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Cannabis Effectiveness on the Motor Symptoms of Parkinson's Disease

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by

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Table of Contents

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Abstract

Fueled by news media reports, cannabis use has been ever growing in popularity for the treatment of both motor and non-motor symptoms of Parkinson's disease (PD). The purpose of this literature review is to evaluate the safety and efficacy of using cannabis to treat the motor symptoms and levodopa-induced dyskinesia of PD. In this literature review electronic databases were searched and included PubMed, CINAHL, Embase, DynaMed Plus, Cochrane Library, Academic Search Premier, and Clinical Key. A variety of keywords and MeSH terms, as listed below, were used to define a set of literature. There were 16 studies chosen for review that were completed within the last 20 years, included only human subjects, and were excluded if it was a case study with only one subject. Much of the research displayed discrepancies on the evidence for cannabis use to treat the motor symptoms and dyskinesia of PD; however, a large amount of the research deems cannabis safe for use in most PD patients. The current research available does not conclusively provide enough quality evidence to suggest using cannabis is an effective treatment for motor symptoms and dyskinesia in PD. Furthermore, there is a significant need for more quality research on the effects of cannabinoids for PD, to better comprehend the pharmacology, therapeutic benefits, and adverse effects of various cannabis formulations.

Keywords: cannabinoids, cannabidiol, CBD, marijuana, cannabis, tetrahydrocannabinol, THC, movement disorders, neurodegenerative disorders, neurodegenerative conditions, Parkinson's disease, levodopa-induced dyskinesia, dyskinesia, adverse effects, adverse events, and safety.

Introduction

Parkinson's disease (PD) is a neurodegenerative condition affecting approximately 60,000 people in the U.S. annually and is characterized by a loss of dopaminergic neurons and an accumulation of Lewy bodies within the substania nigra of the brain. These neurological changes in the brain lead to debilitating motor symptoms in PD patients such as bradykinesia, tremors, limb rigidity, and gait or balance problems. To date, there is no cure for PD and the goal of treatment has been to treat the symptoms, with dopaminergic agents (medications that increase dopamine or mimic dopamine in the brain) being the mainstay of treatment. The purpose of this literature review is to further understand the effects and safety of using cannabis as adjunctive therapy in a PD treatment regimen (Parkinson's Foundation, 2019).

Statement of the Problem

In recent social and news media there has been an outpouring of videos displaying how cannabis seems to be effectively treating the movement-related symptoms of PD, leaving questions to if cannabis therapy is truly effective in treating PD symptoms, or if this is another social media ruse shared to the public (Robledo & Jankovic, 2017). Medical cannabis (MC) has now been legalized in 33 states with 13 of those states considering PD as a medically qualified condition to use MC as a treatment. The basis for using MC as a treatment for PD is due to PD patient's having less cannabinoid type 1 (CB_1) receptors than those without PD, and since MC acts as an agonist on the CB_1 receptors it may hold the potential to improve PD motor symptoms, or levodopa-induced dyskinesias (Parkinson's Foundation, 2019). Although in theory cannabis could be effective, there have been questions raised to the validity of studies showing cannabis success in PD treatment, and if this success is a placebo effect for patients suffering from a debilitating condition. Therefore, in states that qualify PD patients for MC use, medical providers

can benefit from an evaluation of the latest research that may demonstrate if cannabis is truly a useful tool or not in treating their patients suffering from PD.

Research Methods

A literature review was performed using electronic search databases; PubMed, CINAHL, Embase, DynaMed Plus, Cochrane Library, Academic Search Premier, and Clinical Key. Keyword and mesh terms used to define a set of literature for the study included: "cannabinoids, cannabidiol, CBD, marijuana, cannabis, tetrahydrocannabinol, THC, movement disorders, neurodegenerative disorders, neurodegenerative conditions, Parkinson's disease, levodopa-induced dyskinesia, dyskinesia, adverse effects, adverse events, safety". The literature was further searched for safety in cannabis use for PD and the specific use of cannabis to treat dyskinesia caused by levodopa therapy for PD. Several studies were also excluded as they involved non-human subjects or were a case study with only one subject. The initial search did reveal limited data and the search time frame was expanded from 10 years to studies completed within the last 20 years.

Research Question

In patients diagnosed with Parkinson's disease, is there sufficient evidence to suggest cannabis is an effective therapy in treating the motor symptoms and levodopa-induced dyskinesia associated with Parkinson's disease?

Literature Review

Safety of Cannabis Use

Recognizing that the legalization of MC for PD has bypassed typical drug approval processes, Bega, Simuni, Okun, Chen, and Schmidt (2017) conducted a survey study to collect data from National Parkinson's Foundation (NPF) PD experts who could share information on

cannabis prescribing tendencies and experiences, in addition to their attitudes and beliefs towards the safety of cannabis for PD. A total of 56 physicians who had prescribed/recommended cannabis on at least one occurrence within the last 12-months took the 73-item questionnaire, which assessed their familiarity with current evidence on cannabis, their understanding of risks and benefits of cannabis, and their personal prescribing tendencies. Results from the questionnaire found that the two most common places physicians formed their opinions of MC were medical literature and their personal experiences with prescribing MC, with the media/news being the third-highest contributor to opinion. Regarding physicians' views of cannabis evidence-based effects on motor symptoms of PD, the results showed divided statistics with providers feeling that it only benefited tremors 36% (n = 20) and dyskinesia 35% (n = 19) of the time. Regarding physician opinions on the safety and negative side effects (SE) of MC there was little concern for major SE such as lung cancer or overdose with cannabis, but more concern for mild negative SE such as cannabis affecting short-term memory (n = 42), long-term memory (n = 31), executive functioning (n = 44), driving impairment (n = 54), and addictive tendency (n = 47). Another concern from many of the responding physicians was that cannabis prescribing could worsen patients' lack of motivation (n = 32), drowsiness (n = 31), and hallucinations (n = 37). The last major finding of the survey was that most providers (93%) believed cannabis deserved significantly more attention in the medical school curriculum, and 69.6% of physicians believed that cannabis should be eligible to be prescribed for medicinal purposes (Bega et al., 2017).

Some of the strengths of the study by Bega et al. (2017) was the use of experts in PD which was critical for obtaining surveyors who would hopefully remove bias when answering questions of cannabis use for PD, as many of these experts should want the best for their patients

no matter the treatment. It also adds strength to the study that the PD experts are from NPF centers in six different countries which contributes diversity and worldwide PD perspective to the study. Some of the limitations to the study included lack of surveying participants (56), a survey of expert thought versus actual patient data, lack of survey input from pharmacists who distribute MC, and lack of physician participation from other PD foundations or organizations.

Buhmann, Mainka, Ebersbach, and Gandor (2019) conducted a systemic review with the aim to provide an overview of the cannabinoid system, the impact of cannabis for PD treatment, to present the experimental data of cannabis use for PD, and to highlight the safety issues of cannabis therapy including medical risks, tolerability, and contraindications. The methods used by the Buhmann et al., involved reviewing 10 different studies on cannabis for PD; two open anonymous survey studies, three case series, one open-label study, and four randomized control trials (RCT). They then analyzed each study based on active cannabis formula being used and the results of each symptom being evaluated in those studies. After assessing the results of symptom relief for each study, the authors went on further to look at safety, SE, and other risks that were noted with cannabis use. The results on the safety of cannabis use for PD revealed mixed results which trended on the type of cannabis used, patient tolerability, and the time at which patients developed tolerance to SE of cannabis. While cannabis containing tetrahydrocannabinol (THC) seemed to cause more side effects, especially psychotropic or psychiatric SE, two studies in the review found that patients using cannabidiol (CBD) formulations did not seem to experience psychiatric SE. One study treating PD patients with a synthetic THC analogue (nabilone) reported visual hallucinations in 5 of 7 patients, and another study reported 6 of 28 patients dropping out of the study due to psychiatric symptoms. The most common cardiovascular SE appeared to be orthostatic hypotension. Although only one of the studies reviewed by the authors

reported this, it was significant as all seven patients in the study had a drop in systolic blood pressure after cannabis administration. Safety issues also exist with MC use for PD as medical contraindication guidelines are not available for many cannabis products. Although there is a lack of general contraindications for MC use, the consensus is that MC should be avoided in patients with severe psychotic and personality disorders, including those with substance abuse disorders (Buhmann et al., 2019).

