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"Whatever it takes to beat Parkinson's": A Controversial Approach for Symptom Relief

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Introduction

Parkinson's disease is a neurodegenerative brain disorder that affects nearly one million Americans. Currently, there is no cure for the progressive disease, but there are medications to help control and partially relieve patients of its symptoms. Clinical studies continue to be conducted to better understand the disease, its cause, and symptom treatment to improve the quality of life in PD patients. Some studies being performed are looking toward the recently legalized use of marijuana, both medically and recreationally. Physicians and patients, both, are intrigued by the drug as a form of symptom treatment. Marijuana has been an accepted form of treatment for cancer patients undergoing chemotherapy for almost two decades, could this drug also become accepted as treatment for Parkinson's patients? This question carries more weight than just potential benefit in symptom treatment. The unstandardized chemical composition of marijuana poses health-related, criminal and ethical risks as well. The real question is, if marijuana is an effective form of therapeutic treatment, do the benefits outweigh the risks involved? After all, the goal of any symptom treatment for Parkinson's patients is to improve the quality of remaining life for the patient. As the National Parkinson's Foundation slogan states: patients and their families must do "Whatever it takes to beat Parkinson's," … maybe even considering marijuana as a form of treatment.

Parkinson's History, Progression, and Staging

It has been 200 years since James Parkinson described the" Shaking Palsy" disease in an essay written in 1817 (Schulz, Hausmann, & Hardy, 2016). Parkinson wrote the essay as an awareness to further study the disease so that treatments could be developed. Since then, many important discoveries have been made to define the pathophysiology of the disease. Around 1912, a formation of abnormal protein bodies, Lewy bodies, were discovered in the brain of PD patients (Schulz, et al. 2016). It was found that the presence of Lewy bodies was a detection that neurons were in a state of PD related dysfunction. Affected neurons develop Lewy bodies, and can survive for a period of time before they eventually cease functioning and die.

In 2003, Heiko Braak developed a system of staging the disease progression from the presence, location and amount of these Lewy bodies (Burke, Dauer, & Vonsattel, 2015). The Braak Theory of Parkinson's Staging is broken down into six stages, from the initial formation of Lewy bodies in the lower brainstem to the most severe of PD where the disease has fully invaded the neocortex. As the Lewy bodies take over the neurons in each progressive stage, it inhibits them from producing dopamine. This degeneration of dopaminergic neurons is the primary known neuropathological cause of motor impairment in Parkinson's, but many other nerve cells endure similar damage (Dauer & Przedborski, 2003). Although motor functions are the most prevalent impairment symptoms seen in PD patients, non-motor symptoms also occur because the progression of the disease is actually a multisystem disorder. In fact, Braak stages 1 and 2

causes non-motor symptoms before any motor symptoms occur. Non-motor symptoms in these stages include: depression, sense of smell impairment, severe constipation, light-headedness (caused by orthostatic hypotension), and sleep behavior disorder. In stages 3 and 4 of the Braak system, clinical symptoms of Parkinson's begin to appear and it becomes possible for physicians to diagnose the patient with PD (Burke, Dauer, & Vonsattel, 2015). It is estimated that 80% of dopaminergic cells are lost before patients reach these stages and before motor symptoms initially occur (Dauer & Przedborski, 2003). Motor symptoms typically appear as a nuisance in patients as sudden rigidity in limb movement, hypokinesia (reduced movement), bradykinesia (slowed movements), and resting tremors. Cognitive and psychiatric impairments develop as well. PD patients are often faced with deficits in executive decisions such as time management, planning, shifting of attention, working memory, lack of motivation, slower responses to questions, mood disturbances, depression, and anxiety (Dauer & Przedborski, 2003). With more advanced cases of Parkinson's, patients are left with severe postural instability, involuntary movements/spasms, dementia, and inability of swallowing, and speaking, causing need for constant care.

