MDH Minnesota Department *of* Health

Minnesota Medical Cannabis Program
Petition to Add a Qualifying Medical Condition

Making your petition

- ☐ Any person may petition the Minnesota Department of Health ("the department" or "MDH") to add a qualifying medical condition to those listed in subdivision 14 of Minnesota Statutes section 152.22.

Petitions will be accepted only between June 1 and July 31, 2017.
Petitions received outside of these dates will not be reviewed.

Petitions must be sent by certified U.S. mail to:

Minnesota Department of Health
Office of Medical Cannabis
P.O. Box 64882
St. Paul, MN 55164-0882

- ☐ You must mail the original copy of the petition with an original signature.
- ☐ Complete each section of this petition and attach all supporting documents. Clearly indicate which section of the petition an attachment is for.
- ☐ Each petition is limited to one proposed qualifying medical condition. If your petition includes more than one medical condition, it will be dismissed.
- ☐ If you are petitioning for the addition of a medical condition that was considered but not approved in a prior year's petition process, you **must include** new scientific evidence or research to support your petition or describe substantially different symptoms. Please refer to our website to see which medical conditions were reviewed in prior years (http://www.health.state.mn.us/topics/cannabis/rulemaking/addconditions.html).
- ☐ If the petition is accepted for consideration, MDH will send the petition documents to the Medical Cannabis Review Panel ("Review Panel"). MDH staff will also provide information to the Review Panel about the proposed qualifying condition, its prevalence, and the effectiveness of current treatments.
- ☐ You may withdraw your petition any time before the Review Panel's first public meeting of the year by submitting a written statement to the Department stating that you want to withdraw it.

Petition review process

- ☐ An appointed citizens Review Panel will meet to review all eligible petitions.
- ☐ MDH will post notice of the public meetings of the Review Panel on its medical cannabis website.
- ☐ After the public meeting and by November 1, the Review Panel will provide the Commissioner of Health its written report of findings.
- ☐ The Commissioner will approve or deny the petition by December 1.

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Section A: Petitioner's Information			
Name (First, Middle, Last): [redacted]			
Home Address (including Apartment or Suite #): [redacted]			
City: [redacted]		State: MN	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [redacted]		

Section B: Medical Condition You Are Requesting Be Added

Please specify the name and provide a brief description of the proposed qualifying medical condition. Be as precise as possible in identifying the condition. **Optional:** Include diagnostic code(s), citing the associated ICD-9 or ICD-10 code(s), if you know them. *Attach additional pages as needed.*

Parkinson's Disease.

See attached Section B.

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Section C: Symptoms of the Proposed Medical Condition and/or Its Treatment

Describe the extent to which the proposed qualifying medical condition or the treatments cause suffering and impair a person's daily life. *Attach additional pages if needed.*

See attached Section C.

Section D. Availability of conventional medical therapies

Describe conventional medical therapies available and the degree to which they ease the suffering caused by the proposed qualifying medical condition or its treatment. *Attach additional pages if needed.*

See attached Section D.

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Section E: Anticipated benefits from Medical Cannabis

Describe the anticipated benefits from the medical use of cannabis specific to the proposed qualifying medical condition. *Attach additional pages if needed.*

See attached Section E.

Section F (optional): Scientific Evidence of Support for Medical Cannabis Treatment

It will strengthen your petition to include evidence generally accepted by the medical community and other experts supporting the use of medical cannabis to alleviate suffering caused by the proposed medical disease or its treatment. This includes but is not limited to full text, peer-reviewed published journals or other completed medical studies. Please attach complete copies of any article or reference, not abstracts.

☑ ***I have attached relevant articles.*** *(check box if you have attached scientific articles or studies)*

Section G (optional): Letters in Support of Adding the Medical Condition

Attach letters of support for the use of medical cannabis from persons knowledgeable about the proposed qualifying medical condition, such as a licensed health care professional.