The diversity of studies reviewed by Buhmann et al., as well as the diversity in their symptom break down of each study, adds strength to the authors' work, by not limiting their review to the assessment of a singular outcome in MC use for PD. Although, limitations to this review did exist as well which include extreme heterogenicity in the type of cannabis used, the concentration of the cannabis product, route of administration, and timing of administration. An additional limitation to this review is that only four RCT are available and thus data may be skewed based on the quality of studies available (Buhmann et al., 2019).

Although the quality of studies on cannabis use for PD has been in question, one RCT conducted by Carroll et al. evaluated the effect of cannabis extract on the severity and duration of dyskinesias in patients suffering from PD. Additionally, the authors conducted a separate open-label, dose-escalation study to evaluate the tolerability of MC in patients with PD, in regard to cannabis dosing schedule, adverse effects, and effect on PD severity. Methods specific to the study of cannabis on safety and tolerability included six patients who met inclusion criteria of having levodopa-induced dyskinesias and were on fixed anti-Parkinson medication at least one month before the study beginning. The cannabis treatment used was Cannador capsules taken twice daily, standardized with 2.5 mg of THC and 1.25 mg of CBD per capsule, and were dosed based on patient body weight, reaching a max possible dose of 0.25 mg/kg of THC/day. The

study started with a dose-titration phase which entailed escalating the dose at three-day intervals until the patient reached their maximum weight-adjusted dose or started to have intolerable SE, during which the dose would be decreased to the last tolerated dose. After the dose titration phase, the study began and would continue for four weeks. Assessment of patients was completed once at baseline and again at the end of the four-week treatment phase. Outcomes were measured by the Unified Parkinson's Disease Rating Scale (UPDRS) and Parkinson's Disease Questionnaire 39 (PDQ-39) during patients' "off" states, which are times when patients' PD medications are not at full effect. Patients were also contacted every three days via telephone to monitor adverse effects (AE) in addition to every six days for patients to complete an extensive AE checklist. Results from the dose-escalation cannabis safety study yielded two patients having to stop taking the Cannador medication. One patient stopped on day 12 of the study due to worsening "off" periods and the second patient stopped on day 18 of the study due to panic attacks. Some mild AE were reported throughout the four weeks and would increase in incidence with higher doses of Cannador taken but would ameliorate with dose reduction. No AE occurred that required patient hospital admission (Carroll et al., 2004).

Carroll et al. (2004) did emphasize limitations to the study that are inherent to an open-label design and include assessor bias, placebo effect from the Cannador, and lack of external control due to patients returning home with medication. However, considering the dose-escalation portion of this study was assessing the AE of cannabis, bias should be limited by patients not seeking AE from treatment. The small sample size (n = 6) is an additional limitation to the study, especially with 2 of 6 patients dropping from the study. Excluding inherent limitations, the study does hold strength in that AE were further assessed in the primary RCT,

reviewed in the section "*Efficacy of Using Cannabis to Treat Levodopa-Induced Dyskinesia*", which found that Cannador treatment and placebo groups had a similar spectrum of AE.

Another literature review regarding cannabis safety was conducted by MacCallum and Russo (2018) with the objective of presenting concise data on cannabis chemovar pharmacology, methods of administration, therapeutic uses, dosing recommendations, and the adverse effects of cannabis therapy. Methods used by the authors involved using the keywords "cannabis," "cannabinoids," "marijuana," "drug abuse," "psychopharmacology," and "adverse events" which yielded 83 articles that they chose to use in their review. The articles used were then analyzed based on the objectives described above, and pertinent information was distributed by the authors into each objective section.

Regarding the pharmacology of cannabis, the authors begin by reiterating that one of the difficulties in using cannabis to treat a variety of ailments is the vast number of chemovars (strains or types) of cannabis available. Each chemovar contains varying concentrations of cannabinoid components that act via different mechanisms, meaning that some chemovars have sedating properties, some may alleviate short-term memory impairment, some may act as an anti-depressant, etc. (MacCullum & Russo, 2018). Prviously, the majority of chemovars used were THC-predominant (Type I cannabis), but now there seems to be greater interest in mixed THC/CBD (Type II cannabis) and CBD-predominant (Type III cannabis). Type II and III cannabis show broader mechanisms of actions, improved therapeutic indexes, and fewer AE since CBD does not hold the psychoactive properties of THC. Another important difference to understand when prescribing a THC-predominant chemovar versus a CBD-predominant chemovar is that THC works primarily as a weak partial agonist on CB_1 and CB_2 receptors, which has well-understood effects on pain sensation, appetite, emotions, and thought processes.

Contrarily, CBD has little affinity for CB receptors and instead targets serotonin 1A receptor (5-HT_{1A}), transient receptor potential cation channel vanilloid subfamily receptor 1 ($TRPV_1$), adenosine A2A, as well as other non-receptor mechanisms. These receptor targets allow CBD to produce more analgesic, anti-inflammatory, anti-anxiety, and anti-psychotic effects than THC, which is important for physicians to understand when choosing what cannabis chemovar they want to prescribe (MacCullum & Russo, 2018).

The findings by MacCullum and Russo (2018) on modes of cannabis administration were that smoking cannabis (joints, bongs, pipes, etc.) was the most common route used, but produced the most toxic byproducts, and chronic smoking led to a multitude of respiratory symptoms. The second most common route used was vaporization of cannabis, which produced fewer toxic byproducts and pulmonary symptoms than smoking. Oral routes (oils, capsules, edibles, etc.) are becoming increasingly more popular due to its convenience and accuracy of dosing, which has taken hold as the safest route of administration in the medical community. Findings on the dosing methods for cannabis revealed that the best general approach to cannabis dosing is to start at a low dose, slowly titrate the dose, and keep the dose as low as possible to reach therapeutic level while avoiding AEs. Additional best practices for dosing include prescribing CBD-predominant chemovars before THC-predominant chemovars, teaching patients that a dose causing euphoric or psychoactive effect does not mean the dose is efficacious, and that giving a patient's doses of THC greater than 20 – 30 mg/day puts them at greater risk for psychoactive or other AEs (MacCullum & Russo, 2018).

Regarding contraindications and AEs of cannabis use MacCullum and Russo (2018) found that cannabis had a superior safety profile in comparison to other medications and had no reported deaths due to overdose. The most pertinent AEs from cannabis use are THC-mediated

effects but are rate-limiting and dose-dependent. The AEs most reported include the following: fatigue/drowsiness, dizziness, dry mouth, anxiety, nausea, cognitive effects, and if the patient is smoking cannabis (cough, phlegm, and bronchitis). Cannabis is also contraindicated in pregnancy and lactation, psychosis or psychiatric disease (unless using a CBD-predominant chemovar), COPD and asthma (if smoking cannabis), and THC-predominant chemovars should be used with caution in patients with unstable cardiac conditions.

Efficacy of Cannabis Use to Treat Motor Symptoms of Parkinson's Disease

The literature reviewed first on cannabis efficacy for PD motor symptoms includes three separate studies conducted on patients of the Rabin Medical Center in Israel. The first being a telephone interview study conducted by Balash et al. (2017), with a goal of recording the subjective effectiveness of cannabis therapy used by PD patients and to note any adverse effects caused by the cannabis treatment. This retrospective observational telephone survey involved contacting PD patients at Rabin Medical Center. The survey used consisted of 66 questions, broken into three parts: demographic data and patient comorbidities, a clinical picture of patients' PD symptoms, and details of patients' MC use with their assessment of the MC effectiveness on their symptoms, including any AEs experienced. The effects of MC on the patient symptoms and activities of daily living (ADL) were evaluated using a 5-point Clinical Global Impressions Scale, and if any falls had occurred before or after MC use patients would record the fall as a *yes/no* response. Results of the study included 47 total PD patients. The most common delivery method of MC was smoking *Cannabis sativa* flowers using joints (n = 38) with an average daily dose that ranged between .2 – 2.25g/d. The effects of MC on PD motor symptoms after administration revealed that 37 patients found that MC improved their overall symptoms, two reported no difference, six reported feeling worse, and two did not respond to this question. The

effects of MC on motor symptoms showed statistically significant outcomes in the following symptoms: reported improvement on muscle stiffness (32/44 patients, $P < 0.001$), general tremors (30/41 patients, $P < 0.001$), pain reduction (35/43 patients, $P < 0.001$), and patients reporting a complaint/concern of falling (from 22/47 before cannabis to 6/18 patients after cannabis, $P < 0.05$) (Balash et al., 2017).