There are three common methods of measuring the progression of PD motor dysfunction in patients. Evaluating patients using these scales are completed through patient interview and visual activities. It is important to use a standard method of reporting progression, so these two of the three methods used are derivatives of the Unified Parkinson Disease Rating Scale (UPDRS) which is a very complex questionnaire. UPDRS is a rating tool made up of three questioning sections: 1.) Mentation, Behavior, and Mood 2.) Activities of Daily Living and 3.) Motor sections. Each section is then further broken down into questions pertaining to each section and given a scale of 0 to 4 (Owen, n.d.). UPDRS is mostly scaled through interview questions, but it also requires a physical assessment of motor abilities (Owen, n.d.). Hoehn and Yahr Staging of Parkinson's disease is a more simplified version of UPDRS, that requires a visual assessment of the patient. It is broken into five stages of progression that describes patient symptoms. *Figure 1.* Modified Hoehn and Yahr Staging shows an even further simplified scale in staging the progressions of the disease in the patient.

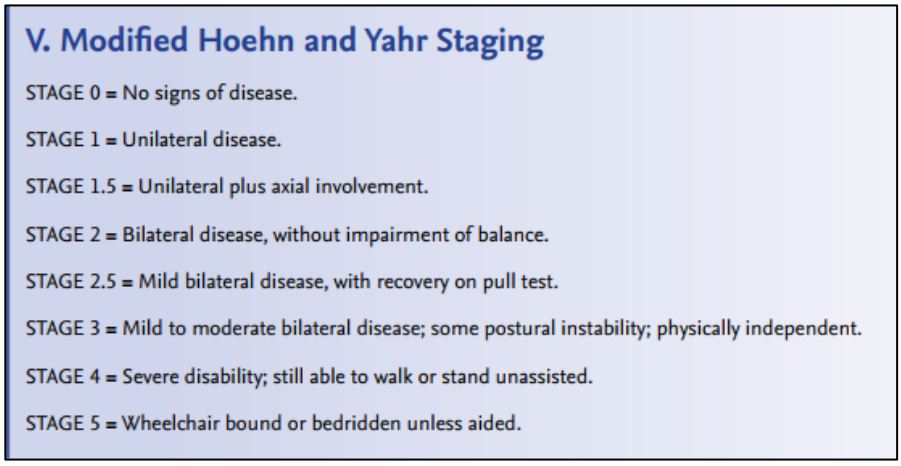
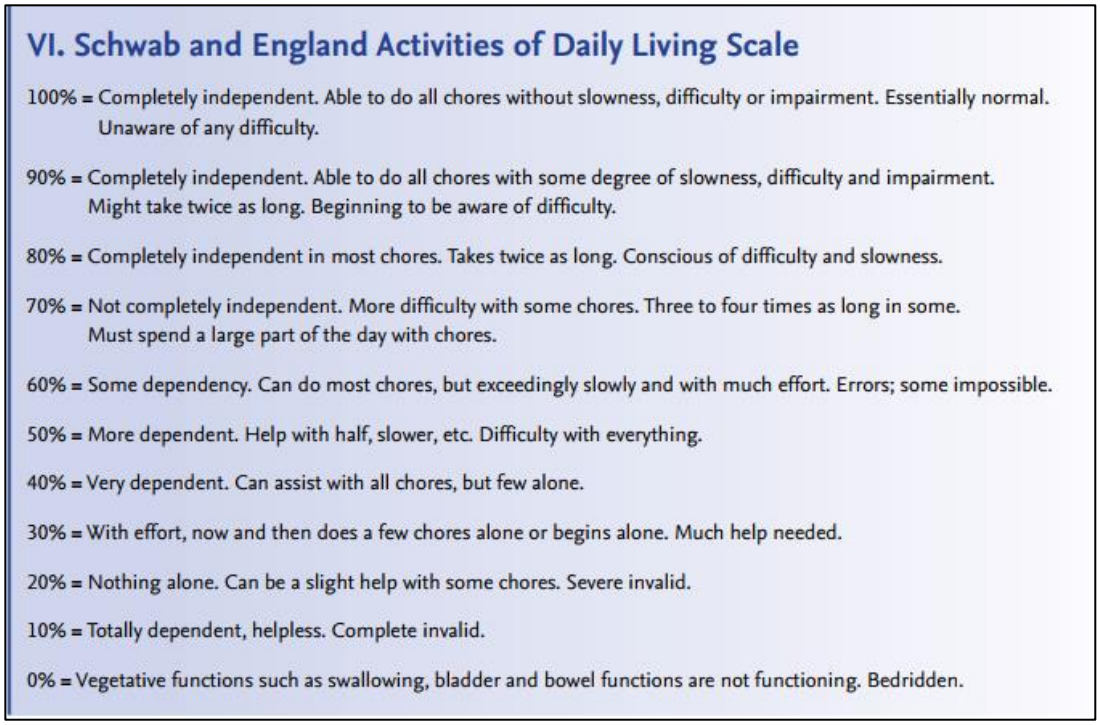


