Parkinson's Disease

ISSUE BRIEF ON PARKINSON'S DISEASE

Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Parkinson's disease (PD) is a chronic, progressive disorder that involves malfunction and death of nerve cells in the brain - neurons. It primarily affects neurons in an area of the brain called the substantia nigra. Some of the dying neurons produce dopamine, a chemical that sends messages to the part of the brain that controls movement and coordination. As PD progresses, the amount of dopamine produced in the brain decreases, leaving a person unable to control movement normally. Scientists are also exploring the idea that loss of cells in other areas of the brain and body contribute to PD. For example, researchers have discovered that the hallmark sign of PD – clumps of protein called Lewy Bodies – are found not only in the mid-brain but also in the brain stem and the olfactory bulb. These areas of the brain correlate to non-motor functions such as sense of smell and sleep regulation. The presence of Lewy bodies in these areas could explain the non-motor symptoms experienced by some people with PD before any motor sign of the disease appears. The intestines also have dopamine cells that

degenerate in PD and this may be important in the GI symptoms that are part of the disease (PDF, 2017a).

Each person with PD will experience symptoms differently. For example, many people experience tremor as their primary symptom, while others may not have tremors, but may have problems with balance. Also, for some people the disease progresses quickly and in others it does not. The diagnosis of PD depends upon the presence of one or more of the four most common motor symptoms of the disease (PDF 2017b):

- Resting Tremor - a shaking or oscillating movement that usually appears when the affected limb (less frequently the face or jaw) is relaxed or at rest.
- Bradykinesia – a general reduction of spontaneous movement, which can give the appearance of abnormal stillness and a decrease in facial expressivity (bradykinesia means "slow movement").
- Rigidity – stiffness and inflexibility of the limbs, neck and trunk. The rigidity can be painful.
- Postural Instability – a tendency to be unstable when standing upright. A person with postural instability has lost some of the reflexes needed for maintaining an upright posture and may topple backwards if jostled even slightly.

Most people with PD also experience non-motor symptoms - those that do not involve movement, coordination, physical tasks, or mobility. While a person's family and friends may not be able to see them, these "invisible" symptoms can actually be more troublesome for some people than the motor impairments of PD. Many researchers believe that non-motor symptoms may precede motor symptoms – and a PD diagnosis – by years. The most recognizable early symptoms include: loss of sense of smell, constipation, sleep disorder (REM behavior disorder), mood disorders, and orthostatic hypotension (low blood pressure when standing up). Other non-motor symptoms include excessive saliva, weight loss or gain, vision and dental problems, fatigue and loss of energy, depression, fear and anxiety, skin problems, and cognitive issues such as memory difficulties, confusion, and dementia (PDF 2017b).

Prevalence

Parkinson's disease is among the most common neurodegenerative conditions. Although its cause is unknown, many investigators believe that the diseases arises from an interaction between genetic and environmental factors. Prevalence of PD increases steadily with age. Prevalence by age grouping is as follows (all per 100,000): 41 for 40-49 years, 107 for 50-59 years, 428 for 60-69 years, 1087 for 70-79 years, and 1903 for age 80+ (Pringsheim 2014).

Current Therapies

No available therapies alter the underlying neurodegenerative process of PD, but treatments exist to treat the disease's symptoms. Levodopa, a dopamine precursor, is generally considered the most effective treatment for motor symptoms of PD. However, it has important

limitations: fluctuating effect over time and dyskinesia as a common side effect. Levodopa's beneficial effect wears off over hours and, over years, it can become decreasingly effective. There are strategies to try to minimize this fluctuation. The dyskinesia side effect can be quite severe, causing abnormal, involuntary movements. Drugs are available to try to minimize the development and severity of dyskinesia. In addition to levodopa, other types of drugs are also used to control motor symptoms, including dopamine agonists, anticholinergic drugs, beta-blockers, and monoamine oxidase type-B inhibitors. These drugs are sometimes used in addition to levodopa or instead of levodopa. Therapies are available for many non-motor symptoms including cholinesterase inhibitors for PD dementia, antidepressants and pramipexole for depression, botulinum toxin injections for excessive saliva, and clozapine for hallucinations. Axial motor symptoms, including falls, difficulty swallowing, and postural instability tend to be treatment-resistant (Connolly 2014).