Of additional significance to the review of cannabis safety, Balash et al. (2017) found that out of 47 patients, five of them chose to spontaneously stop the MC treatment. Two stopped due to lack of cannabis causing desirable effects, two stopped after developing hallucinations, and one stopped due to postural instability. Adverse effects throughout the MC treatment were reported in 28 of 47 patients. Among the AEs reported were confusion (8/47 patients), anxiety (8/47 patients), hallucinations (8/47 patients), short-term amnesia (3/46 patients), cough from smoking MC (15/43 patients), dyspnea (2/43 patients), dizziness (6/47 patients) and unsteadiness (7/45 patients).

Limitations to this specific study at Rabin Medical Center include the varying dosages and administration types of cannabis used, which could cause drastic variation in its efficacy towards treating the motor symptoms of PD, especially considering most of the population used cannabis joints as their method of delivery. Another possible limitation is the initial response rate of eligible patients before exclusion criteria was applied was 61 of 98 patients (62.2%), which suggests the sample population was highly motivated, and that motivation could have led to significant reporting bias to inflate the success of cannabis effects and minimize reporting of AEs (Balash et al., 2017)

Lotan, Treves, Roditi, and Dialdetti (2014) conducted the second study at Rabin Medical Center, an open-label observational study to evaluate the efficacy of cannabis treatment in

alleviating non-motor and motor symptoms of PD in a controlled clinical setting. Methods used by Lotan et al. involved 22 PD patients from Rabin Medical Center, who had been approved to smoke cannabis as adjunctive therapy to their anti-Parkinson medication regimen. These 22 patients were eligible for the study after they had smoked cannabis daily, for at least two months, with no major AEs recorded. The day the study begin patients were asked not to use their regular anti-Parkinson medications so that the authors could assess their baseline motor status, and the patients with fluctuations of their PD could have their motor status assessed during "off" periods. The baseline data on patient motor symptoms was gathered using the UPDRS part III (*motor examination*). After all baseline data was collected, patients were asked to smoke their typical dose of cannabis (0.5g inhaled), and 30 minutes later the motor testing was repeated. Results found that after administration of cannabis the UPDRS part III scores showed significant improvement dropping from 33.1 at baseline to 23.2 after cannabis use ($P < 0.001$). Specific motor symptoms also showed significant UPDRS score improvement after cannabis consumption including tremor (7.55 at baseline to 3.64 after MC, $P = 0.000$), rigidity (7.55 at baseline to 6.48 after MC, $P = 0.004$), and bradykinesia (13.12 at baseline to 8.62 after MC, $P = 0.000$); however, posture did not show significant improvement ($P = 0.056$) (Lotan et al., 2014).

The authors did try to add strength to the study by using two raters to assess motor function and did end up having a low interrater variability before cannabis treatment (Pearson correlation: 8.4) and after cannabis treatment (Pearson correlation: 8.8). However, the open-label design of the study still has limitations which include the possibility of cannabis causing a placebo effect or patient bias leading to favorable vs. unfavorable results. The effects of MC on PD symptoms were assessed only one-time, and without any follow-up, which is a major

limitation in understanding if there would be a long-term benefit to MC therapy for PD (Lotan et al., 2014).

The last study conducted at Rabin Medical Center was an open-label, uncontrolled, observational study completed by Shohet, Klebtovsky, Roizen, Roditi, and Dialdetti (2017). The goal of the study was to determine the effects of cannabis on motor symptoms and pain parameters of PD patients. Methods used specific to motor symptoms involved 20 PD patients, who had been using cannabis as adjunctive therapy to their anti-Parkinson medication. On the day of the study patients were asked to take their typical anti-Parkinson medications at home as usual, and then to use 1.0 gram of their MC when they arrived at the clinic. Once patients arrived at the clinic they were assessed upon arrival and then 30 minutes after MC consumption. Motor function was evaluated using the UPDRS part III (*motor examination*), and findings were rated by a physician who physically examined the patients, and by another physician who watched a video recording of the patients separately. Results of motor function yielded a significant decrease in the UPDRS score after MC consumption, with scores going from 38.1 ± 18 before MC to 30.4 ± 15.6 after MC consumption ($P < 0.0001$) (Shohet et al., 2017).

Limitations specific to this Rabin Medical Center study are inherent to open-label uncontrolled study design and include assessor bias and cannabis causing a placebo effect. Other limitations include unaccounted for drug interactions between MC and patient's anti-Parkinson medications, and the study only assessing motor symptoms a single time after MC administration. Shohet et al. (2017) did counteract some of these limitations by acknowledging potential sources that added strength to their study. First, the authors used two raters separated from each other who had consistency in their findings (Interrater Variability Coefficient [ICC] =

0.91), and secondly, they acknowledged that allowing PD patients to remain on their current medications may have made it possible to isolate cannabis effects.

The Rabin Medical Center in Israel was not the only facility to host multiple studies on the efficacy of cannabis to treat PD. The University Hospital in Ribeirao Preto, Brazil additionally had two studies conducted within its facility. The first study by Zuardi et al. (2008), was conducted to evaluate the efficacy of CBD on PD patients with psychotic symptoms, and secondarily to assess CBD efficacy on the motor symptoms of PD. The study used patients from the movement disorder outpatient clinic of the University Hospital in Ribeirao Preto. PD patient's in the study were eligible if they had psychosis for at least three months, their psychosis could not be controlled by reducing their anti-Parkinson medications, and patients had been on anti-Parkinson medication for at least seven days prior to evaluation. PD patients from the clinic were excluded if they already had been diagnosed with a primary psychotic disorder, had been diagnosed with atypical PD, had the presence of dementia, or if their motor symptoms would require increased dosing of anti-Parkinson medications throughout the study. After inclusion and exclusion criteria were applied six PD patients remained (n = 6). Subjects were then given identical CBD and placebo capsules in addition to their usual PD therapy for four weeks. All patients were started on 150 mg/day CBD capsule for the first week, and the dose was then increased weekly by 150 mg as tolerated by the patient. Evaluation and assessment of patient motor symptoms were completed before initiating CBD therapy and then performed again at the end of the fourth week and was completed by the same unblinded neurologist and psychiatrist. Data collection for motor symptoms and function was done using the UPDRS. Results of the study regarding secondary outcome of motor symptoms and function found that CBD had a statistically significant effect on the total score of the UPDRS (P = 0.046) from before CBD

therapy to the end of week four. However, there was no statistical significance found in the *motor score*, *activities of daily living*, or the *mentation, behavior, and mood* portions on the UPDRS. These results suggest that CBD therapy did not have a significant effect on the improvement of motor symptoms of PD, but it should be noted that CBD did not worsen motor symptoms either (Zuardi et al., 2008).

Zuardi et al. acknowledged that this open-label observation study had many limitations. First, the authors noted that only having one psychiatrist and one neurologist perform weekly testing on separate objectives never allowed for inter-rater reliability during testing. Second, the study had a small sample population (n = 6) with no diversity as all patients were from the same clinic. Third, there was almost a complete lack of control for external factors after the patients left the clinic each week with their CBD formulation. The patients had the free will to take multiple CBD capsules a day, to take no CBD capsules at all and could take the CBD without regard to the timing of administration. Fourth, there are intrinsic limitations to this open-label design which includes CBD causing a placebo effect on patients who may be desperate to alleviate their PD (Zuardi et al., 2008).