Figure 1. Modified Hoehn and Yahr Staging

And finally, the last rating scale is used in combination with Hoehn and Yahr's scale. Schwab and England Activities of Daily Living can be assessed by the patient or by a physician. It focuses on the daily activity impairments in percentage scaling on how the patient can perform daily functions. See *Figure 2*. Schwab and England Activities of Daily Living.



VI. Schwab and England Activities of Daily Living Scale

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.

90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.

80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.

70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.

60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.

50% = More dependent. Help with half, slower, etc. Difficulty with everything.

40% = Very dependent. Can assist with all chores, but few alone.

30% = With effort, now and then does a few chores alone or begins alone. Much help needed.

20% = Nothing alone. Can be a slight help with some chores. Severe invalid.

10% = Totally dependent, helpless. Complete invalid.

0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

Figure 2. Schwab and England Activities of Daily Living Scale

Current Treatment Options

Thousands of people are living with Parkinson's disease and coping with its symptoms, mostly in thanks to pharmacological treatment. The most effective drug in symptom management is Levodopa. Developed in the 1960's, Levodopa synthesizes into dopamine and it is stored in the neurons until needed by the body for movement (Parkinson.org, n.d.). Patients endure side effects from Levodopa alone that decreases their quality of life with intense nausea, vomiting, sleepiness, and lightheadedness. Levodopa is commonly combined with Carbidopa, a Levodopa enhancer that decreases Levodopa side effects, while increasing its effectiveness. Carbidopa-Levodopa is found to be the most effective, but it is often delayed to be prescribed because its effectiveness lasts only a few years. Levodopa induced dyskinesia (abnormal uncontrolled movement) develops in the patient within 4-6 years of treatment, and then it is considered totally ineffective after 10 years (Voon, et.al, 2017).

Another form of symptom treatment that is similar to Levodopa, are dopamine agonists. Dopamine agonists differ from Levodopa, as they mimic the effects of dopamine instead of synthesizing into dopamine. This pharmacological treatment is often used in early stages of Parkinson's, but can also be used in late progression of the disease. It is very important that physicians consider the patient case before deciding on which course of treatment to implement.

This especially pertains to dopamine agonists in young early onset patients. The most detrimental side effect of dopamine agonists in young patients, aside from excessive sleepiness and confusion, is impulse control disorder. Uncontrolled shopping, gambling, eating and sexual urges are among the compulsive behaviors found in patients taking dopamine agonists such as Ropinirole (Voon, et. al., 2017). One can imagine the financial and social effects of this disorder on a patient's life and relationships.

