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Commentary

Advice to People with Parkinson's in My Clinic: Cannabis

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Abstract. Cannabis (in all the varied methods of delivery) continues to garner significant attention as a potential therapeutic intervention for neurodegenerative disorders, including Parkinson's disease (PD). The recent legalization of personal use of cannabis products in some parts of the world has increased this interest and with it, potential availability to many more people. However, such access has led to more questions than answers for both patients and health care professionals. These include what symptom(s) of PD will cannabis products treat; what dose; what type of cannabis product to use and what are the side effects?

Keywords: Cannabis, marijuana, Parkinson's disease

Cannabis (in all the varied methods of delivery) continues to garner significant attention as a potential therapeutic intervention for neurodegenerative disorders, including Parkinson's disease (PD). The lack of effective treatments for many symptoms in PD is what drives patients to ask for alternative options. The recent legalization of personal use of cannabis products in some parts of the world has increased this interest and with it, potential availability to many more people. However, such access has led to more questions than answers for both patients and health care professionals. These include what symptom(s) of PD will cannabis products treat; what dose; what type of cannabis product to use and what are the side effects? Here we summarize the latest pre-clinical and clinical data on cannabis for treatment of PD symptoms, currently available products and the most frequently reported side effects in the literature. We also provide our personal recommendation regarding the use of cannabis products for patients with PD (see Box 1).

CANNABINOID PHARMACOLOGY AND AVAILABLE PRODUCTS

The phytocannabinoid, *Cannabis sativa* (marijuana), has been used for centuries as a treatment for medical symptoms, including pain and seizures. *Cannabis sativa* contains more than 100 chemicals (called cannabinoids); the two principal components include Delta-9-tetrahydrocannabinol ($^{\Delta 9}$THC) and cannabidiol (CBD) [1]. The biological effects of

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Box 1. Cannabis-products for Parkinson Disease symptoms

Clinical Evidence

Motor symptoms

- Patient surveys have reported subjective benefits on tremor and no subjective benefit on other motor issues including dyskinesia. Higher $^{\Delta 9}$THC content seems to be more beneficial [33, 34].
- A metanalysis of 3 RCT studies reported a non-significant improvement in PD motor signs as assessed using the UPDRS III [35].
- In 2 small open-label, single-arm trials, there were improved UPDRS III scores within 30 min of vaping or smoking *Cannabis* [36, 37].
- Open-label trials of CBD reported improved UPDRS III scores compared to baseline over 2–4 weeks [38, 39].
- Three small RCT studies did not show improvement of levodopa-induced dyskinesia using a range of cannabis products (CBD and THC containing) [17, 40, 41].

Non-motor symptoms

- Patient surveys report the positive effects of *Cannabis* on anxiety, pain and sleep disorders. In two surveys, cannabinoids with higher THC content were reported as more effective [32–34, 43].
- RCT with small sample sizes and variable cannabis formulations and dosing regimen showed improvement in pain, insomnia and RBD [36, 37, 44–49].

Most common side effects

Abdominal pain, asthenia, blurred vision, constipation, drowsiness, dry mouth, headache, heart palpitations, orthostatic hypotension, psychosis, and vertigo [32–42].

What do we tell our patients?

1. There is a lack of evidence-based data on the effectiveness and safety of cannabis products in PD.
2. Cannabinoids may be an alternative therapeutic option for certain non-motor symptoms including insomnia, anxiety and pain; when other options for these non-motor symptoms have failed.
3. Patient surveys have shown that benefits may wane after a few weeks of use.
4. Overall from evidence to date, higher THC content does appear to provide more benefit, however with higher risk of psychosis as a side effect compared to CBD.
5. Caution that there may be variability in the amount of THC /CBD in any bought product due to lack of regulatory quality control of production.
6. Discourage the use of cannabis products in patients with cognitive impairment, behavioral disorders, orthostatic hypotension, or daytime sleepiness due to an increased risk of side effects.
7. There is a risk of substance abuse with use of any cannabis product.
8. Respiratory complications are a concern with use of inhaled cannabis products (vaping or smoking).