The second study performed in the movement disorders clinic of Ribeirao Preto was an RCT by Chagas et al. (2014a). The authors conducted a double-blind, placebo-controlled clinical trial with the goal of assessing the effects of cannabidiol (CBD) in PD, using neurological assessments of motor, functional, and psychiatric symptoms. The methods used in the study involved initially selecting 119 PD patients after they had been assessed by a neurologist, psychiatrist, and neuropsychiatrist over two years. Inclusion criteria to the study included a diagnosis of idiopathic PD, age $\geq$ 45, use of anti-Parkinson medication for at least 30 days prior to the clinical trial, and a score of at least 1 on the Hoehn and Yahr staging scale. Exclusion

criteria to the study involved any presence of atypical PD, a previous psychiatric or dementia diagnosis, a relevant co-morbidity, and any previous use of cannabis by the patient. After criteria were applied 21 patients remained and were then divided into three groups with a placebo group (n = 7), a CBD 75 mg capsule group (n = 7), and a CBD 300 mg capsule group (n = 7). Study design consisted of first completing a week-long baseline assessment of the subjects. After baseline data was collected patients were then administered the identical placebo or CBD capsules daily for six weeks under caretaker supervision, with the final week being used to reevaluate each patient's baseline assessment. Outcome measures used were the UPDRS, PDQ-39, and the Udvalg for Kliniske Undersogelser (UKU) side effect rating scale (Chagas et al., 2014a).

Results from the study found no statistically significant differences in mean score variations between the three groups for the UPDRS. However, the PDQ-39 results did find statistically significant differences in a total score between placebo vs. CBD 300 mg/day groups ($P < 0.05$). PDQ-39 scores in the specific portions of ADL and stigma also had statistically significant differences between the groups that took placebo versus CBD 300 mg/day ($P = 0.02$) and between groups that took CBD 300 mg/day vs. CBD 75 mg/day ($P = 0.04$). Additionally, there were no significant AEs recorded in any groups assessed with the UKU side effect scale. According to Chagas et al. (2014a) the overall results of the study related to cannabis effects on PD motor symptoms suggest that CBD did not show any significant differences in alleviating the motor symptoms of PD with either the PDQ-39 or the UPDRS assessments.

Although sample size (n = 21) is a limitation to the study, it also displays strengths in the study through the authors excluding external factors that could affect bias in assessment, such as the exclusion of PD patients with psychiatric or dementia diagnoses and exclusion of patients

who had used cannabis previously. Further strength was added to the study by controlling the route of administration and dosage of CBD with capsules under the supervision of a caretaker, blinding researchers and subjects to the treatment groups, and using three separate assessment tools to evaluate outcomes (UPDRS, PDQ-39, and UKU). Limitations to the study include sample size as previously mentioned, all patients in the study being from the same medical center and region which could limit diversity, and differences in patient's anti-Parkinson therapy before starting the trial. Another limitation of importance is that the only positive statistically significant difference in using CBD for PD came from the PDQ-39 which is a self-report instrument and could be displaying subjective bias (Chagas et al., 2014a)

The authors of the previous study reviewed also conducted an additional case series study with the goal of determining if cannabidiol (CBD), the non-psychotropic component of the *Cannabis sativa* plant, could aid in the treatment of rapid eye movement (REM) sleep behavior disorder (RBD) in patients with PD (Chagas et al., 2014b). To conduct this case series the authors included four patients without current or previous psychiatric diagnoses. Additional inclusion criteria were patients having a complete clinical assessment for RBD done by a neurologist who specialized in sleep disorders, and the patient averaging at least two episodes of complex sleep behaviors a week. Of the four patients, two were confirmed to have definite RBD by symptoms and a positive polysomnography (PSG) result, and two were considered to have probable RBD as they were symptomatic but not confirmed by PSG testing. Before patient selection, none of the four subjects had been treated for their RBD symptoms. The dosing parameters for the case series were to treat three patients with CBD 75 mg/day for six weeks and to treat one patient with CBD 300 mg/day for six weeks.

The results of the study displayed that the patients' most common reported symptoms during their RBD episodes tended to be talking, yelling, pushing, kicking, punching, laughing and gesturing. Three of the patients reported these RBD symptoms would occur between 2 – 4 times per week, and one patient reported that the RBD symptoms would occur up to seven times per week. After starting the daily treatment with CBD, the frequency of symptoms dramatically decreased. The first two subjects who were experiencing symptoms 2 – 4 times a week, reported 0 symptoms after treatment with CBD 75 mg/day for the remaining six weeks of treatment. The third subject who was experiencing symptoms up to seven times a week also reported 0 further symptoms after CBD 75 mg/day within the six weeks of treatment. The last subject, who was reporting symptoms 2 – 4 times a week, was treated with CBD 300 mg/day and reported the frequency of symptoms to be one time per week for the remaining six weeks of treatment (Chagas et al., 2014b).

Some limitations to the case series should be noted. First, the study had a small sample size (n =4). Second, it was examining secondary outcomes, which inhibits a detailed clinical examination of the cases. Third, only two of four patients had confirmed RBD using a PSG, and that there was not further PSG testing after administration of the CBD treatment to develop a comparative measure. Last, the short treatment period of six weeks, as there could be a large variation in RBD symptoms after continued use or tolerance to CBD treatment (Chagas et al., 2014b).

A study by Finseth et al. 2015) had a goal of determining what complementary and alternative medicines (CAM) are used by PD patients in Denver, Colorado, and which of those CAMs seem to be the most efficacious. Finseth et al. also gave specific attention to cannabis use as a CAM since it has been available to PD patients with a prescription in Colorado since 2010.

Methods for this study involved an anonymous self-administered survey that was provided to PD patients by the University of Colorado Hospital and Movement Disorder Clinic and PD support groups in the Denver area. The survey asked patients to identify which past and current CAM modalities they have used and what specific PD symptoms they are using that CAM for. Specific results of the study regarding cannabis use as a CAM for PD found that of the 207 patients who partook in the survey only nine of them had used cannabis as a CAM. Of the nine, seven reported that cannabis caused improvement in their symptoms. Of the seven patients reporting improvement, five reported "great improvement" of their symptoms, specifically their mood and sleep, while two reported improvements in their motor symptoms and quality of life. None of the nine patients who used cannabis as a CAM reported worsening of PD symptoms or any AEs (Finseth et al., 2015).

Pitfalls of this study specific to cannabis use for PD include: a small number of participants using cannabis as a CAM for PD in the survey (9 of 207), surveying in a state that has legalized cannabis recreationally holds potential for reporting bias, a lack of control from external factors due to the study being conducted via survey has inherent limitations, a lack of follow-up due to the survey being anonymous, and self-administration of the survey leads to multiple concerns of patients falsifying information (Finseth et al., 2015).

Friedman (2014) performed a study to determine if MC use in a movement disorders clinic in Rhode Island would show potential benefits for treating the movement symptoms from PD, and other neurodegenerative disorders. To assess MC effect on PD, Friedman used a survey administered to all Butler Hospital (BH) Movement Disorders Clinic patients who were approved for legal MC use. The survey consisted of 10 questions related to the patient's MC use. In the clinic, 26 patients were using MC for their condition with 16 of them having a diagnosis of

idiopathic PD. Of additional importance, within this survey, Friedman does not specify the type of MC used or route of MC administration.

The survey revealed that 15 of 16 PD patients were using MC for non-motor related problems, anxiety was the most common reason, but also for sleep, appetite, and pain. One PD patient did report using it specifically for rigidity and mobility. Four of 16 PD patients reported that MC did lead to an improvement in tremors, and two of sixteen reported that MC improved their gait. Regarding the AEs of MC use, eight of sixteen patients reported some sense of euphoria, and two PD patients had to stop MC use. One patient stopped after reporting worsening motor function after increasing MC consumption, and the other patient, who used MC daily for forty years prior, stopped after developing hallucinations and paranoia. Regarding motor symptoms specifically, the study did not seem to find that any of the patients in the BH Movement Disorders Clinic were using MC for that purpose, regardless of the disorder they had. It seemed that any improvement in a motor symptom, typically tremors, seemed to be an additional benefit, which the author noted could be from MC reducing patient anxiety (Friedman, 2015).

Friedman's study had many limitations including lack of patients with PD taking the survey (16), lack of control in administration and dosage of MC, a non-random sample population, and potential patient bias in MC benefit due to previous uncontrolled use.

