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Parkinson's Disease & A Multidisciplinary Approach: The Bridge Between Exercise, Physical Therapy, And Medication Management

Grant Morgan, PharmD Candidate 2020
Gaige Rassman, DPT Candidate 2021
Lydia Chasteen, PharmD Candidate 2021
Erica Hagen, PharmD 2019
Nicole Babiak, PharmD Candidate 2020
Ahmed Mohamed, PharmD Candidate 2020
University of Findlay

University of Findlay
College of Pharmacy
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Introduction:

Parkinson's disease (PD) is a neurodegenerative disease that leads to a decreased quality of life and significant disability. Risk factors for developing Parkinson's are age, genetics, and sex.[1] Parkinson's generally begins in middle or late life, with the risk increasing with age. Generally, patients will develop the disease around age 60 or older. Having a closely related relative with PD increases the chances of developing the disease; however this is still a small risk unless a person has multiple family members with Parkinson's.[2] Men are more likely than women to develop the disease. There are no proven ways to prevent the development of Parkinson's.[1]

Hallmark symptoms of the disease are resting tremor, rigidity, bradykinesia, and asymmetric onset.[1] Symptoms generally begin gradually and progress over time. There are currently several drug classes that can be used to treat Parkinson's disease. These include levodopa, dopamine agonists, COMT inhibitors, MAO-B inhibitors, muscarinic receptor antagonists, and amantadine. Currently, levodopa is the primary treatment option; however long term use is limited due to motor complications and drug-induced side effects, including dyskinesia.[2] Other drug classes can be added to levodopa to try to offset some of these adverse effects. Physical therapy can also be indicated and used to help maintain the overall health of the patient. Treatment should be individualized to the patient to try to decrease adverse effects.[2]

Pathophysiology:

Voluntary movement is controlled by the basal ganglia, which includes various structures.[3] Of these structures, the nigrostriatal pathway is most important regarding movement. The neurotransmitter that is important in this pathway is dopamine, binding to both D1 and D2 receptors.[3] Dopamine binding to D1 receptors leads to stimulation of GABA neurons while dopamine binding to D2 receptors leads to inhibition of GABA neurons.[3] This physiology is important to be able to not only understand how PD can lead to motor dysfunction, but also understand how various drugs are used in aiding the treatment of a patient with PD. When a patient has PD, there is decreased activation of these receptors. With the decreased activation, this leads to problems associated with movement.

It is important to note that PD can be medication induced. An example includes antipsychotic medications, specifically first generation, which leads to PD motor symptoms due to the antagonism of the dopamine receptors. The lack of dopamine

binding to the receptors ultimately mimics the symptoms of PD.

Other features that can lead to a decline in a patient with PD are the presence of Lewy bodies and depigmentation of dopamine producing neurons.[3] A Lewy body is an area in the brain with filaments made up of alpha-synuclein. When these filament structures are present in particular areas of the brain, this can lead to psychiatric symptoms in addition to peripheral symptoms.[3]

Psychiatric symptoms can include depression, anxiety, and sleep disturbances. Peripheral symptoms can include constipation and impaired olfaction.[3] Both of these symptoms begin prior to the onset of motor symptoms. Motor symptoms include bradykinesia or slow movement, resting tremor, rigidity, and instability with an asymmetrical presentation.[3] Further progression may lead to hypokinetic movements or lack of movements, decreased dexterity, difficulty swallowing, freezing at movement initiation, and micrographia or small handwriting.[3] Generally motor symptoms bring a patient in for assessment of their disease state as compared to non-motor symptoms. Differential diagnosis can be difficult for patients presenting with the initial non-motor symptoms because of the overlap with various other disease states.

Exercise and Physical Therapy Intervention:

Even though anti-Parkinsonian medications may be beneficial for most, they may only be a piece of the puzzle in treatment of the disease. Bradykinesia, tremor, and rigidity often respond well to dopaminergic therapy while other signs and symptoms such as autonomic failure, hypersomnolence, imbalance, dysarthria, and dysphagia are largely unaffected.[4] Imbalance is another modifiable factor which can have a large impact in terms of quality of life for a patient with PD. Exercise and physical therapy have been shown to be effective intervention strategies to address some of the resultant complexities in the PD population.[5]

Although rigidity responds well to dopaminergic therapy, postural instability and imbalance are disabling features of Parkinson's disease. Both often lead to one of the most common complications of the disease: falls, which can be frequent and often devastating in PD. The PD population has a fall incidence rate of roughly 40-70%.[5] Falls correlate with detrimental outcomes and decreased quality of life in addition to increased physical injury rates, increased fear avoidance of movement patterns, and increased prevalence of poor psychological outcomes.[5] Exercise interventions, and

especially those within a facility-based environment (i.e. physical therapy clinic), have shown to have a direct impact on balance.

There is current evidence supporting not only short-term benefits associated with exercise training (i.e. balance training, walking, muscle strengthening, stretching), but also the long-term effects of training.[5] These long-term benefits are more clinically significant as patients with Parkinson's face a progressive disease course. A meta-analysis of 38 articles, 25 having moderate to high methodological quality, were reviewed with new evidence concluding that in addition to positive balance and gait outcomes, exercise training could decrease fall rates of PD participants by about 60% over both short- and long-terms.[5] Subgroup analysis also showed facility-based training produced greater training effects on improving PD participant's balance and gait ability ($P< 0.05$).[5] Facility-based training with instruction from a physical therapist had the potential to provide the most optimal learning environment.