THC, tetrahydrocannabinol; CDB, cannabidiol; RCT, randomized clinical trials; PD, Parkinson's disease; UPDRS III, Unified Parkinson Disease Rating Scale part III; RBD, REM-sleep behavioral disorder.

cannabinoids are mediated primarily through two G-protein coupled receptors, cannabinoid receptor 1 and 2 (CB_1 and CB_2). CB_1 receptors are located in high concentrations in basal ganglia and spinal circuits while CB_2 are mainly located in peripheral immune system including spleen, thymus and leukocytes but also in brainstem and hippocampus as well as activated microglia [2–4]. $^{\Delta 9}$THC is the major psychoactive component of *Cannabis* and acts as a partial CB_1 and CB_2 agonist with antinociceptive, psychotropic, and muscle relaxant effects [5]. CBD, a non-psychoactive component of cannabis, has a low affinity for CB_1 and CB_2 receptors and functions as a negative allosteric modulator of CB_1 and also has non-CB receptor actions [5]. CBD also has potential antioxidant and anti-inflammatory properties [6].

The challenge with use of phytocannabinoids is that inhalation (smoking) may lead to respi-

ratory complications [5]. Thus for medical uses, three purified/synthetic oral or nasal spray delivery exogenous synthetic cannabinoids were developed. These include nabilone, dronabinol, and nabixamols respectively that are approved and licensed in many countries for patients with cancer, chronic pain, and epilepsy [7–9]. Dronabinol is a synthetic $^{\Delta 9}$THC used for anorexia and weight loss in AIDS and chemotherapy-induced nausea and vomiting (CINV) [10]. Side effects include heart palpitations, asthenia, abdominal pain, and amnesia. Nabilone is also synthetic $^{\Delta 9}$THC, approved for treatment of CINV [11]. The most frequently reported side effects include orthostatic hypotension, dry mouth, drowsiness, vertigo, psychosis, and headache. Nabiximols are *Cannabis sativa* plant extract that contain equal amounts of $^{\Delta 9}$THC and CBD administered as oromucosal spray [11] for spasticity, and the most reported side effects include dizziness, blurred vision and constipation. Thus although these synthetic CB_1 agonists are clinically available, the indications are restricted to the licensed use, and side effect profile is not insignificant.

Legalised personal use of cannabinoids has now led to a plethora of administration options, including oral oil suspension; sprays; oral edibles as well as vaping methods amongst others. The $^{\Delta 9}$THC:CBD ratio and other cannabinoid content varies in these products. Indeed there is variability in $^{\Delta 9}$THC:CBD content of the same plant depending on the extraction method used potentially leading to variable and higher than expected amounts of $^{\Delta 9}$THC vs. CBD [12]. Thus a major challenge is the lack of standardization for these personal-use preparations and potential variability in quantities/rations of cannabinoids in the same product between different providers.

PRECLINICAL EVIDENCE

There is evidence supporting a role for the cannabinoid system on motor control. Classic behavioural pharmacological studies showed high doses of CB_1 agonists in rodents affect motor function by inducing the '*cannabinoid tetrad*' of hypomobility; catalepsy, as well as analgesia and hypothermia [13]. Interest in cannabinoids for PD first arose from the finding that CB_1 receptors are selectively located on presynaptic GABA and glutamatergic terminals within basal ganglia circuits where stimulation can modulate pallidal and striatal activity, and thus reduce hyperkinetic movements such as levodopa-induced dyskinesia in PD [14, 15]. Preclinical studies in models of PD reported CB_1 agonists significantly reduce levodopa-induced dyskinesia, without affecting PD motor symptoms [16, 17]. However, CB_1 antagonists were also found to reduce levodopa-induced dyskinesia, thus illustrating the complexity of the pharmacology of cannabinoids [15]. These opposing effects may be due to endogenous cannabinoids, which are also implicated in basal ganglia function [18–22].

Changes in levels of the endocannabinoids, anandamide and 2-arachidonoylglycerol (2AG) have been shown in models of PD, both in untreated and following levodopa therapy and dyskinesia [15, 22]. The role of endocannabinoids on movement is likely linked to a neuromodulatory action as they are released on demand in active neurons and reduce neurotransmitter release with subsequent changes in striatal activity, with effects on long-term potentiation and depression neuroplasticity [20, 23–25]. However, to date, there is little evidence that cannabinoid agonists or antagonists have an antiparkinsonian action per se. Although a recent meta-analysis suggested efficacy of cannabinoids in improving some measures of bradykinesia and postural instability in rodent models of PD [26], the clinical applicability of these findings is unclear.

To date there are no preclinical studies evaluating cannabinoids in PD tremor due to lack of a validated model of PD rest tremor. Many PD patients also have postural tremor and a recent study using a rodent harmaline model of essential tremor, showed that a CB_1 agonist reduced tremor via an action on spinal astrocytes; possibly mediated via endocannabinoid modulation of purines within spinal neuronal networks [27].