Recognizing that the positive and negative effects of cannabis on PD and Multiple Sclerosis (MS) are not fully understood, Kindred et al. (2017) developed a study with the goal of assessing cannabis use in PD and MS and to further compare the results from self-reported assessments of neurologic disability between current cannabis users and non-users.

To conduct the study the Kindred et al. developed a digitalized survey that consisted of 185 total items. The scales used to measure the survey included the following: Guy's Neurological Status Scale (GNDS), Nottingham Health Profile (NHP), Fatigue Severity Scale (FSS), Activities of Balance Confidence (ABC), and the International Physical Activities Questionnaire (IPAQ). Cannabis use in the scale was measured as past or current cannabis use, times per week cannabis was used, and administration methods of cannabis. Cannabis use was further measured as a dichotomous variable (users vs. non-users), and if the participant was a user, cannabis efficacy was measured using the 8-point Likert Scale (0: *Not helpful* – 7: *Very helpful*). After three months of survey trial testing, the link for the complete survey was then posted on the websites for the Michael J. Fox Foundation (for PD patients) and the National Multiple Sclerosis Society and opened to participants (Kindred et al., 2017).

The study yielded 538 complete surveys, with 76.3% (n = approximately 410) being made up from the PD patients. Results of cannabis use characteristics from the PD group found that 66.3% reported past use of cannabis and 36.6% reported current use of cannabis. Of those using cannabis, 72.3% reported using it for medicinal use, but only 38.4% reported possessing a medical cannabis card. The most common form of cannabis administration for PD patients was *smoking only* at 40.9%, with 6.3% using *edibles only*, and 19.5% using a *combination* (smoking and edibles). On average the PD patients reported using cannabis 4.6 days/week. The results from the 8-point Likert scale revealed that 85% of cannabis users found moderate or greater improvement of their symptoms (represented by a 4 – 7 on the Likert scale). Unfortunately, the Likert scale scores do not give results for the specific symptom which patients found cannabis effective for, which is a drastic limitation to the study's results (Kindred et al., 2017). Of additional importance, there was no improvement in the scores of the ABC scale or the IPAQ

which both focus on physical activity and motor movement of patients, which Kindred et al. suggest may indicate cannabis use is not improving motor symptoms of PD patients.

Some of the strengths of this study are the large sample size (n = 538) in addition to the sample being made up of randomized internet users visiting the Michael J. Fox Foundation website and the National Multiple Sclerosis Society websites. The study further held strength in that it compared PD patients who used cannabis to patients who did not, which allowed for a sort of control group with the patients who did not use cannabis. To add further strength to the survey of this study the authors excluded any participants who tried to take the survey twice by using an IP address verifier, excluded participants who did not report a diagnosis, excluded participants who had a diagnosis other than PD or MS, and excluded surveys that were not entirely completed (Kindred et al., 2017).

Limitations of this study were numerous and were acknowledged by the authors. The first limitation noted by Kindred et al. is that cannabis is used as a broad term in the study, due to there being no way to track the concentration, administration, and strain of cannabis used by the participants in an online survey format. Also, there is question if the patients taking the survey are taking a CBD or THC dominant chemovar, which would favor certain symptom treatment, and skew results. Another limitation is that the survey could be accessed by anyone who was on the internet and visited the two websites the survey was posted on. There is also potential that people taking the survey could have falsely stated they had a PD or MS diagnosis and skewed results, which has concerns for serious reporting bias. Self-reporting bias could have also occurred with patients who were already using cannabis for non-medical reasons and continued to use it after receiving a PD diagnosis (Kindred et al., 2017).

Venderová, Růžička, Voříšek, and Višňovský (2004) performed a study using an anonymous questionnaire to evaluate the frequency and patterns of cannabis use in PD patients, with an emphasis on subjective changes in patients' motor symptoms and levodopa-induced dyskinesias. The methods used by Venderová et al. (2004) involved asking all PD patients at the Prague Movement Disorders Centre in the Czech Republic, to complete an anonymous questionnaire about their experiences with cannabis. The questionnaire collected basic demographic data (age, gender, PD duration), and questions on patient cannabis use (does the patient use cannabis, how frequently and regularly, how long have they used cannabis for, which part of the plant was used, how did cannabis affect motor symptoms of PD, how did cannabis effect levodopa-induced dyskinesia, and if cannabis caused an effect when did it appear). If the patient did notice subjective changes in any of their movement symptoms the patient was then asked to rate the change in symptoms using the following scale: *substantial improvement, mild improvement, no change, mild worsening, substantial worsening, or I do not know*.

The study returned 339 questionnaires from PD patients, with 85 patients reporting cannabis use. Of the 85 patients most of them were smoking approximately a half-teaspoon of fresh or dried cannabis leaves once daily (52.9%), and with their meals (43.3%). Most patients reported choosing to try cannabis for their PD after seeing cannabis success in the media, but no patients reported using cannabis recreationally before taking it for their PD symptoms. No patients reported being advised by their neurologist to use cannabis, and all patients kept taking the anti-Parkinson medications prescribed initially by their neurologist. Regarding motor symptoms, Venderová et al. found that after cannabis use 39 patients (45.9%) reported mild or substantial relief of general PD symptoms, 26 (30.6%) found improvement of resting tremor, 38 (44.7%) found alleviation of bradykinesia, 32 (37.7%) found alleviation of muscle rigidity, 12

(14.1%) found improvement of levodopa-induced dyskinesias and only 4 (4.7%) reported worsening of symptoms from cannabis use. Of additional importance, patients who reported using cannabis for at least three months had statistically significant improvement of their motor symptoms compared to patients who used cannabis for less than three months. If a patient used cannabis for at least three months results showed mild or substantial relief of general PD symptoms ($P < 0.001$), improvement of resting tremor ($P < 0.01$), improvement of bradykinesia ($P < 0.01$), and improvement of muscle rigidity ($P < 0.01$). However, this suggests that patients were stopping cannabis use sooner if they did not find relief, versus the longer cannabis use correlating with better outcomes. Dyskinesia did not seem to be affected by patient's duration of cannabis use, but patients who used cannabis at least once a day did report improvement in their dyskinesias significantly more than patients who did not take it every day ($P < 0.05$) (Venderová et al., 2004).

Although the survey was useful in creating a large sample size for the study, it was still limited by many factors. Intrinsic limitations to the survey format include self-reporting bias, the placebo effect of cannabis, and inability to control external factors (dosage and timing of cannabis use, administration route, concomitant anti-Parkinson therapy with cannabis, the strain of cannabis used, etc.). Another limitation to study is that when the study was conducted cannabis was illegal in the Czech Republic, which could have led to false reporting on the questionnaire, especially regarding cannabis use before a PD diagnosis (Venderová et al., 2004).

Efficacy of Using Cannabis to Treat Levodopa-Induced Dyskinesia

The globus pallidus (GPI) is believed to be overactive in levodopa-induced dyskinesia in PD, and stimulation of cannabinoid receptors in the GPI reduces gamma-aminobutyric acid (GABA) reuptake and enhances GABA transmission which could potentially alleviate

dyskinesia. With this theory, Sieradzan et al. (2001) developed a study with the aim of assessing whether the cannabinoid receptor agonist, nabilone, would decrease GABA reuptake in the GPI through activation of cannabinoid receptors and thus reduce levodopa-induced dyskinesia in patients with PD. The methods used to conduct this randomized, double-blind, placebo-controlled crossover study included seven patients (n = 7) with a clinical diagnosis of idiopathic PD, who were all experiencing stable levodopa-induced dyskinesia 25% to 50% of the day. The study involved two levodopa challenges performed two weeks apart, and in one phase the patient would receive nabilone and in the other phase, the patient would receive the placebo. The dose of nabilone given to patients was 0.03 mg/kg to the nearest whole milligram and was identical in appearance to the placebo supplement given. Nabilone or placebo would be administered to patients in a double-blind fashion, in two split doses (at 12 hours and 1 hour prior to levodopa administration). All patient assessments were made after the second dose of nabilone/placebo was administered, and the patient's dyskinesias would then be assessed by an assessor blinded to the treatment using post-hoc videotape analysis. The dyskinesia assessment would be performed during "off" periods and every 20 minutes after levodopa treatment during "on" periods. The primary outcome measure was total dyskinesia disability scored using the Rush Dyskinesia Disability Scale, and secondary outcomes measures that pertain to this review included the following: the modified Webster Scale (to measure PD disability during off-period), the on-period duration, and the percentage of on-period dyskinesia (Sieradzan et al., 2001).

