



Review of Parkinson's Disease Treatment and Future Therapies

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Abstract

Parkinson's Disease (PD) is a progressive neurodegenerative disorder that can affect an individual's ability to perform daily activities. The disease belongs to a group of motor system disorders and is characterized by the result of a loss of dopamine-producing brain cells. There are no definitive causes of this condition, but there are many factors currently being studied. Genetics, environmental factors, or a combination of both may be potential causes of the disease. This article will review current treatment regimens used in practice, previous studies done on novel therapies, and future therapies that could have clinical significance.

The review will go through each medication class and highlight their mechanisms, potential side effects, and use in the treatment of Parkinson's disease. Clinical trials researching newly approved medications are referenced in the article. Areas of future drug development that are being studied are also reviewed. New information is constantly being discovered regarding the pathophysiology of Parkinson's Disease, which in turn leads researchers to look into new potential therapies.



Background

Parkinson's Disease (PD) is a progressive neurodegenerative disorder that can affect an individual's ability to perform daily activities. The disease belongs to a group of motor system disorders and is characterized by the result of a loss of dopamine-producing brain cells. PD is estimated to affect 0.3% of the United States' population, and 4-5% of individuals 85 years old or older.¹ It is most commonly seen in people over the age of 60. Currently there are no blood or laboratory exams that have been able to help with the specific diagnosis of PD. The disorder is difficult to diagnose accurately, as the diagnosis is based on medical history and a neurological examination.

There are no definitive causes of this condition, but there are many factors currently being studied. Genetics, environmental factors, or a combination of both may be potential causes of the disease.² A mutation in the gene called LRRK2 is estimated to be the most common genetic mutation that triggers PD.^{3,4} This defect is more frequent in individuals of North American descent.³ Mutations in the protein alpha-synuclein have also been found to trigger PD, but these are quite rare and this protein is being studied extensively.³ Exposure to pesticides, certain heavy metals and repeated head injuries can increase the risk of developing PD.³ Many individuals that have developed Parkinson's do not have a clear environmental cause, as the connection is often difficult to establish.³ Environmental causes like insecticides, herbicides, and head injuries are just a few

potential causes. Sadly, there is presently no cure for Parkinson's Disease, but there are an assortment of medications that have been shown to provide a dramatic relief from the symptoms.

Dopamine is a neurotransmitter that is released by the brain that has a large variety of roles in different functions in the body that include: memory, behavior, attention, pleasurable reward, and most importantly for Parkinson's – movement.² PD is caused from dopamine cell loss in the substantia nigra. This chemical imbalance is responsible for the manifestation of the symptoms.² The importance of dopamine is why many treatment goals of PD are to increase the levels of dopamine in the brain.

Symptoms

Symptoms of Parkinson's Disease vary greatly from individual to individual, both in terms of intensity and progress. PD symptoms are classified into two categories: motor and non-motor. Observing the motor symptoms of PD is the main way physicians diagnose PD.⁵ These motor symptoms include: tremor, rigidity, bradykinesia, postural instability, and walking/gait difficulties.⁵ Tremor will characteristically occur at rest, and is a classic slow, rhythmic tremor usually starting in one hand, foot, or leg before progressively affecting both sides of the body. Rigidity can be wrongly attributed to arthritis or orthopedic problems. The slow movement of PD is commonly demonstrated by a reduced or mask-like expression of the face, a decreased blink rate of the eyes, and problems with fine motor coordination. Vocal symptoms are common in individuals





with PD. The individual's voice may become softer, or start off strong and then fade away. There are many non-motor symptoms that are common in patients with PD. These include: decreased sense of smell, inability to stay asleep, depression, anxiety, fatigue, cognitive changes, weight loss, drooling, and gastrointestinal issues.⁵ Early detection of all of these symptoms is important for the patient's overall health and quality of life so treatment can begin as soon as possible.

Treatment

Treatment of Parkinson's Disease is broken down into two categories: early-stage and late-stage. Early-stage PD usually includes patients who have had the disorder for less than 5 years or have not developed motor complications from levodopa use.⁶ Late-stage PD is described as patients who have received carbidopa/levodopa for at least five years and have developed motor complications.⁶ Motor complications, such as the wearing-off phenomenon and dyskinesias, develop with increasing frequency in patients after 5-6 years of dopaminergic therapy.⁶ About half of elderly individuals with PD experience dyskinesias and almost 100% of younger patients under the age of 40 experience dyskinesias after 6 years of levodopa therapy.⁶