Additional forms of pharmacological treatment include MAO-B and COMT inhibitors. MAO-B inhibitors provide modest benefits in early stage patients that still have dopamine producing neurons. MAO-B is an enzyme that breaks down dopamine, thus, the inhibitor blocks the breakdown so that dopamine is available for the body's motor functions. COMT inhibitors perform a blocking function as well, but can only be used when Levodopa treatment is in place. COMT inhibitor blocks an enzyme, Catechol-O-Methyl Transerase, that prevents Levodopa from being fully functional. Risks of liver function abnormalities, prostate cancer, and cardiovascular issues are the largest concerns from the U.S. Food and Drug Administration in COMT inhibitors (parkinsons.org, n.d.).

Lastly, the most invasive form of treatment for motor symptoms is deep brain stimulation. This surgical procedure is only suggested for patients whose symptoms cannot be controlled through pharmaceutical medications. Electrical signals are targeted to areas of the brain that control movement, and block the abnormal nerve signals that cause tremors and motor impairments (Unemura, et.al., 2016). Long term outcomes of patients who undergo deep brain stimulation show positive results. 5 years after surgery, the majority of patients display improvements in tremors, rigidity, and bradykinesia, but speech, gait (manner of walking), and postural instability worsened (Unemura, et. al., 2016). As with any brain surgery, risks and complications are high in the form of hemorrhages, stroke, and death.

Controversial Treatment Option

Based off the current forms of symptom treatment discussed, it is prevalent that there is a need for PD therapy that improves the quality of life of patients that comes with reduced health risks and costs, until a cure is found. With the recent legalization of recreational use of marijuana in some states, patients who were in desperate need of symptom relief, tried the drug as a form of self-treatment. Anecdotal reports and social media posts began to spark interest from researchers to look into Marijuana's chemical composition and the effects it could have in Parkinson's patients. What the researchers found was promising. In relation to symptom treatment for cancer patients in the 1990's, it was found that the brain contains an endocannabinoid system containing cannabinoid receptors. CB1 receptors are found in the basal ganglia, cerebellum, hippocampus, neocortex, hypothalamus and limbic cortex. Respectively, these areas of the brain are responsible for motor activity, motor coordination, short-term memory, thinking, appetite and sedation. CB2 receptors are found in cells and tissue and affect inflammatory and immunosuppressive activity (Borgelt, Franson, Nussbum, & Wang, 2013). Marijuana contains chemicals, cannabinoids, that respond to both CB1 and CB2 receptors. The use of cannabis has been found to interact with these receptors, but because of the inconsistency in uncontrolled production of medical cannabis, it is difficult to determine the concentration of cannabinoid compounds in each product and preparation. This in turn makes it difficult to "predict what pharmacologic response any cannabis product is likely to elicit" (Bolgelt, et al., 2013). Clinical studies are still be conducted to verify,

with data, if CB1 and CB2 receptors in Parkinson's patients respond effectively to cannabinoids in marijuana. The likelihood of legalizing marijuana for PD patients is dependent on these studies.

The medicinal use of marijuana is now legal in 28 states and Washington D.C., but it is still illegal under federal law. Without legalization on a federal level, physicians are cautious about suggesting marijuana for treatment. Technically, physicians cannot prescribe marijuana to patients, instead they can issue certifications to obtain medicinal marijuana. Each state has regulations on conditions that qualify for cannabis treatment, and how the treatment can be used. Out of the 28 states, only 3 states (Minnesota, New York, and Ohio) do not allow it to be smoked. 9 out of the 28 states consider Parkinson's disease a qualifying condition for treatment. Currently, Ohio is not one of those of states (Choo & Emery, 2017;2016;). Due to the Controlled Substance Act of 1970, that classified marijuana as a drug that carried no medical use and high potential of abuse, marijuana has retained that stigma it was designated with. This stigma, and unsupportive clinical results, have made it a challenge for physicians to consider marijuana as a treatment option. In a study that surveyed physicians belonging to National Parkinson's Centers of Excellence, it was found that data collected in clinical studies show that there is not enough sufficient evidence to recommend cannabis treatment for motor symptoms of PD and even less evidence on the safety of it for PD patients (Bega, 2016). Physicians would be more apt to consider the drug if it were regulated through the FDA that provided dosage recommendations and instructions, to keep their patients safe. The root of insufficient evidence lies within the lack of limitation controls in clinical studies that factor the staging of PD participants, specifically describing what impairments are affected, and controlling the chemical composition of marijuana used. Without controlling these factors in trials, how can we be sure if the drug is effective or not?