The results of Sieradzan et al. primary outcome measure (Rush dyskinesia scale) found that nabilone significantly reduced levodopa-induced dyskinesia compared to the placebo ($P < 0.05$), with median total dyskinesia score after nabilone treatment being 17 (range, 11 – 25) and after placebo administration being 22 (range, 16 – 26). However, results from the secondary

outcome measures revealed no statistically significant differences between nabilone treatment and placebo. Regarding reports of AEs experienced from nabilone, two patients were withdrawn from the study, one for vertigo and the other for symptomatic postural hypotension. The remaining seven patients in the study had mild, transient AEs including dizziness, partial disorientation, and formed visual hallucinations.

There were few limitations to this study as it was double-blinded and placebo-controlled. However, limitations still exist including the small sample size (n = 7), testing only being completed on a singular occasion with nabilone protocol, and a lack of similar findings in primary versus secondary outcome measures (Sieradzan et al., 2001). A final limitation, however unlikely, is that there appears to be only one assessor used in this study to record outcome measures, which could have caused assessor bias in the results.

Another RCT by Mesnage et al. (2004) evaluated the effects of three dopaminergic antagonists of the receptors NK_3 (neurokinin B, SR 142801), NT_1 (neurotensin, SR 48692), and CB_1 (anandamide, SR 141716) on their ability to control the severity of PD motor symptoms and levodopa-induced dyskinesias in PD patients after receiving a single dose of levodopa. SR 141716 is an antagonist acting on the cannabinoid receptor and will be the focus of reviewing this specific study. Patients and methods used in this randomized, double-blind, placebo-controlled study included 24 PD patients who presented with motor fluctuations and levodopa-induced dyskinesias for at least six months and additionally had a response to the levodopa treatment that exceeded 50%. After patient selection, three different studies were designed, and each protocol was comprised of four patients receiving the drug (SR 142801, SR 48692, or SR 141716) and four patients receiving the placebo. All patients were randomly allocated to SR or placebo groups and there was no difference in clinical characteristics of patients who were

receiving the drug vs those receiving the placebo. Patients were then evaluated by videotape procedure after they were administered a single suprathreshold dose of levodopa (50 mg higher than the usual effective dose taken in the morning by each patient) before and at the end of the administration of the SR treatments or placebo. Assessment of patient motor disability and the severity of levodopa-induced dyskinesias was initially done using the UPDRS part III (*motor examination*) and part IV (*complications of therapy*) respectively. Dyskinesias severity was further assessed from 0 (*no abnormal movements*) to 4 (*abnormal movements resulting in severe disability*) every minute for 90 minutes after administration of levodopa. The dyskinesias severity, type, localization, and the timing were also analyzed by the same blinded investigator. The dose of SR 141716 used was 20 mg and was administered once daily, one hour before the administration of first-intake levodopa, for 16 days (Mesnage et al., 2004).

Results of the study found no significant differences in the percentage of PD motor improvement (UPDRS part III) or the severity of levodopa-induced dyskinesias between the group receiving the cannabinoid antagonist (SR 141716) and placebo group. Further, the qualitative analysis did not detect any differences in the type, localization, or timing of dyskinesias before and after SR 141716 or placebo administration. The results led Mesnage et al. to suggest that in this study the neuropeptide antagonist SR 141716, affecting cannabinoid receptors, should not be used to treat motor symptoms or levodopa-induced dyskinesias in PD.

The study held strength in being a randomized, double-blind, placebo-controlled study with few limitations. Limitations do exist though including the small sample number of patients assigned to each of the three protocols (n = 8), which means only four patients were used in assessing the effects SR 141716 (cannabinoid receptor antagonist) on PD against four patients using the placebo. Another potential limitation is that the 20 mg drug dose was too low, which

may be possible as no AEs were reported or observed with treatment. A possible final limitation is that the suprathreshold dose of levodopa had such pronounced effects on the PD patients that any influences of SR 141716 on dyskinesias or motor symptoms were masked (Mesnage et al., 2004).

The final study and RCT addressing cannabis use for levodopa-induced dyskinesia was conducted by Carroll et al. (2004), in order to evaluate the effects of cannabis extract on the severity and duration of dyskinesias in patients suffering from PD, accompanied by secondary objectives assessing the effect of cannabis on motor symptoms of PD and the impact of dyskinesia on function. The authors randomized placebo-controlled double-blind crossover study included 17 patients who met inclusion criteria of having levodopa-induced dyskinesias and were on fixed anti-Parkinson medication at least one month before the study begin. The cannabis treatment used was Cannador capsules taken twice daily, which are an extract of the *Cannabis sativa* plant that is standardized with 2.5 mg of THC and 1.25 mg of CBD per capsule, and were dosed based on patient body weight, reaching a max possible dose of 0.25 mg/kg of THC/day. The study started with a dose-titration phase which entailed escalating the dose at three-day intervals until the patient reached their maximum weight-adjusted dose or started to have intolerable side effects, during which the dose would be decreased to the last tolerated dose. Carroll et al. used two treatment phases, each of four-week duration, and separated by a two-week washout period. Patients were randomized to receive the Cannador for four weeks followed by the placebo for four weeks or vice versa, with the two-week washout period between treatments. Patients completed assessment visits at baseline and then at the end of each treatment phase, with the primary outcome measure being the UPDRS Part IV (*items 32 – 34*) which specifically measure patient levodopa-induced dyskinesias. Secondary outcome measures used

that apply to this review include the following: dyskinesia ADL scale, UPDRS Part III (*motor examination*), Bain dyskinesia scale, Rush dyskinesia scale, and the dyskinesia tablet arm drawing task. On assessment days patients took their trial medication as normal and then arrived at the clinic for the UPDRS to be performed with the patient in an "off" state. A levodopa challenge dose was then administered, during which video recording took place and the patient completed tasks of the Rush dyskinesia and Bain dyskinesia scales every 30 minutes for four hours. Throughout this time frame, when the objectively defined worst dyskinesia occurred patients were asked to copy a spiral on a digitalized tablet that analyzed the amplitude and frequency of abnormal movements. Lastly, the UPDRS would be repeated during the subjectively defined best "on" state (Carroll et al., 2004).

Results of the primary outcome measure, UPDRS Part IV (*items 32 – 34*), found that the overall treatment effect of cannabis on levodopa-induced dyskinesias worsened the patient's dyskinesia (UPDRS score of +0.52), although it did not reach statistical significance (P = 0.09). There was no statistically significant effect of cannabis treatment on any secondary measures, including no treatment effect on overall dyskinesia assessed using the Rush (P = 0.44) and Bain (P = 0.90) scale. Regarding the safety of cannabis in the study, no major AEs occurred requiring hospitalization and similar adverse effects were reported by treatment and placebo groups (Carroll et al., 2004).

There were few limitations to this study as it was double-blinded and placebo-controlled, as well as having a multitude of outcome measures that yielded similar results. In addition, Carroll et al. took extra steps to add strength to the study by collecting medication containers and obtaining blood samples at the final assessment of each treatment phase to measure THC levels and assure patient medication compliance. Carroll et al. also blinded all assessors of the study to

treatment group allocation, while using a separate physician to monitor patient progress and track AEs. Although unlikely, some possible limitations to this study may be inadequate dosing of the cannabis extract or insensitive assessment methods that may miss small changes in dyskinesia.

Discussion

Studies on the use of cannabis to alleviate motor symptoms and levodopa-induced dyskinesia of PD have shown conflicting evidence throughout the course of this literature review. Evidence seems to lean in favor of cannabis use in self-reporting and open-label observational studies, but evidence tends to wane against cannabis use in randomized control trials.