Pre-Clinical Research

It is well established that the cannabinoid and dopamine signaling systems interact in the parts of the brain involved with Parkinson's disease. A review by Garcia et al (Garcia 2015) provides a readable, though rather technical, introduction to the very complex interactions between these systems. Until recently, it had been thought that the cannabinoid system exerted influence indirectly on the dopamine system, due to absence of CB1 receptors on the dopamine-producing neurons. The influence was thought to be only through nerves nearby, which have CB1 receptors, that stimulate and inhibit the dopamine neurons. Recently, research has also shown direct influence, through a receptor other than CB1 (TRVP1 and, perhaps, CB2 receptors), on dopamine neurons. It has been observed that, in parts of the brain affected in Parkinson's disease, where dopamine levels are reduced, endocannabinoid levels are elevated.

Preclinical studies using different models of experimental PD have investigated the effects of both agonists (activators) and antagonists (prevent activation) of cannabinoid receptors, as discussed in a review by Bassi et al (Bassi 2017). Studies administering different CB1 (cannabinoid receptor 1) agonists have had different results – some exacerbating but most improving motor impairment. Studies of CB1 antagonists more consistently show improvement in motor symptoms. These authors caution, "emerging contradictory results from animal models simulating PD demand development of new pharmacological tools, improved screening models, upgraded technologies, and specific ligands for evaluating the therapeutic potential of cannabinoids in PD."

There is intriguing evidence that cannabinoids protect nerves from damage through reducing oxidative injury, excitotoxicity, and calcium reflux. They are thought to also decrease inflammation by modulating glial processes that are associated with neuron survival. So there is some hope that cannabinoids may provide neuroprotection in PD through these processes (More 2015). Injection of the cannabinoid THCV in mice with an animal model of PD both improved motor symptoms and reduced the loss of dopamine-producing neurons in sections of the brain relevant to PD (Garcia 2011).

Clinical Trials

Clinical trials to date show limited evidence of effectiveness of cannabis for treating symptoms of PD or for treating levodopa-induced dyskinesia. Both completed trials are limited by small sample size and relatively short duration. The CBD trial now being organized (described below) will have a longer treatment period and larger sample size than the completed trial.

Chagas MH, Zuardi AW, Tumas V, Pena-Pereira MA, Sobreira T, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial. *J Psychopharm* **2014;28:1088-1092.**

This double-blind, placebo-controlled trial studied the effects of cannabidiol (CBD) on 21 Parkinson's disease patients with no psychiatric co-morbidities and no prior cannabis use. Three groups of participants (n=7 in each group) were randomly assigned to 300 mg CBD daily, 75 mg CBD daily, or placebo as an adjunct to their stable dosages of anti-parkinson medications. Placebo and CBD were administered in gelatin capsules with the drug dissolved in corn oil. Three assessments were done at baseline and at the end of the six-week treatment period:

- Unified Parkinson's Disease Rating Scale (UPDRS). The four parts of the UPDRS assess, 1) mentation, behavior, and mood, 2) activities of daily living, 3) motor exam, 4) complications of therapy.
- Parkinson's Disease Questionnaire-39 (PDQ-39) to assess functioning and well-being
- Udvalg for kliniske undersegelser (UKU) side effect rating scale to evaluate possible adverse effects of CBD

No statistically significant differences were observed between the three study groups in either UPDRS or UKU. The total PDQ-39 scores showed a greater improvement in the 300 mg CBD group than in the placebo group. Improvement was also significantly better in the 300 mg CBD group than in the placebo group for two of the PDQ-39 subsections: daily life activities and stigma.

The authors concluded they found no statistically significant differences concerning the motor symptoms of PD, though they found a possible effect of CBD in improving measures related to qualify of life. They acknowledge their study was limited by very small sample sizes and by not measuring specific symptoms of Parkinson's disease.