☐ ***I have attached letters of support.*** *(check box if you have attached letters of support)*

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Section H: Acknowledgement and Signature

Please Note: Any individually identifiable health information relating to any past, present, or future health condition or health care contained in this Petition is classified as a health record under Minnesota Statutes §144.291, and is not subject to public disclosure.

I certify that the information provided in this petition is true and accurate to the best of my knowledge.

[redacted] 07/31/2017

SIGNATURE DATE (mm/dd/yyyy)

To obtain this information in a different format, call:
(651) 201-5598 in the Metro area and (844) 879-3381 in the Non-metro.

Section A: Petitioner's Information

[redacted]

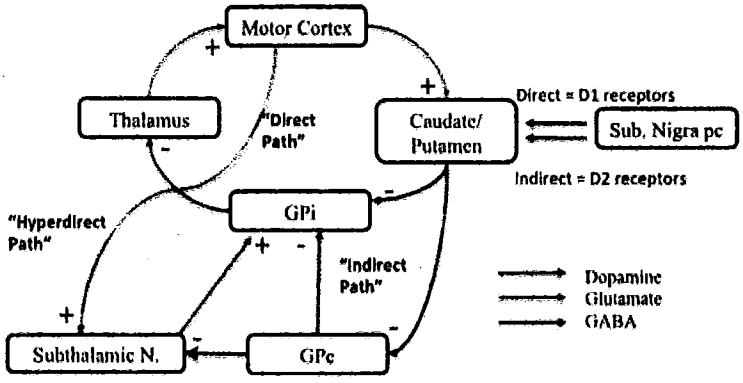
Section B: Description[1]

Parkinson's disease is a progressive neurological disorder of the basal ganglia, a group of nuclei located at the base of the forebrain that affects movement. The striatum is the largest nuclear complex of the basal ganglia, which receives excitatory input from the cerebral cortex and both inhibitory and excitatory inputs from the dopaminergic cells of the substantia nigra pars compacta (SNc). These inputs are received by two types of spiny projection neurons: 1) the internal segment of the globus pallidus (GPi) which is the major output site of the basal ganglia; and 2) the external segment of the globus pallidus (GPe) which establishes an indirect pathway to the GPi through the subthalamic nucleus (STN). These direct and indirect pathways regulate the neuronal output from the GPi that provide a tonic inhibitory input to the thalamic nuclei that project to the primary and supplementary motor areas. There are no standard criteria for the neuropathologic diagnosis of Parkinson's as characteristic findings have not been solidified. There are however, two major neuropathologic findings:

1) The loss of dopaminergic neurons of the SNc; approximately 60-80% of the dopaminergic neurons are lost PRIOR to the emergency of noticeable decline in motor skills emerge

2) **The presence of Lewy bodies and Lewy neuritis:** In Parkinson's disease, a dopamine deficiency in the nerve terminals of the striatum in the forebrain result from the destruction of dopaminergic cells in the SNc. These changes impair cognitive and affective abilities, motor output and control, and neuropsychological systems. While the loss of neuronal cells is unknown, the trigger of dopaminergic degeneration appears to result from a multitude of factors including both environmental and genetic factors.

Basal Ganglia Pathways



Section C: Symptoms of the Proposed Medical Condition and/or its Treatments

Symptoms

The onset of motor impairments is typically asymmetric in nature; most common initial finding being asymmetric resting tremor in an upper extremity. As time progresses the afflicted may notice symptoms akin to progressive dyskinesia, tremors, rigidity, and dystonia.[2]

Tremors: vary considerably from stress induced to the classic resting tremor (occurs with the extremity in a resting position) and dissipates with movement, although voluntary movement initiation via inhibition of tremors is progressively impaired. Asymmetrical in nature, they begin in one upper extremity (typically the fingers or thumb) and may be intermittent. Tremors spread at varying rates (months to years) to the ipsilateral lower extremity or the contralateral upper extremity before becoming more generalized. In late stages of the disorder, they affect motoric output, speech production, and fine and gross motor control.