Motor Symptoms

Ten different studies were reviewed regarding cannabis effectiveness for alleviating the motor symptoms caused by PD, with seven studies suggesting cannabis may aid in the treatment of PD motor symptoms. The first three studies reviewed were all conducted using patients of Rabin Medical Center in Israel, with one study being a self-reporting survey design, and the other two studies being open-label observational design. All three studies showed promise in using cannabis cigarettes as an adjunctive treatment to PD motor symptoms; however, this evidence should still be taken with caution due to the collective limitations created by these studies. The first limitation is that all three studies were conducted within a three-year window and at the same medical center which creates a major lack of diversity in the study population, and the second limitation is that all studies had unblinded subjects whom used the same form of cannabis administration, but with different doses which could have caused a significant placebo effect from cannabis use (Balash et al., 2017; Lotan et al., 2014; Shohet et al., 2017).

Multiple studies were also held at another movement disorders clinic in Ribeirao Preto, Brazil. The first study conducted (Zuardi et al., 2008) used an open-label design to assess the

secondary outcome measure of CBD effects on motor symptoms of six PD patients, and the second study conducted (Chagas et al., 2014a) was a double-blind, placebo-controlled trial studying CBD effects on motor symptoms of 21 PD patients. Contradictory to the evidence for cannabis use at Rabin Medical Center, both the studies in Ribeirao Preto found no statistically significant evidence to suggest CBD treatment for the motor symptoms of PD. When assessing the evidence between the studies conducted at Rabin Medical against the studies performed at the clinic in Ribeirao Preto, it eludes to the thought that possibly cannabis containing THC might have a greater effect on PD motor symptoms over a CBD only chemovar. However, other possibilities must be considered as well, some of which include that the study designs at Rabin Medical would be more susceptible to a placebo effect from cannabis than would the double-blind randomized-control trial performed by Chagas et al. in Ribeirao Preto. Another possibility for the contradictory evidence may be accounted for by the lack control in dosing and administration of cannabis in all three studies at Rabin Medical; for example, the more cannabis a patient chose to smoke could cause drastic differences in patient motor symptoms presentation (Balash et al., 2017; Chagas et al., 2014a, Lotan et al., 2014; Shohet et al., 2017; Zuardi et al., 2008).

The remaining four studies reviewed to assess cannabis efficacy in treating PD motor symptoms were of self-reporting design administered via survey/questionnaire, but only one of four studies returned evidence to suggest cannabis use for PD motor symptoms (Finseth et al., 2015; Friedman, 2014; Kindred et al., 2017; Venderová et al., 2004). The study with suggestive evidence for cannabis to treat PD motor symptoms was done by Venderová et al. (2004). This study surveyed 85 patients using cannabis for their PD with only 39 of the 85 patients using it for motor symptoms. 30.6% found tremor relief, 44.7% bradykinesia relief, 37.7% muscle rigidity

relief, and 14.1% found cannabis improved their levodopa-induced dyskinesia. Of additional note the study by Kindred et al. (2017) surveyed 410 PD patients with 66.3% of them claiming to have used cannabis at some point to try and alleviate their PD symptoms. Of those that used cannabis 85% reported significant improvement of their symptoms. However, the assessment tool used was the 8-point Likert scale which does not give results in terms of specific symptoms alleviated, which leaves no effective way of measuring motor symptom relief (Kindred et al., 2017).

There does not seem to be enough evidence in the literature overall to suggest that cannabis use is an effective therapy to alleviate the motor symptoms of PD. The current literature lacks quality studies that support using cannabis for motor symptoms, and the only RCT (Chagas et al., 2014a) found results that suggested cannabis does not have a beneficial effect on motor symptoms of PD. In addition, the studies that are available have significant limitations including small sample size and lack of cannabis dose, administration, and chemovar control. Furthermore, many studies are limited through not being able to account for the effects caused by patient's current anti-Parkinson's medications versus cannabis administration.

Levodopa-Induced Dyskinesia

The results from the RCTs evaluating cannabis effectiveness for alleviating levodopa-induced dyskinesia seems to vary based on the mechanism of action of the cannabis formulation used in each study. In one randomized, double-blind, placebo-controlled crossover study, a cannabinoid receptor agonist, nabilone, was seen to cause significant reduction in levodopa-induced dyskinesia compared to the placebo ($P < 0.05$) (Sieradzan et al., 2001). Contrarily, two other RCTs using Anandamide, a cannabinoid antagonist, and Cannador, *Cannabis sativa* extract, found no statistically significant differences in either the UPDRS part IV or part III scores which

are specific to motor symptoms and levodopa-induced dyskinesia (Carroll et al., 2004; Mesnage et al., 2004). Furthermore, the study by Carroll et al. actually showed that Cannador capsules worsened UPDRS levodopa-induced dyskinesia scores, although it did not reach statistical significance ($P = 0.09$).

Considering all three studies had strong study designs, but only Sieradzan et al. study with nabilone relieved levodopa-induced dyskinesia, there is the possibility that cannabinoid receptor agonists may have the potential to decrease levodopa-induced dyskinesia. However, it seems more likely that the results from the two more recent studies by Carroll et al. and Mesnage et al. should be considered and cannabis supplementation should not be suggested to relieve levodopa-induced dyskinesia in PD. Of additional importance, neither the RCT by Carroll et al. or Mesnage et al. found statistically significant improvement in PD patient motor scores on the UPDRS part III, which adds strength to the previous conclusion that there is not enough evidence to firmly suggest cannabis use for PD motor symptoms.

Cannabis Safety and Chemovar Preference

Cannabinoids appear to be well tolerated overall throughout the literature, and none of the studies reviewed reported any incidence of hospitalization or overdose from using cannabis. Adverse effects (AEs) vary greatly by the chemovar of cannabis used in each study, but the recurring theme in most studies trends on THC-predominant chemovars having more AEs than CBD-predominant chemovars (Buhmann et al., 2019; MacCullum & Russo, 2018). When a THC chemovar is used the most common AEs tend to be fatigue or drowsiness, dizziness, dry mouth, anxiety, nausea, inhibited cognition, and smoking induced cough, phlegm, and bronchitis (MacCullum & Russo, 2018); furthermore, it is suggested that THC-predominant chemovars not be used in patients with psychosis, psychiatric disease, dementia, active hallucinations, substance

abuse disorder, COPD, asthma, pregnancy, and lactation as THC chemovars tend to worsen these conditions (Balash et al., 2017; Buhmann et al., 2019; Carroll et al., 2004; Friedman, 2015; MacCullum & Russo, 2018). Of additional importance, the drug Nabilone used in the RCT by Sieradzan et al., should be used with great caution in patients with cardiac conditions as it caused all seven subjects in the study to have a drop in systolic blood pressure and caused two patients to drop out of the study due to symptomatic orthostatic hypotension (Buhmann et al., 2019; Sieradzan et al., 2001).

Prescribing cannabis safely is a challenge for medical providers due to lack of education on cannabinoids in medical curriculum and the lack of quality studies on cannabis (Bega et al., 2017). However, if a provider is considering prescribing cannabis for a patient, no matter the condition a few general guidelines should apply. First, always try to dose cannabis as low as possible while still eliciting therapeutic effects and avoid methods of administration involving smoking/burning of the cannabis as this is associated with the development of multiple other respiratory conditions. Second, use a CBD-predominant chemovar or a Type II cannabis (CBD/THC mixed chemovar), as CBD has shown throughout the literature to have more analgesic, anti-inflammatory, and anti-psychotic effects than THC, while reaping the additional benefit of having minimal to no AEs (Bega et al., 2017; MacCullum & Russo, 2018).

