98.2% ± 0.1% vs. 96.1% ± 1.7%), nabilone without effect on antiparkinsonian levodopa action	Sieradzan et al. (2001)
	Double-blind, randomized, placebo-controlled crossover study	17	2×4 weeks, 2 weeks wash-out phase	UPDRS IV, Rush Scale, Dyskinesia ADL	Orally	2.5 mg THC + 1.25 mg CBD (Cannador) or placebo	No positive effect on LID	Carroll et al. (2004)
	Questionnaire survey	339	Once	Improvement of parkinsonian symptoms	"Fresh or dried leaves orally"	"Half a teaspoon"	14.1% improvement of LID	Venderova et al. (2004)
	3-Arm, explorative, randomized, double-blind, placebo-controlled	21	6 weeks	UPDRS IV	Orally	75 or 300 mg CBD or placebo	No changes of UPDRS IV	Chagas et al. (2014b)
	Exploratory, randomized, double-blind, placebo-controlled	4	16 days	UPDRS IV after suprathreshold dose of levodopa	Unknown	20 mg rimonabant	No improvement of UPDRS IV	Mesnage et al. (2004)
Sleep	Observational case series	4	6 weeks	PD patients with REM sleep disorder	Orally	75 or 300 mg CBD	(complete) Reduction of agitation, limb movements and nightmares in all patients	Chagas et al. (2014a)
	Open-label observational study in patients at least 2 months on cannabis medication	22	single evaluation, 30 min after inhalation of cannabis	Improvement of sleep quality on visual analogue scale	Smoking of cannabis	0.5 g (THC/CBD content unknown)	12 patients reported greatly improved quality of sleep, 8 had mild relief	Lotan et al. (2014)
	Double-blind, randomized, placebo-controlled crossover study	17	2×4 weeks, 2 weeks wash-out phase	Visual analogue sleep scale	Orally	2.5 mg THC + 1.25 mg CBD (Cannador) or placebo	No positive effect on sleep	Carroll et al. (2004)

Table 2 (continued)

Symptom	Design	Sample size	Duration	Primary outcome	Application form	Dosage	Outcome	References
Pain	Open-label observational study in patients at least 2 months on cannabis medication	22	Single evaluation, 30 min after inhalation of cannabis	Improvement of Short-Form McGill Pain Questionnaire, pain intensity scale	Smoking of cannabis	0.5 g (THC/CBD content unknown)	Present pain intensity significantly improved from 2.7 ± 1.7 vs. 0.8 ± 1.1	Lotan et al. (2014)
	Double-blind, randomized, placebo-controlled crossover study	17	2 x 4 weeks, 2 weeks wash-out phase	McGill Pain Score	Orally	2.5 mg THC + 1.25 mg CBD (Cannador) or placebo	No positive effect on pain	Carroll et al. (2004)
Psychosis	Open-label pilot study	6	4 weeks	Brief Psychiatric Rating Scale, Parkinson Psychosis Questionnaire	Orally	150 mg CBD starting dose, weekly dosage increase by 150 mg depending on clinical response	Significant decrease of psychotic symptoms	Zuardi et al. (2009)
Quality of life	Double-blind, randomized, placebo-controlled crossover study	17	2 x 4 weeks, 2 weeks wash-out phase	PDQ-39	Orally	2.5 mg THC + 1.25 mg CBD (Cannador) or placebo	No positive effect on quality of life	Carroll et al. (2004)
	3-Arm, explorative, randomized, double-blind, placebo-controlled	21	6 weeks	PDQ-39	Orally	75 or 300 mg CBD or placebo	Significant improvement of quality of life (300 mg CBD group)	Chagas et al. (2014b)
PD symptoms	Web-based survey	454	Once	Effectiveness on Likert scale (0: not helpful, 7: very helpful)	Unknown	Unknown	High efficacy of cannabis (6.2 ± 1.8)	Kindred et al. (2017)

Conclusion

Changes in legislation allow for the treatment of severely affected PD patients with medical cannabis or cannabinoids when standard therapy remains insufficient to adequately control PD symptoms.

However, based on the currently available data from only four double-blind randomized placebo-controlled trials with altogether not more than 49 patients, no profound treatment recommendation can be given at present.

Moreover, trials were extremely heterogeneous regarding applied subtype of cannabinoids, route and time course of administration, drug concentration and assessment period. Only one RCT showed improvement of motor symptoms with reduction of LID. Even considering results of all available non-RCTs, i.e. one open-label study, three case series and two surveys, cannabinoids showed little to no effect on motor symptoms and only some minor influence on non-motor symptoms in PD patients.

However, a growing body of preclinical research demonstrates the influence of cannabis and cannabinoids on the dopaminergic system. Thus, further evidence-based clinical studies on the efficacy and tolerability of cannabinoids in patients with Parkinson's disease are needed to elicit potential therapeutic effects and allow for an evidence-based treatment recommendation.

Compliance with ethical standards

Conflicts of interest Prof. Carsten Buhmann, MD: fees for advisory board participation: UCB Pharma, Zambon. Lecture fees: AbbVie Pharma, BIAL Pharma, Desitin, GE Healthcare, Grünenthal Pharma, Licher GmbH, Medtronic, Novartis, TAD Pharma, UCB Pharma, Zambon Pharma; Dr. Tina Mainka: royalties: Urban Fischer in Elsevier Verlag. Honoraria for lectures: GE Healthcare. Dr. Florin Gandor, MD: fees for advisory board participation: AbbVie Pharma. Lecture fees: MERZ Pharma, BIAL Pharma; Prof. Georg Ebersbach, MD: consultancy fees: AOK Nordost. Fees for advisory board participation: AbbVie Pharma, Grünenthal Pharma, Neuroderm Inc., Stada Pharma, Neurocrine Inc. Lecture fees: AbbVie Pharma, BIAL Pharma, Britannia Pharma, Desitin Pharma, Licher GmbH, UCB Pharma, Zambon Pharma, royalties: Kohlhammer Verlag, Thieme Verlag.

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