Bradykinsia: is slowness in movement and may result in a sense of weakness, loss of dexterity, fatigue, or achiness when preforming repeated actions. Patients have described it as the "message not getting to the limb." Facial bradykinesia early onset may be marked by softer, monotone speech while advanced cases speech because slurred and difficult to understand. It is also tied to a decreased blink rate or lack of facial expression. Truncal bradykinesia results in slowness or difficulty in rising from a chair, turning over in bed, or walking. If walking is affected, patients may take smaller steps and gait cadence is reduced. In the upper extremities, bradykinesia can cause small, effortful handwriting (ie, micrographia) and difficulty using the hand for fine dexterous activities such as using a key or kitchen utensils. In the lower extremities, unilateral bradykinesia commonly causes scuffing of that foot on the ground, as it is not picked up during leg swing. This may also be described as dragging of one leg.

Rigidity: may be described as stiffness in the limbs, though this may reflect bradykinesia more than rigidity. Occasionally, individuals may describe a feeling of ratchety stiffness when moving a limb, which may be a manifestation of cogwheel rigidity.

Dystonia: is a common initial symptom in young-onset Parkinson disease (before age 40). Dystonia in Parkinson disease commonly consists of a foot involuntary inversion or plantar. Common dystonia in Parkinson disease is adduction of the arm and elbow, causing the hand to rest in front of the abdomen or chest. Dystonic postures can wax and wane, occurring with fatigue or exertion.

Initial symptoms include:[3]

- Tremor; occurs in approximately 70% of patients
- A subtle decrease in dexterity; for example, a lack of coordination with activities such as playing golf or dressing (about 20% of patients first experience clumsiness in one hand)
- Decreased arm swing on the first-involved side

- Soft voice
- Decreased facial expression
- Sleep disturbances
- RBD, in which there is a loss of normal atonia during REM sleep: In one study, 38% of 50-year-old men with RBD and no neurologic signs went on to develop parkinsonism; patients "act out their dreams" and may kick, hit, talk, or cry out in their sleep
- Decreased sense of smell
- Symptoms of autonomic dysfunction, including constipation, sweating abnormalities, sexual dysfunction, and seborrheic dermatitis
- A general feeling of weakness, malaise, or lassitude
- Depression or anhedonia
- Slowness in thinking

Section D: Availability, Effects, and Efficacy of Conventional Medical Treatments

There currently isn't a cure for Parkinson's disease; however, therapies available target the motor symptoms by correcting dopamine deficiencies including:

1) Brain synthesis enhancement via levodopa, a dopamine precursor
2) Stimulating the dopamine receptors
3) Decreasing dopamine catabolism
4) Stimulating the release of dopamine and inhibition of dopamine reuptake from presynaptic sites

Drugs available only address the motor symptoms of Parkinson's disease and are associated with a number of adverse effects. Levodopa is considered the "standard" pharmaceutical treatment for PD. A noted complication in the long-term treatment of Parkinson's disease with levodopa (see below) is that it induces dyskinesia. In response clinicians add additional drugs to the levodopa regime such as dopamine agonists, catechol-O-methyl transferase inhibitors (COMTIs) or monoamine oxidase type B inhibitors (MAOBIs).

Previous trials have shown that these drugs are beneficial compared to placebos; though, no conclusive evidence was presented suggesting the best way to treat patients experiencing motor complications and whether one class of drug is more effective than another.[3]

The most commonly used medications for motor symptoms include:[4]

Levodopa: is considered the standard treatment when coupled with a peripheral dopa decarboxylase inhibitor, such as Carbidopa, because it provides the greatest benefits with fewest adverse effects in the short term. Levadopa participates in the metabolic synthesis of monoamines (including dopamine), thus enhancing dopamine production and its availability at neuronal synapses. The efficacy of Levadopa is limited to the early to mid-stages of the disease, and is largely obstructed by gradual loss of dopaminergic neurons necessary for

neurotransmission. Levodopa/carbidopa is introduced at a low dose and is escalated slowly as higher doses and long term use increases the risk for dyskinesia.[5] Noted side effects include nausea, dizziness, and headaches. Elderly patients exhibit confusion, delusions, agitation, hallucinations, and psychosis more commonly, which is likely attributable to both neurodegeneration and high dopamine concentrations in midbrain and cortical areas.