Levodopa is the most common and most effective agent for the treatment of Parkinson's Disease.⁶ It is the primary treatment for symptomatic patients in both early and late stages.⁶ Levodopa is usually combined with carbidopa in a combination medication called Sinemet. Carbidopa is needed to prevent peripheral conversion of

levodopa to dopamine by blocking dopa decarboxylase. This allows levodopa to cross the blood-brain barrier and be converted into dopamine without being broken down in the plasma.⁶ This medication is most effective in controlling bradykinesia and rigidity.⁷ Some side effects of Sinemet include nausea/vomiting, confusion, orthostatic hypotension and hallucinations.⁷ Levodopa/Carbidopa has been shown to be very effective in the treatment of PD, yet long-term treatment with this medication has been shown to be associated with motor fluctuations and dyskinesias.⁶ Individuals being treated with Sinemet commonly suffer from the "On-Off Phenomenon", which is a very important challenge in the long-term treatment of PD. After receiving levodopa for 5-10 years, at least 50% of PD patients develop motor complications that are a major cause of disability in advanced PD.⁶ Evidence suggests that these motor complications are associated with non-physiological, pulsatile stimulation of dopamine receptors.⁶ During the "On-Phase", the patient has improved mobility as they are responding well to the levodopa therapy. The patient will then fluctuate to the "Off-Phase", where they will develop impaired motor functions as the levodopa therapy wears-off. The changes are rapid, severe, and frequent, which makes this phenomenon very unique. Smaller, more frequent doses, or larger, less frequent doses, may be more effective in some patients.⁶ A decrease in dietary protein or the use of bromocriptine and selegiline may be helpful, but only for temporary improvement.⁶ Subcutaneous Apomorphine, controlled-release formulations of levodopa with a peripheral dopa-decarboxylase





inhibitor, and continuous intra-duodenal administration of levodopa are also options in the management of the “On-Off Phenomenon”.⁸

Dopamine agonists are a common medication in the treatment of Parkinson’s Disease. These medications directly stimulate the dopamine receptors. Bromocriptine (Parlodel), pergolide (Permax), pramipexole (Mirapex), and ropinirole (Requip) are medications in this class. This class of medications have been shown to be effective as monotherapy, or combined with levodopa, in the treatment of PD during the early stages of the disease.^{6,7} Dopamine agonists are commonly one of the first anti-parkinson’s medication used in newly diagnosed patients. Side effects include: impulse control disorders, sedation, dizziness, fatigue, hypotension, weakness, and increased risk of infection.⁷

Monoamine oxidase B (MAO-B) inhibitors irreversibly and selectively inhibit brain MAO-B, which reduces the breakdown of dopamine.⁷ Monoamine oxidase B causes the breakdown of dopamine. Medications in this class are: selegiline (Eldepryl) and rasagiline (Azilect). These medications are effective in symptomatic control of PD.⁷ The benefits are usually mild to moderate. MAO-B inhibitors are also useful as adjuvant therapy for patients with PD and motor fluctuations. Side effects include orthostatic hypotension, dyskinesias, falls, depression, headaches, and dyspepsia.⁷ It is important to use caution with the concomitant use of cyclobenzaprine, dextromethorphan, methadone, propoxyphene, St. John’s Wort or tramadol.⁷ The MAO-B inhibitors will

increase the concentrations of these medications.

Catechol-O-methyltransferase (COMT) inhibitors will reversibly and selectively inhibit COMT, which blocks COMT conversion of dopamine in the gut and periphery. This will help prolong the half-life of levodopa/carbidopa and the AUC, which allows for a decrease in the daily levodopa dose. The two COMT-inhibitors are: entacapone (Comtan) and tolcapone (Tasmar). Side effects include: diarrhea, liver failure, and exacerbation of levodopa adverse effects.⁷

Another PD medication, Amantadine (Symmetrel), is a NMDA-receptor inhibitor. This medication has a somewhat debated mechanism, but it seems to increase dopamine release from the striatum by stimulating dopamine receptors. It will also reduce dopamine uptake along with inhibiting NMDA receptors. Amantadine is useful for treating akinesia, rigidity, tremor, and dyskinesia.⁷ Some side effects include nausea, hallucinations, insomnia, confusion, depression, and orthostatic hypotension.⁷ It is important not to discontinue this medication abruptly, as it could lead to an increase in dyskinesia. A decreased dose is needed in renally impaired patients. Patients with a creatinine clearance between 30-50ml/min will have to take 200 mg on day 1 and decrease their dose to 100 mg daily from day 2 on. With a CrCl of 15-29ml/min, patients will have to take 100mg on alternate days after the initial 200mg dose. Lastly, if a patient has a CrCl <15ml/min or are on hemodialysis, they will need to be administered 200mg every 7 days.⁷

In the last 15 years, there have been many studies suggesting the effectiveness of





deep brain stimulation (DBS) in the treatment of PD. The best results have been reported in patients who have had advanced PD with at least five years of disease duration, positive response to levodopa therapy, relatively younger age for PD, low axial non-levodopa responsive motor symptoms, very mild or lack of cognitive impairment and absence of or well-controlled psychiatric disease.⁹ With these criteria, a very small percentage of patients suffering from PD may be eligible for DBS treatment.