Neuroprotective properties of cannabinoids have also been suggested via elevated CB_2 expression in microglial cells within the substantia nigra of humans and animal models of PD [28]. A systematic review of *Cannabis*-derived phytocannabinoids in PD preclinical models demonstrated neuroprotective effects evidenced by increased dopamine levels and prolonged dopaminergic neuronal survival [29].

There is limited preclinical evidence for benefit of cannabinoids for non-motor symptoms of PD. The rationale for pain, anxiety, and sleep has primarily come from clinical use in non-PD conditions. Preclinical evidence in (non-PD) rodent models of pain has demonstrated that cannabinoids alleviate allodynia or hyperalgesia probably via CB_1 receptors in the amygdala, thalamus, spinal cord and dorsal root ganglion.

In addition, effects on pain may be via non-CB receptors. For instance, $^{\Delta 9}$THC inhibits prostaglandin E-2 synthesis, stimulates lipoxygenase and decreases serotonin release in the trigemino-vascular system. $^{\Delta 9}$THC also activates the vanilloid-transient receptor potentials (TRPV2, TRPV3, TRPV4) located in the dorsal root ganglia and trigeminal ganglia, as well as the transient receptor potential ankyrin 1 (TRPA1) located in peripheral sensory neurons. CBD also functions as a TRPV-1 or capsaicin receptor agonist [4].

CLINICAL EVIDENCE: MOTOR SYMPTOMS

The largest challenge in sorting through the evidence is variability in types of cannabinoid used ($^{\Delta 9}$THC or CBD); the mode of administration (inhaled, vaporized, oils); variable doses and duration of use. Despite preclinical studies showing theoretical evidence for a role of cannabinoids in basal ganglia function, there remains low-level and conflicting clinical evidence of efficacy on motor symptoms, from patient-facing surveys and a small number of RCTs [30–32].

Patient-surveys, using a variety of cannabinoids, are helpful as large numbers of people are included and have more 'real-world' data compared to small RCTs. However, such surveys have inherent bias and subjectivity. Most surveys report mixed outcomes on all PD symptoms including motor and non-motor. Overall, surveys have reported subjective benefits on tremor and no subjective benefit on other motor issues including dyskinesia. To date, it is unclear as to the most effective type of cannabinoid or ratio of CBD: $^{\Delta 9}$THC used, although higher $^{\Delta 9}$THC content seems to be more beneficial.

In a large recent survey of 1,373 people with PD on cannabis use, where 86.7% knew the ratio/type of cannabis product they were using; 54.6% used products with higher CBD content, 30.2% higher $^{\Delta 9}$THC, and 15.2% similar amounts of $^{\Delta 9}$THC and CBD [33]. There were no significant differences in reported symptomatic improvements between the "higher $^{\Delta 9}$THC" and "similar $^{\Delta 9}$THC /CBD" groups except for tremor (OR 1.7, 95% CI 1.17, 2.57, $p = 0.01$), with "higher $^{\Delta 9}$THC" more likely to improve than "similar $^{\Delta 9}$THC /CBD". The most common use was oral administration, once daily, for less than six months. Most patients reported short duration of cannabis use (52.5% $\leq$6 months) compared to 33.0% who reported greater than one-year duration of use. Dry mouth, dizziness, and cognitive changes were common adverse effects (20.9%–30.8%, mean 1.13 to 1.21) [33].

In another recent survey of 261 PD patients on cannabis use [34], 66% used cannabis for tremor, but 23.0% had stopped in the previous six months, primarily due to a lack of symptom improvement. Method of use included spray or sublingual drops (in 29.1%), smoking (27.2%) and eating or swallowing (19.2%). A proportion, (22.2%) of all users did not know details about the type of cannabis used or concentration of CBD or $^{\Delta 9}$THC. Among those who did (77.8%), almost half did not know the specific type (48.8%) or dosage (47.0%) they used. Overall, higher $^{\Delta 9}$THC users reported better efficacy ($p = 0.02$) [34].

There are few RCTs evaluating the effect of cannabis on PD motor symptoms. A metanalysis of three trials reported a small but non-significant improvement in PD motor signs as assessed using Unified Parkinson's Disease Rating Scale part III (UPDRS III) score vs. placebo [35]. In 2 small open-label, single-arm trials, there were improved UPDRS III scores compared to baseline within 30 min of vaping or smoking *Cannabis*, including a reduction in tremor, rigidity, and bradykinesia subscores [36, 37]. Open-label, trials of CBD at ascending doses up to 25 mg/kg/day reported improved UPDRS III scores compared to baseline over 2–4 weeks [38, 39].