Carroll CB, Bain PG, Teare L, Liu X, Joint C, et al. Cannabis for dyskinesia in Parkinson's disease: A randomized double-blind crossover study. *Neurology* **2004;63:1245-1250.**

This paper describes a small randomized, double-blind, placebo-controlled crossover trial of an oral cannabis extract as therapy for levodopa-induced dyskinesia. The study drug was Cannador, an extract (in ethanol) of cannabis standardized to 2.5 mg Δ9-THC and 1.25 mg cannabidiol per capsule. To enroll, patients had to be on a stable anti-Parkinson's drug regimen for at least one month and remained on that mediation throughout the study. The 19 PD patients enrolled were randomized to either four weeks of active treatment followed by four weeks of placebo or vice versa, with a two-week washout interval between the two treatment periods. During the active drug treatment period patients were started on a low dose (unspecified) and the dose was increased every three days to a target of 25 mg/kg/day THC in

two divided doses. Assessments were done at baseline and at the end of the two treatment periods. The primary outcome measure was change in score for the part of the Unified Parkinson's Disease Rating Scale related to dyskinesia (Part 4; questions 32-34). There were also multiple secondary outcomes that assessed activities of daily living, quality of life, and additional dyskinesia severity scales. Two patients withdrew after the baseline assessment: one developed diarrhea (on placebo), the other had a family bereavement. Data from the remaining 17 participants were analyzed. Eleven patients failed to reach their target dose on active treatment, as did nine patients on placebo. During the active drug treatment period average dose was 0.146 mg/kg/day (range 0.034 to 0.25) THC. Results showed no evidence of treatment effect on levodopa-induced dyskinesia as assessed by the UPDRS or on any other secondary outcome measures. The authors also note there was no evidence of pro- or anti-parkinsonian effect of the cannabis extract.

A study of tolerability and efficacy of cannabidiol on tremor in Parkinson's disease: NCT02818777 (registered on www.clinicaltrials.gov)

This study will occur in two stages. Stage 1 is an open-label study of 10 Parkinson's disease patients where the dose of the study drug, an oral solution that is 98% CBD, is gradually increased to manufacturer's (GW Pharma) recommended target dose. Tolerability will be evaluated at each dose level. Based on the results of Stage 1, a target dose will be set for stage 2. The major purpose of Stage 2 is to assess the safety and tolerability of the study drug at the determined dose, and secondarily to study efficacy, particularly regarding tremor. Stage 2 is a crossover, double-blind, randomized controlled trial with 50 subjects and a 19-week treatment period. The study is being conducted in Colorado. It began in July, 2016 and is now recruiting participants. Estimated study completion date is June, 2019.

Observational Studies

Surveys and observational studies provide mixed evidence of effectiveness of cannabis on PD motor symptoms. A small study reported reduced motor symptoms after a single dose of smoked cannabis (Lotan 2014), a survey of PD patients at a movement disorder clinic in Prague (Venderova 2004) reported reduced motor symptoms in approximately one-third of PD patients, and a different survey at a Colorado movement disorder clinic indicated a smaller proportion of cannabis-using PD patients experiencing reduction in motor symptoms (Finseth 2015). The Colorado survey suggested a greater effect of cannabis on non-motor symptoms – especially sleep and mood – than on motor symptoms. The small case series of PD patients with REM sleep behavior disorder (Chagas 2014) supports the sleep-improving effect of cannabidiol for PD patients.

Lotan I, Treves TA, Roditi Y, Djaldetti R. Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: An open-label observational study. *Clin Neuropharmacol* 2014;37:41-44.

This single-administration study was carried out at a movement disorder clinic in Israel. It enrolled 28 Parkinson's disease patients who used cannabis daily for at least two months with no major adverse effects. Data was collected before and 30 minutes after patients smoked their

regular amount of cannabis. Six patients discontinued the dose due to severe side effects (inability to smoke, vomiting, dizziness, psychosis). On the day of testing patients were asked to arrive at the clinic without having taken their usual anti-PD medications so that their baseline motor status could be assessed. Assessments included the motor components of the Unified Parkinson's Disease Rating Scale (USPDS) and visual analog scales for non-motor symptoms. Both motor and non-motor symptoms were reported as improving significantly after the cannabis dose.