Risks and Concerns

As complex as both Parkinson's and chemical composition of marijuana, it is near impossible to gain substantial data that simulates repeatable results. Trial outcomes are separated by patient reported effectiveness of marijuana versus effectiveness from prescribed drugs, and the quality of life of the patient versus the "symptomatic" improvement for the patient (Turner, et al., 2017). The variability to control is widely acknowledged through all levels involved, as stated in Movement Disorders Clinical Practice Research Article, *Medicinal Cannabis for Parkinson's Disease: Practices, Beliefs, and Attitudes Among Providers at National Parkinson Foundation Centers of Excellence:*

> Ultimately, the legalization process is resulting in a much more heterogeneous level of knowledge and clinical practice patterns than is expected through the typical regulatory approval process. Seldom in the modern history of medicine has there been a similar situation. (94)

There are various preparations of marijuana for patient use. Most commonly it is smoked. Smoking cannabis absorbs within minutes, and half of the THC is lost from the heat, smoke or amount that is not inhaled. The THC level in marijuana cannot be controlled due to variation in plants and the preparation of the finished product. THC is responsible for the "euphoric" effect that comes from marijuana, this compromises the safety of patients. Smoking marijuana has been shown to produce the most effective results of symptom relief, but as with inhaling any sort of

smoke, comes with risk of respiratory complications, and cancer. Vaporization of cannabis is also a very popular method of ingestion. Cannabinoids are aerosolized when heated air is drawn through it and inhaled without the typical exhalation of smoke (Borgelt, et al., 2013). Cannabis can also be ingested orally, but the effectiveness is dependent on each individual's digestive system. Most patients report a reaction time between 1 and 3 hours. Safety concerns arise with oral digestion in self-medicating patient's due to the delayed absorption that poses threat to inappropriate dosing (Borgelt, et al., 2013).

The most unfavorable risk that comes with using cannabis for treatment is that it produces a variety of effects dependent on the formulation of the marijuana, the dosage and the patient reaction to it. As with any medication, results produced vary from person to person. More adverse effects of marijuana use can include dizziness, balance impairment, disorientation, anxiety, and cognition impairment. These side effects are what physicians fear could be extremely harmful for patients who already are affected by instability and anxiety, especially to those patients whose tremors are triggered by anxiety. However, the benefiting factors of using marijuana are patients reporting sedation, relaxation, hunger, managed pain and release of anxiety.

Conclusion

Given the considerable amount of uncertainty about the medical benefits and risks associated with cannabis treatment for Parkinson's patients, it is fair to say that the focus should be placed on the quality of remaining life of the patient, until the gaps in research have been closed. If a patient can find relief from rigidity in muscles, tremors, anxiety, and aid in sleep by the use of marijuana, and they reside in a state that will allow the use of the drug, then who are we to decide that if it is an acceptable form of treatment for the individual patient? The long-term effect of Parkinson's alone is inevitable, as is the chronic use of Levodopa. When a patient has exhausted all forms of treatment options, as well as incurred a large sum of medical costs, the use of cannabis looks more and more appealing. Focus on standardizing clinical studies to pave the way for future acceptance and legalization of marijuana as a form a treatment is desperately needed to end the controversy around the subject. Until that day comes, it is imperative to obtain a better quality of life for our loved ones affected by the disease by doing "Whatever it takes to beat Parkinson's," even if that includes using marijuana as a form of symptom treatment.

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