Compared to placebo, adjuvant therapy reduces off-time, levodopa dose, and improves UPDRS scores in PD patients who develop motor complications on levodopa therapy. Unfortunately, this is at the expense of increased dyskinesia and numerous other side-effects. Indirect comparisons suggest that dopamine agonist therapy may be more effective than COMTI and MAOBI therapy, which have comparable efficacy. However, indirect comparisons should be interpreted with caution. Direct head-to-head randomized trials assessing the impact of these different drug classes on overall patient-rated quality of life need to be conducted.

MAO-B Inhibitors[6] are used during the early stages of treatment of motor symptoms and depression. MAO-Bs break down dopamine and prolongs the action of dopamine in the brain. In early stages of treatment MAO-Bs are regarded as safe and well tolerated by patients, though their efficacy is only modest. Pharmaceuticals such as selegiline and rasagiline are commonly prescribed. Typical side effects of these treatments include dry mouth, anxiety, sleep disturbances, confusion, nausea, dizziness, orthostatic hypotension, and hallucinations. When used in combination with levodopa in advanced PD, selegiline may cause dyskinesia and is more likely to cause orthostatic hypotension. Elevated liver function tests have been reported but are rare enough that regular monitoring of liver function is not performed in clinical practice. Selegiline is metabolized to amphetamines, which may be cardiotoxic. Zydis selegiline, an orally dissolving tablet, does not produce the same level of amphetamine metabolites as conventional selegiline, but the clinical significance of this is unknown.

Dopamine agonists: offer mild symptomatic benefit that is comparable to levodopa/carbidopa in the early stages but lack sufficient efficacy when used alone in more advanced stages. Dopamine Agonists rarely cause dyskinesia alone, but have more adverse side effects than levodopa. Side effects include: sleepiness, hallucinations, edema, and impulse control disorders. As such, use is reserved for patients less than 65 years in age who exhibit normal cognitive function. Dopamine agonists are typically prescribed prior to the use of levodopa. Once the cells expressing the receptors to which dopamine binds are dead, dopamine agonists no longer help.

Given the limited efficacy of available conventional medical treatments on motor symptoms, their adverse effects furthering motor complications, they fail to address disease progression. Therefore patients are in urgent need of safer pharmaceuticals that both treat the manifested symptoms and slow the disease progression.

Section E: Anticipated Benefits from Medicinal Cannabis

Available clinical studies are controversial and inconclusive given several limitations included small sample size, lack of standardized outcome measures, and expectancy bias. There is a need for the collection of larger sample sizes, appropriate dosing, and use of objective biological measures. Note: Parkinson's is a qualifying condition for medical marijuana in: Arizona, Connecticut, Florida, Illinois, Maine, New Mexico, New York, Pennsylvania and Rhode Island.

Observational studies have shown cannabis improves motor symptoms such as tremors, bradykinesia, rigidity, and other non-motor symptoms including pain and sleep disorders.[7] In Colorado a survey of PD patients noted that cannabis was effective in alleviating non-motor symptoms of PD.[8] Cannabidiol (CBD) has been beneficial for the treatment of sleep disorders in PD patients.[9,10] Neuroprotective effects in an animal disease study of PD have been demonstrated with the use of Δ9 tetrahydrocannabivarin (Δ9-THCV, THCV).[11]

A study of 339 PD patients were queried and noted that cannabis made significant improvements to 46% of patient respondents: 31% reported resting tremors improved, 38% reported rigidity relief, 45% defined bradykinesia reduced, and 14% reported dyskinesia symptoms were reduced.[12] Note that high urine concentrations (>50ng/ml) of the THC primary active metabolite was associated with PD symptom relief; dose and frequency of administration play an important role in symptom relief.[12]