For levodopa-induced dyskinesia the evidence is that cannabinoids do not significantly reduce symptoms. Small randomized, controlled, cross-over or parallel trials evaluating the combination of $^{\Delta 9}$THC 2.5 mg/CBD 1.25 mg or CBD alone at 75 mg or 300 mg demonstrated no changes in dyskinesia measures [40], or (UPDRS) scores [41], compared to placebo over 4–6 weeks. Nabilone, the synthetic $^{\Delta 9}$THC was evaluated in a pilot, single-dosing RCT cross-over trial in 7 subject with PD and dyskinesia with a small improvement in levodopa-induced dyskinesia, with possible benefit on off-dystonia (but only $n = 2$) [17]. A randomized, placebo-controlled, parallel trial of longer term nabilone, however, showed no significant changes from baseline in motor symptoms over 4 weeks in 38 patients [42].

CLINICAL EVIDENCE: NON-MOTOR SYMPTOMS

There are many patient-surveys reporting positive effects of *Cannabis* products on non-motor symp-

toms in PD. A survey of 530 PD patients in Norway reported sleep (52.5%) and pain (37%) were the most frequently perceived benefits of *Cannabis* [43]. Two large survey studies (as reported above) comprising almost 3,000 patients with PD in the United States revealed that a large range of *Cannabis*-based interventions were helpful for anxiety, pain, and sleep disorders [33, 34]. In both surveys, cannabinoids with higher THC content were reported as more effective [32, 33].

Clinical trials have suggested possible benefits on pain, and sleep in PD. A RCT in 38 PD patients demonstrated efficacy of nabilone (0.25 mg once daily to 1 mg twice daily) on the non-motor subscale of the UPDRS II [44], particularly on sleep, insomnia and fatigue [45]. In a study assessing patients with PD and REM sleep-behavioral disorder (RBD), CBD 75 to 300 mg for 14 weeks was associated with improved sleep satisfaction, but there was no difference in the frequency of nights with RBD compared to placebo or in measures of restless leg syndrome burden [46, 47].

For pain in PD, a pilot phase-1b trial evaluated safety and tolerability of three cannabis oil formulations ($^{\Delta 9}$THC/CBD 18:0, 10:10, 1:20); in eight subjects with pain, and showed a reduction in the pain visual analogue scale (VAS) after exposure to 18:0 $^{\Delta 9}$THC /CBD oil [48]. Two prior studies have shown similar pain improvement on VAS or pain rating index after smoking or vaping *Cannabis* [36, 37]. Another open-label study using 1:1 CBD: $^{\Delta 9}$THC tincture reported reduced need for opioids in pain/cramping in 56% of users [49].

The efficacy of *Cannabis*-based treatments on motor and non-motor functions warrants cautious interpretation and limited generalizability due to small samples sizes and variable *Cannabis* formulations and dosing regimens. Also, these studies are frequently susceptible to biases and type 1 and 2 errors given open-label design and underpowered outcomes.

SIDE EFFECTS OF CANNABINOIDS IN PD

A recent umbrella review of 101 metanalysis of cannabis studies in multiple medical indications noted safety concerns of any cannabinoids [50]. To date it is unclear if $^{\Delta 9}$THC vs. CBD targeting cannabinoids have a different safety and tolerability profile in PD. A patient-reported survey on personal use of cannabinoids in PD separated $^{\Delta 9}$THC predominant vs. CBD predominant cannabis products and noted that $^{\Delta 9}$THC- predominant were generally more likely to cause more side effects; the commonest being worsening of dry mouth, cognitive complaints, dizziness, increased appetite and poor balance [33]. Psychoactive effects of $^{\Delta 9}$THC -based cannabinoids could potentially cause psychosis; however, there is evidence that CBD-based cannabinoids have been suggested to reduce psychosis in non-PD populations [51]. Preclinical studies have shown that CBD ameliorates symptoms of psychosis through an action on CB_1, CB_2, and 5-HT1A receptors as well as through neurogenesis factors [38]. Functional neuroimaging studies revealed that CBD attenuates dysfunctions in mediotemporal and prefrontal brain regions and hippocampal-striatal functional connectivity in patients with psychosis and improves the attenuation of brain activation associated with reward processing in patients at risk for psychosis [38, 52]. In the small RCTs performed to date there was no increased incidence of PD psychosis reported [37, 39, 53]. In patient-surveys, hallucinations were reported in 425 out of 1881 respondents with slight more in $^{\Delta 9}$THC than CBD [33]. A recent open-label study reported on long-term (1–3 years) use of whole plant medical cannabis containing 10% $^{\Delta 9}$THC and 4% CBD in PD, with no worsening of any neuropsychiatric symptoms reported compared to a group of PD non-users [54].