Previous Studies

With Parkinson's Disease having an unknown cure as well as a significant prevalence, many clinical trials are being done on new treatment options for the disease. Studies exploring the potential of Coenzyme Q10 (CoQ10) in the treatment of PD have been published. In 2014, a randomized clinical trial was published on the effects of high-dosage Coenzyme Q10 in early PD.¹⁰ 600 participants were randomly assigned to receive placebo, 1200 mg/d, or 2400 mg/d of CoQ10 and all participants also received 1200 IU/d of vitamin E.¹⁰ Even though the Coenzyme Q10 was well tolerated and shown to be safe in this population, there was no evidence of clinical benefit.¹⁰

Another clinical trial in 2014 investigated the safety, tolerability, and urate-elevating capability of the urate precursor inosine in early PD.¹¹ Urate is an antioxidant that researchers believe may have the potential for being effective in PD treatment. The antioxidant showed neuroprotection against oxidative stress-

induced dopaminergic neuron death in rodent models of PD.¹¹ The trial showed that inosine was generally safe, tolerable, and effective in raising serum and cerebrospinal fluid urate levels in early PD. More studies in humans need to be developed to support inosine as a potential disease-modifying therapy for PD.

Many patients suffering from Parkinson's disease may experience delusion and hallucination symptoms during the course of their illness. These symptoms cause decreased quality of life and make treatment more difficult for patients. In April 2016, pimavanserin (Nuplazid) was approved for the treatment of delusions and hallucinations of PD. The medication is a second generation atypical antipsychotic and is a novel 5-HT_{2A} inverse agonist and antagonist. While it reduces activity at serotonin 5-HT_{2A} receptors, it does not block dopamine receptors, which is why it is believed to not worsen Parkinson symptoms while many other antipsychotics do.¹² Some adverse effects of this medication include peripheral edema, confusion, nausea, and urinary tract infections. This medication is very costly (\$2,000/month) and is mainly used in a specialty pharmacy environment, so widespread clinical practice use is limited.

Published in April 2017, a randomized trial studied the effectiveness of low-dose rasagiline and pramipexole as a combination agent (P2B001) in early stage Parkinson's Disease.¹³ Patients enrolled in the study were randomized into one of three groups: two groups received the combination with one group receiving a higher dose, and the third group received a placebo for 12 weeks. The primary endpoint





of the study was the change from baseline to final visit in Total-UPDRS score versus placebo.¹³ 136 patients completed the study and significant benefits were observed for both doses of the combination, P2B001.¹³ Nausea and somnolence were more common with P2B001 treatment, yet adverse events were overall comparable to placebo. Pramipexole is FDA-approved as monotherapy for early PD, and with this study showing promising results, the future of early PD treatment could begin to involve more than just dopamine agonists. More studies need to be completed before clinically significant changes occur.

New and Future Therapies

As it was stated previously, many anti-Parkinson's medications are add-on therapies to levodopa to improve motor fluctuations without exacerbating dyskinesia. In March 2017, a new anti-Parkinson's medication, safinamide (Xadago) was FDA-approved.¹⁴ It is an MAO-B inhibitor approved for adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes. This medication was studied in clinical trials to assess its effectiveness in patients with motor fluctuations on levodopa therapy. The primary endpoint of the study was total "on" time with no or non-troublesome dyskinesia.¹⁴ Patients enrolled in the study were given 100 mg/day of safinamide, 50 mg/day of safinamide, or placebo for 24 weeks.¹⁴ The study found the addition of safinamide, 50mg or 100mg, to current levodopa therapy in patients with PD and motor fluctuations significantly increased total "on" time with no or non-troublesome

dyskinesia.¹⁴ The study also found decreased "off" time, improved parkinsonism, and no significant differences for adverse events between groups.^{1,14} With this medication it is important to monitor the patient's liver function, as it is recommended to not be used in severe hepatic impairment.^{7,14} The next step for safinamide, now that this medication is approved, would be for studies to compare the effectiveness of safinamide with other MAO-B inhibitors to assess if it is non-inferior or superior to other MAO-B inhibitor agents.

As there is still unknown causes of PD, future therapies are always in development. Intrajejunal constant-rate infusion of levodopa is a fairly new therapeutic option to help provide a constant dopaminergic level in the blood.⁶ This will help increase the "on" time for patients by preventing motor fluctuations and intractable dyskinesias of patients with advanced Parkinson's disease. Studies are being conducted to further support and validate this treatment approach as well as look at technical liabilities for long term therapy.⁶ Newer molecules are being evaluated for reducing dyskinesias which include: glutamate receptor antagonists, cannabinoid receptor antagonists, α 2-adrenergic receptor antagonists, adenosine A2A-receptor antagonists, and 5-HT1A-receptor agonists.

Conclusion

Parkinson's disease is a complex disease that affects more individuals on a daily basis. The current therapeutic options have been shown to be effective in the treatment of Parkinson's. Sadly, these





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medications are not as effective after long periods of time due to their side effect profiles and the nature of the disease. New treatment options are constantly being studied to decrease dyskinesias and increase the “on” time for levodopa.



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