In the late 1980's a study noted that the inhalation of cannabis did not reduce symptoms in five patients with idiopathic Parkinson's disease and severe tremors.[13] However, inadequate dosing may have played a role with only one gram (2.9% THC by weight) of cannabis administered once over a four day drug rotation: 1) cannabis as described above, 2) diazepam, 5mg orally, 3) levodopa/ carbidopa, 250mg/25mg, 4) apomorphine, 1.5mg subcutaneously. All drugs were administered in the morning after patients went into withdrawal from their normal nightly medication regime. One of the few randomized, double-blind, clinical trials conducted included nineteen PD patients of (six patients with levodopa-induced dyskinesia) demonstrated that oral cannabis extracts were ineffective for alleviating symptoms associated with PD. Again, inadequate dosing is present—active treatments consisted of cannador capsules, an ethanolic extract of cannabis standardized to 2.5mg of THC and 1.25 mg of cannabidoil per capsule. The doses were administered for four weeks based on body weight with a maximum dose of 0.25mg/kg of THC per day.[14]

PD clinicians are finding that dosing should be tailored to meet the needs of each patient. In 2016 Dr. Bonni Goldstein stated in her book, *Cannabis Revealed*, that "A number of my patients with PD have reported the benefits of using different methods of delivery and different cannabinoid profiles. Some patients have found relief of tremors with inhaled THC and other have not. A few patients have found relief with high doses of CBD-rich cannabis taken sublingually. Some patients are using a combination of CBD and THC ... Trial and error is needed to find what cannabinoid profile and method will work best. Starting a low-dose and titrating up

is recommended, particularly with THC-rich cannabis. Unfortunately, THCV-rich varieties are not readily available."[15]

Ethan Russo, MD, a board-certified neurologist, psychopharmacology researcher, and former Senior Medical Advisor to GW Pharmaceuticals complied dosing regimes from various studies. Generally speaking, he found "2.5 mg of THC is a threshold dose for most patients without prior tolerance to its effects, while 5 mg is a dose that may be clinically effective at a single administration and is generally acceptable, and 10 mg is a prominent dose, that may be too high for naïve and even some experienced subjects. These figures may be revised upward slightly if the preparation contains significant CBD content ... it is always advisable to start at a very low dose and titrate upwards slowly." Further research is needed to understand exactly how cannabis interacts with the Endocannabinoid System and PD patients specifically to determine correct dose appropriation.

Parkinson's Disease and the Endocannabinoid System

The endocannabinoid system (ES) is highly expressed in the neural circuit of the basal ganglia with several studies notating the ES play a crucial role in Parkinson's disease. The basal gangli are part of a complex neuronal system that (as mentioned above) is involved in motor control and motor output. The ES communicates with the dopamine rich basil ganglia; endocannabinoids impact the signal transmission between cortical and striatal neurons, the induction of a specific form of synaptic plasticity, and the control of motor functions.[16]

In PD patients the dopaminergic neurons die—resulting in lower striatal levels of dopamine. When this occurs the equilibrium between the direct and indirect pathways located in the basal ganglia and the ECB signaling are altered. As PD progresses biphasic patterns emerge in the cannabinoid signaling system.[17] Before PD patients display symptoms there is little evidence of neuronal death or malfunction associated with the desensitization/down regulation of CB1 receptors, excitotoxicity, oxidative stress, and glial activation.[17] Conversely, intermediate and advanced symptoms manifest they are associated with upregulation of CB1 receptors and the endocannabinoid ligands.[18] CB1 upregulation could be involved in the efficacy of cannabinoids in alleviating symptoms of advanced PD.