Cognitive dysfunction is a potential concern of cannabis use, and particularly in the elderly PD population. The endocannabinoid system modulates the circuits between the hippocampus and the prefrontal cortex via CB_1 receptors, and cannabinoids can potentially impair working and episodic memory consolidation [55–57]. In humans, cannabinoids can also be associated with impairment of attention [57], conceptual disorganization, depersonalization and derealization, disrupted sensory perceptions and psychosis [58]. To date, there are few studies evaluating the primary effects of *Cannabis* on the cognitive function of PD patients. Ellmerer et al. [42] demonstrated no difference in frontal-lobe-associated cognitive performance measured by eye-tracking anti-saccadic paradigms in 24 PD patients randomized to nabilone or placebo for 4 weeks. In contrast, a recent RCT evaluated a neurocognitive battery in 29 PD patients 1.5 h after exposure to high-dose CBD (100 mg) and low-dose $^{\Delta 9}$THC (3.3 mg) [53]. The CBD/$^{\Delta 9}$THC group performed worse than the placebo group on animal verbal fluency and sustained concentration during activities [53]. Overall, adverse cognitive events were

reported at least twice as often by the CBD/$^{\Delta 9}$THC than the placebo group [53].

In the phase-1b trial for PD pain, evaluating three cannabis oil formulations ($^{\Delta 9}$THC/CBD 18:0, 10:10, 1:20) in doses ranged from 0.5 ml to 1.0 ml/day (average dose 0.68 g/day), all formulations were well tolerated with no serious adverse effects [48]. No participants withdrew because of adverse events. Mild-to-moderate adverse effects included drowsiness ($n = 3$) and dizziness ($n = 3$), which resolved in all patients after reduction in dose [48].

WHAT DO WE TELL PEOPLE WITH PARKINSON'S IN MY CLINIC?

Evidence-based medicine is unlikely to help the practicing clinician to determine the questions arising about cannabis in PD. The 'genie is out of the bottle' when it comes to funding and performing RCTs for cannabis products in PD. As more cannabinoid preparations have become legalized for recreational or medical use in multiple jurisdictions, large placebo-controlled trials have become less feasible and with it, high-level efficacy evidence may not be attainable. The recruitment rate can be slow as patients with PD may not consent to a controlled study and may seek off-label access to *Cannabis*-based compounds.

The Michael J. Fox Foundation and Parkinson Foundation have both provided consensus statements on the use of medical cannabis for PD (www.parkinson.org/sites/default/files/documents/medical_cannabis_statement_finalv2_5.pdf; www.michaeljfox.org/sites/default/files/media/document/Medical_Marijuana_03.04.22.pdf). These statements highlight the lack of evidence-based data on the effectiveness and safety of medical cannabis in PD as well as the conflicting results and lack of standardization of the available products. They also raise concerns about safety profile in PD patients and risk of addiction. The Parkinson Foundation does not endorse the use of medical cannabis in PD but encourages patients to discuss this topic with their healthcare providers.

In this state of equipoise, our perspective is that cannabinoids may be an alternative potential therapeutic option for certain symptoms of insomnia, anxiety and pain in PD, particularly when other options for these non-motor symptoms have failed. We do not endorse the use of cannabis products for the management of motor symptoms, given the lack of evidence-based data in the literature (see Box 1). A common finding from patient-facing surveys is that benefits may wane after a few weeks of use, and this is important to advise patients.

The appropriate *Cannabis* formulation and dose needs to be assessed on an individual basis with a comprehensive discussion about the uncertain efficacy, risk of side effects, access, insurance coverage and costs. Overall, from evidence to date, higher THC content does appear to provide more benefit. However, THC is the component with more psychotropic properties and a higher risk of developing psychosis as a side effect, which is a main drawback in our elderly PD population. As noted above, concerns remain about variability in THC:CBD content in available formulations that can be purchased. We encourage patients to carefully review the THC:CBD content before using medical cannabis and start on the lowest dose possible to minimize the risk of side effects. We do not endorse the use of smoking or vaping medical cannabis due to established harmful effects on oral and respiratory tissues.

Patients with current cognitive impairment, behavioral disorders, orthostatic hypotension, and daytime sleepiness are at increased risk of *Cannabis* adverse events, therefore we discourage the use of cannabis for these patients. Risk of substance abuse [57] and respiratory complications of vaping or smoking are other important factors to be considered and discussed prior to commencing off-label *Cannabis*.

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