Secondary Outcomes Observed

CBD for non-motor symptoms of Parkinson's disease. Parkinson's disease is debilitating to patients beyond just the motor symptoms experienced. It has been observed that many of the patients throughout these trials are also experiencing troubles with mood disorders, pain, fatigue, lack of appetite or early satiety, weight loss, troubled sleeping, and cognitive changes such as memory loss or dementia. Although there may not be a place for cannabis to

treat the motor symptoms of PD, there still may be a use for cannabis to alleviate the non-motor symptoms of PD. Many studies throughout this review saw patients either already using cannabis to treat non-motor symptoms of PD, or finding a benefit from cannabis use when taken during clinical trials (Balash et al., 2017; Chagas et al., 2014a; Chagas et al., 2014b; Finseth et al., 2015; Friedman, 2014; Kindred et al., 2017; Venderová et al., 2004; Zuardi et al., 2009). Although it is suggested that cannabis should not be used to specifically treat motor symptoms of PD, it must be acknowledged by providers that cannabis, especially CBD chemovars, may have a therapeutic, and safe, effect on the non-motor symptoms of PD.

CBD for RBD. Rapid eye movement (REM) sleep behavior disorder (RBD) is a condition that often presents in patients suffering from PD. It characterized by an odd blend of motor and non-motor symptoms occurring while a patient sleeps which include: talking, yelling, kicking, punching, and gesturing. RBD occurs as a result of the loss of atonia or paralysis during the REM sleep cycle, and thus allows patients to act out their dreams since motor activity inhibition is lost. In the study by Chagas et al. (2014b), the authors found that CBD may have a beneficial effect on relieving the RBD experienced in these PD patients. The administration of CBD to three patients yielded relief of RBD symptoms from 2 – 7 times a week to 0 symptoms per week for six consecutive weeks, and in the last patient from 2 – 4 times per week to only once a week for six consecutive weeks. Although this was a small case series, it still holds significant implications for the future use of CBD to relieve RBD in patients with PD (Chagas et al., 2014b).

Conclusion

While there are trials suggesting cannabis may be effective in treating motor symptoms and dyskinesia in PD, a conclusion could not be made due to lack of quality evidence, low

number of trials conducted, and lack of quality study design in the trials displaying cannabis efficacy. Due to the debilitating and progressive nature of PD, it is suggested that cannabis use for motor symptoms and dyskinesia be used stringently in cases where patients motor symptoms may be refractory other treatment, or the patient has become desperate for any sort of symptomatic relief. Furthermore, if a provider does choose to use cannabis to treat motor symptoms or dyskinesia, it is suggested they prescribe a CBD-predominant chemovar in order to reduce AEs of treatment and to not exacerbate any underlying psychiatric condition. As cannabis use gains popularity in PD treatment, clinicians and the general public can benefit from more adequately controlled clinic trials evaluating the pharmacology, safety, drug interactions, and efficacy of cannabis use in PD.

Applicability to Clinical Practice

Medical cannabis is becoming more frequently requested by patients in a multitude of clinical settings and for a variety of reasons. PD is one of the reasons in question, and many providers could benefit from further education on cannabis efficacy, chemovar preference, drug interactions, and side effects when they are considering therapies for their patients with PD. The research conducted in this literature review can act as a guiding factor to medical providers when deciding whether they want to prescribe medical cannabis in their practice.

References

Balash, Y., Bar-Lev Schleider, L., Korczyn, A., Shabtai, H., Knaani, J., Rosenberg, A., … Gurevich, T. (2017). Medical cannabis in Parkinson disease: Real-life patients' experience. *Clinical Neuropharmacology*, *40*(6). https://dx.doi.org/10.1097/WNF.0000000000000246

Bega, D., Simuni, T., Okun, M., Chen, X., & Schmidt, P. (2017). Medicinal cannabis for Parkinson's disease: Practices, beliefs, and attitudes among providers at National Parkinson Foundation Centers of Excellence. *Movement Disorders Clinical Practice*, *4*(1), 90–95. https://dx.doi.org/10.1002/mdc3.12359

Buhmann, C., Mainka, T., Ebersbach, G., & Gandor, F. (2019). Evidence for the use of cannabinoids in Parkinson's disease. *Journal of Neural Transmission*, *126*(7), 913–924. https://dx.doi.org/10.1007/s00702-019-02018-8

Carroll, C., Bain, P., Teare, L., Liu, X., Joint, C., Wroath, C., … Zajicek, J. (2004). Cannabis for dyskinesia in Parkinson disease: A randomized double-blind crossover study. *Neurology*, *63*(7), 1245. https://dx.doi.org/10.1212/01.WNL.0000140288.48796.8E

Chagas, M., Eckeli, A., Zuardi, A., Pena-Pereira, M., Sobreira-Neto, M., Sobreira, E., … Crippa, J. (2014). Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: A case series. *Journal of Clinical Pharmacy and Therapeutics*, *39*(5), 564–566. https://dx.doi.org/10.1111/jcpt.12179

Chagas, M, Zuardi, A., Tumas, V., Pena-Pereira, M., Sobreira, E., Bergamaschi, M., … Crippa, J. (2014). Effects of cannabidiol in the treatment of patients with Parkinson's disease: An

exploratory double-blind trial. *Journal of Psychopharmacology*, *28*(11), 1088–1098. https://dx.doi.org/10.1177/0269881114550355

Finseth, T., Hedeman, J., Brown, R., Johnson, K., Binder, M., & Kluger, B. (2015). Self-reported efficacy of cannabis and other complementary medicine modalities by Parkinson's disease patients in Colorado. *Evidence-Based Complementary and Alternative Medicine*, *2015*, 1–6. https://dx.doi.org/10.1155/2015/874849

Friedman, J. (2014). "Medical marijuana" use in a movement disorders clinic in Rhode Island. *Parkinsonism & Related Disorders, 20*(11), 1293–1294. https://dx.doi.org/10.1016/j.parkreldis.2014.07.006

Kindred, J., Li, K., Ketelhut, N., Proessl, F., Fling, B., Honce, J., … Rudroff, T. (2017). Cannabis use in people with Parkinson's disease and Multiple Sclerosis: A web-based investigation. *Complementary Therapies in Medicine*, *33*, 99–104. https://dx.doi.org/10.1016/j.ctim.2017.07.002

Lotan, I., Treves, T., Roditi, Y., & Djaldetti, R. (2014). Cannabis (medical marijuana) treatment for motor and non–motor symptoms of Parkinson disease: An open-label observational study. *Clinical Neuropharmacology, 37*(2). https://dx.doi.org/10.1097/WNF.0000000000000016

MacCallum, C., & Russo, E. (2018). Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine*, *49*, 12–19. https://dx.doi.org/10.1016/j.ejim.2018.01.004

Medical Marijuana. (2019). Retrieved from https://www.parkinson.org/Understanding-Parkinsons/Treatment/Medical-Marijuana.

Mesnage, V., Houeto, J., Bonnet, A., Clavier, I., Arnulf, I., Cattelin, F., … Agid, Y. (2004). Neurokinin B, neurotensin, and cannabinoid receptor antagonists and Parkinson disease: *Clinical Neuropharmacology*, *27*(3), 108–110. https://dx.doi.org/10.1097/00002826-200405000-00003

Robledo, I., & Jankovic, J. (2017). Media hype: Patient and scientific perspectives on misleading medical news: Perspectives on Misleading Medical News. *Movement Disorders*, *32*(9), 1319–1323. https://dx.doi.org/10.1002/mds.26993

Shohet, A., Khlebtovsky, A., Roizen, N., Roditi, Y., & Djaldetti, R. (2017). Effect of medical cannabis on thermal quantitative measurements of pain in patients with Parkinson's disease. *European Journal of Pain*, *21*(3), 486–493. https://dx.doi.org/10.1002/ejp.942

Sieradzan, K., Fox, S., Hill, M., Dick, J., Crossman, A., & Brotchie, J. (2001). Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: A pilot study. *Neurology, 57*(11), 2108. https://dx.doi.org/10.1212/WNL.57.11.2108

Venderová, K., Růžička, E., Voříšek, V., & Višňovský, P. (2004). Survey on cannabis use in Parkinson's disease: Subjective improvement of motor symptoms. *Movement Disorders*, *19*(9), 1102–1106. https://dx.doi.org/10.1002/mds.20111

Zuardi, A., Crippa, J., Hallak, J., Pinto, J., Chagas, M., Rodrigues, G., … Tumas, V. (2008). Cannabidiol for the treatment of psychosis in Parkinson's disease. *Journal of Psychopharmacology*, *23*(8), 979–983. https://dx.doi.org/10.1177/0269881108096519