Cannabis and the Endocannabinoid System

The various compounds found in cannabis and their efficacy remains largely unexplored, necessitating a need for further research. THC and CBD have been studied primarily for their medicinal properties. THC is the major psychoactive cannabinoid impacting brain function in the central nervous system. CBD is a non-psychoactive cannabinoid that produces neuro-protective and anti-inflammatory effects.[19]

Some endogenous cannabinoids (or ECBs) occur naturally in the human body. They were initially discovered in the brain and produced in cultured cells. ECBs activate two guanine nucleotide-binding protein coupled cell membrane receptors known as cannabinoid type 1

(CB1) and type 2 (CB2).[20] The CB1 receptors are located in the central and peripheral neurons and the CB2 receptors are found in immune cells. CB1 receptors may impact the modulation of neurotransmitters in a way that maintains homeostasis by preventing the development of excessive neuronal activity in the central nervous system.[21] Studies have shown that the activation of CB1 receptors by their endogenous ligands resulted in neuroprotective effects and may prevent epileptic seizures.[22] Other studies suggest the activation of CB1 receptors offer neuroprotection against dopaminergic lesions and the development of L-DOPA-induced dyskinesias.[23]

The globus pallidus and the substantia nigra are the two prominent areas that control movement and also have the highest densities of CB1 receptors and ECBs especially AEA.[24] In animal models, a blockade of CB1 receptors led to increased motor stimulation produced by enhanced D2 receptor function.[25] These results could suggest that agonism of CB1 receptors increase motor output resulting from D2.[25] Therapeutic effects of THC result due to its structure similarity the endogenous cannabinoid AEA.[26]

Conclusions

Approval of Parkinson's disease as a qualifying condition is suggested based on a number of factors including, but not limited to:

- Existing treatments only address the manifestation of symptoms and fail to slow disease progression;
- Inconclusive efficacy of existing treatments;
- Adverse side effects of existing treatments currently available including further disease progression (L-DOPA- induced Dyskinesia);
- Observational studies have implicated cannabis improving motor symptoms such as tremors, bradykinesia, rigidity, and other non-motor symptoms including pain and sleep disorders;
- Studies suggesting the activation of CB1 receptors offering neuroprotection against dopaminergic lesions and the development of L-DOPA-induced Dyskinesia;
- PD patients reporting symptom alleviation after oral ingestion occurring an average of 1.7 months after they started using cannabis;
- Detracting studies demonstrate inadequate dosing, short duration of study, and were conducted prior to breakthroughs in our understanding of the endocannabinoid system as it relates to cannabis and PD;
- Providing Minnesota PD patients with a much needed alternative care option, that has demonstrated positive results in other states with medicinal marijuana programs (Colorado) and internationally (Czech Republic); and
- Ability to track and monitor potential symptom alleviation.

Section F: Supporting Research

The following research is enclosed:

Chagas, M. H., Zuardi, A. W., Tumas, V., Pena-Pereira, M. A., Sobreira, E. T., Bergamaschi, M. M., . . . Crippa, J. A. (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. doi:10.1177/0269881114550355

Duncan, R., Patterson, J., Hadley, D., & Bone, I. (1990). Marijuana for parkinsonian tremor. Journal of Neurology, Neurosurgery and Psychiatry,53(5), 436-437. Letter to the Editor

Finseth, T. A., Hedeman, J. L., Brown, R. P., Johnson, K. I., Binder, M. S., & Kluger, B. M. (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. doi:10.1155/2015/874849

García, C., Palomo-Garo, C., García-Arencibia, M., Ramos, J., Pertwee, R., & Fernández-Ruiz, J. (2011). Symptom-relieving and neuroprotective effects of the phytocannabinoid Δ9-THCV in animal models of Parkinsons disease. British Journal of Pharmacology,163(7), 1495-1506. doi:10.1111/j.1476-5381.2011.01278.x

Liu, Z., Song, L., Yang, X., Ma, Y., & Wu, N. (2014). The CB1 cannabinoid receptor agonist reduces L-DOPA-induced motor fluctuation and ERK1/2 phosphorylation in 6-OHDA-lesioned rats. *Drug Design, Development and Therapy,*2173. doi:10.2147/dddt.s60944