Venderova K, Ruzicka E, Vorisek V, Visnovsky P. Survey on cannabis use in Parkinson's disease: Subjective improvement of motor symptoms. *Mov Disord* 2004;19:1102-1106.

A survey was mailed to all patients with PD registered at Prague Movement Disorders Centre (Czech Republic). The questionnaire could be returned anonymously and it asked about cannabis use, effect of cannabis on PD symptoms, use of other PD medications, and demographics. The authors note that, prior to development of the study, a PD patient's remarkable benefit from cannabis had received a lot press coverage and they observed a growing number of their patients were starting to use cannabis to relieve PD symptoms. Of 630 questionnaires sent, 339 were returned (54% response rate). Average age was 65.7 years with mean PD duration of 8.5 years. Cannabis use was reported by 85 respondents (25.1%). None had any experience with recreation use of cannabis before taking it to alleviate PD symptoms and none had been advised to use cannabis by a doctor. All continued using the antiparkinsonian therapy recommended by their neurologist. After cannabis, 39 respondents (46% of all using cannabis) described mild or substantial alleviation of their symptoms in general, 31% improvement of rest tremor, 25% alleviation of bradykinesia, 38% alleviation of muscle rigidity, and 14% improvement of levodopa-induced dyskinesias. Four patients (5%) reported that cannabis worsened symptoms. Symptom alleviation occurred, on average, 1.7 months after cannabis initiation (range=1 hour to 6 months). This relatively long period of use before symptom reduction makes placebo effect seem a less likely explanation for perceived benefit. The study's limitations include potential response bias: those responding might differ systematically from those who did not respond.

Finseth TA, Hedeman JL, Brown RP, Johnson KI, Binder MS, Kluger BM. Self-reported efficacy of cannabis and other complementary medicine modalities by parkinson's disease patients in Colorado. *Evid Based Complement Alternat Med* 2015;2015:874849. doi: 10.1155/2015/874849.

The investigators administered a survey regarding complementary and alternative medicine (CAM) therapies to PD patients at a movement disorder clinic at the U of Colorado Hospital. They did not track refusal rate, but estimated it at 10%. The survey inquired about use and helpfulness of 23 forms of complementary and alternative medicine, including cannabis. The survey was administered between November 2012 and August 2013 – shortly after recreational cannabis was legalized in Colorado and after the state's medical program had been in place for several years. Respondents were of relatively high socioeconomic status: 82% had at least some college education and 60% reported an income above %60,000. Nine of the 207 respondents (4.3%) reported past or current use of cannabis as treatment for their PD. Five reported "great improvement" in their symptoms with cannabis. In particular, five reported improvement in their mood and sleep and two reported improvement in their motor symptoms

and quality of life. Among all 27 CAM treatment modalities, cannabis was rated among the most effective for sleep and mood improvement.

Chagas MHR, Eckeli AL, Zuardi AW, Pena-Pereira MA, Sabreira-Neto A, et al. Cannabidiol can improve complex sleep-related behaviors associated with rapid eye movement sleep behavior disorder in Parkinson's disease patients: a case series. *J Clin Pharm Ther* **2014;39:564-566.**

Persons with RBD tend to have nightmares during the REM (rapid eye movement) phase of sleep. And, instead of having the usual atonia (sleep paralysis) during REM sleep, patients with RBD exhibit such behaviors as shouting, hitting and kicking – sometimes injuring their sleeping partner. Persons with RBD are at increased risk of developing PD later in life. Four PD patients who participated in prior studies of cannabidiol therapy were identified as having RBD. During the period of CBD therapy three of the four had complete cessation of their RBD symptoms and one had a large reduction in RBD symptoms.

National Medical Organization Recommendations

In the National Academy of Sciences 2017 report, *The Health Effects of Cannabis and Cannabinoids*, there is a short section on the potential of cannabis or cannabinoids as treatment for Parkinson's disease or its symptoms. It's conclusion (Conclusion 4-11): "There is insufficient evidence that cannabinoids are an effective treatment for the motor system symptoms associated with Parkinson's disease or levodopa-induced dyskinesia" (NAS report 2017).

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