Mcsherry, J. W., Carroll, C. B., Zajicek, J., Teare, L., & Bain, P. (2005). Cannabis for dyskinesia in Parkinson disease: A randomized double-blind crossover study. Neurology,64(6), 1100-1100. doi:10.1212/wnl.64.6.1100

Price, D. A., Martinez, A. A., Seillier, A., Koek, W., Acosta, Y., Fernandez, E., . . . Giuffrida, A. (2009). WIN55,212-2, a cannabinoid receptor agonist, protects against nigrostriatal cell loss in the MPTP mouse model of Parkinson's disease. European Journal of Neuroscience, 29(11), 2177-2186. doi:10.1111/j.1460-9568.2009.06764.x

Russo, E., & Guy, G. W. (2006). A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Medical Hypotheses,66(2), 234-246. doi:10.1016/j.mehy.2005.08.026

Venderová, K., Růžička, E., Voříšek, V., & Višňovský, P. (2004). Survey on cannabis use in Parkinsons disease: Subjective improvement of motor symptoms. Movement Disorders,19(9), 1102-1106. doi:10.1002/mds.20111

[1] Bratzke, Hansjurgen. "Stages in the development of Parkinson's disease-related pathology." Cell and Tissue Research 318.1 (2004): 122-34. PubMed. Web. 20 June 2017.

[2] Alexander, Garrett E. "Biology of Parkinson's disease: pathogenesis and pathophysiology of a multisystem neurodegenerative disorder." Dialogues in Clinical Neuroscience 6.3 (2004): 259-80. PMC. Web. 20 June 2017. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181806/>.

[3] Stowe, R. "Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications." *The Cochrane Database of Systematic Reviews*7.7 (2010): *PubMed*. Web. 22 June 2017. <https://www.ncbi.nlm.nih.gov/pubmed/20614454>.

[4] Hurtig, H. "Problems with current pharmacologic treatment of Parkinson's disease." *Experimental Neurology*144.1 (1997): *PubMed*. Web. 22 June 2017. <https://www.ncbi.nlm.nih.gov/pubmed/9126144>.

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[9] M. H. N. Chagas, A. W. Zuardi, V. Tumas et al., "Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial," Journal of Psychopharmacology, vol. 28, no. 11, pp. 1088–1092, 2014.

[10] M. H. N. Chagas, A. L. Eckeli, A. W. Zuardi et al., "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, vol. 39, no. 5, pp. 564–566, 2014. <http://onlinelibrary.wiley.com/doi/10.1111/jcpt.12179/abstract>

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[12] K. Venderova, E. Ruzicka, V. Vorisek, and P. Visnovsky, "Survey on cannabis use in Parkinson's disease: subjective improvement of motor symptoms," Movement Disorders, vol. 19, no. 9, pp. 1102–1106, 2004.

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[14] C. B. Carroll, P. G. Bain, L. Teare, X. Liu, C. Joint, and C. Wroath, "Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study," Neurology, vol. 63, pp. 1245–1250, 2004.

[15] Goldstein, B. (2016). Cannabis revealed: how the worlds most misunderstood plant is healing everything from chronic pain to epilepsy. Place of publication not identified: Bonni Goldstein.

[16] B. D. Heifets and P. E. Castillo, "Endocannabinoid signaling and long-term synaptic plasticity," Annual Review of Physiology, vol. 71, pp. 283–306, 2009.

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[18] J. M. Brotchie, "CB1 cannabinoid receptor signalling in Parkinson's disease," Current Opinion in Pharmacology, vol. 3, no. 1, pp. 54–61, 2003.

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[21] R. G. Pertwee, "The diverse CB 1 and CB 2 receptor pharmacology of three plant cannabinoids: Δ 9-tetrahydrocannabinol, cannabidiol and Δ 9-tetrahydrocannabivarin," British Journal of Pharmacology, vol. 153, no. 2, pp. 199–215, 2008.

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