Physical therapy is often prescribed in the disease process to aid in the mobility deficits. The intervention strategies used within the plan of care (POC) for those patients has never had true practice recommendations. In an evidence-based analysis, 6 core areas of intervention were identified: transfers (i.e. rising from a chair), posture (particularly neck and back), reaching and grasping, balance and associated falls (including fear avoidance), gait, physical capacity and activity or the lack of.[6] Serving as one of the first recommendations for physical therapy treatment for PD patients, a firm basis for practice was established. Although physical therapy is unlikely to influence the actual disease process, it can be beneficial to improve daily functioning. Physical therapy offers a way for patients with PD to be educated and trained in the use of compensatory movement strategies and also helps to decrease secondary health problems such as decreased strength, endurance, and other comorbidities.[6]

Recently, there has been growing evidence supporting the use of "Lee Silverman Voice Treatment (LSVT) BIG" programs in individuals with Parkinson's Disease. LSVT BIG is designed to treat specific symptoms related to deficits in movement patterns including bradykinesia or akinesia, decreased postural control and awareness, decreased gait mechanics and stability, and decreased balance.[7] The goal is to teach participants to carry over and sustain bigger movements in their daily activities.[7] BIG is achieved by targeting damaged basal

ganglia and dopaminergic centers through repetitive activation across motor regions in the brain that are involved in normal amplitude movements.[7] Physical therapists and occupational therapists alike, can be certified through the LSVT BIG program to utilize these techniques. The program incorporates shaping techniques with therapist modeling or tactile/visual cues, improving self-perception and overall improvement in compensatory movement patterns.[7] A 2017 clinical study, analyzed the effect of LSVT BIG on gait speed, balance, motor symptom rating, and quality of life in those with Stage I Parkinson's Disease. In the study, participants benefited from the LSVT BIG Exercise Program, indicated by improvements of the primary outcomes measures.[7] Improved primary outcomes at levels of minimal clinically important difference (MCID) were noted in: Gait speed, Berg Balance Assessment, Unified Parkinson's Disease Rating Scale III Motor Section (UPDRS), and/or the Functional Gait Assessment (FGA).[7] The improvements were initially achieved through 16 one-on-one LSVT BIG sessions with certified therapists and maintained in 8 of 9 participants at 3 months with community class implementation as well.[7]

Overall, it is important to understand the effects of exercise, especially guided, facility-based exercise by physical and occupational therapists, on the quality of life in those with Parkinson's disease. Its impact on all stages of PD, in conjunction with medication management, has the potential to help individuals maintain an improved quality of life throughout the disease process.

Treatment Options: Medications

While there is no cure for Parkinson's disease, symptoms can be managed with medications to help improve quality of life.[8] There are six major classes of drugs that can be used for PD (Table 1). Although medications can mitigate or delay symptoms of PD, they are not devoid of adverse effects.[8]

Levodopa, an effective Parkinson's disease medication, is a natural chemical that crosses the blood-brain barrier (BBB) and is converted to dopamine.[9] Levodopa is combined with carbidopa, which protects levodopa from early conversion to dopamine outside the brain.[9] This helps lessen side effects such as nausea.[9] Excessive nausea can lead to discontinuation of levodopa and prevent disease control.[9] Other common side effects of levodopa-carbidopa are listed in Table 1. As the disease progresses, the benefit from levodopa may become less stable, with a tendency to wax and wane (also called "wearing off").[9] In addition, dyskinesia is common with higher doses of

levodopa.[8] This requires dosage and timing adjustment to help control these effects.

Dopamine agonist medications mimic dopamine effects in the brain. Dopamine agonists include bromocriptine, pramipexole, ropinirole, pergolide, and rotigotine (given as a patch).[9] Apomorphine is a short-acting injectable dopamine agonist used for quick relief.[9] They are not as effective as levodopa in treating symptoms.[9,10] In a multicenter, double-blinded, randomized control trial comparing pramipexole versus levodopa as initial treatment, the mean improvement in total UPDRS score from baseline to 23.5 months was greater in the levodopa group than in the pramipexole group (9.2 vs 4.5 points; $P < 0.001$).[10] However, dopamine agonists have a longer half-life and may be used in conjunction with levodopa to flatten the "off-and-on" effect of levodopa.[9] Some of the side effects of dopamine agonists are similar to the side effects of levodopa, but they can also include hallucinations, sleepiness, and compulsive behaviors such as hypersexuality, gambling, and eating.[9]

Monoamine oxidase B (MAO-B) inhibitors include selegiline, rasagiline, and safinamide.[8] These medications reduce the breakdown of dopamine by inhibiting the enzyme MAO-B in the brain.[9] Side effects may include nausea or insomnia.[9] When added to levodopa, these medications may increase the risk of hallucinations.[9] Other side effects are listed in Table 1. MAO-B inhibitors are not used in combination with most antidepressants or certain narcotics due to potentially serious drug interactions.[9]

Catechol O-methyltransferase (COMT) inhibitors include entacapone and tolcapone.[8] Entacapone is the primary medication from this class since tolcapone has a risk of serious liver damage and liver failure.[9] These medications mildly prolong the effect of levodopa therapy by blocking COMT, which breaks down dopamine.[9] Side effects may include an increased risk of dyskinesia (Table 1).[9]

Anticholinergics are used primarily to help control the tremor associated with Parkinson's disease.[9] Medications in this class include benztropine and trihexyphenidyl.[8] Side effects may include impaired memory, constipation, dry mouth, blurred vision, and urinary retention.[9]

Amantadine can be used alone to provide short-term relief of symptoms of mild, early-stage Parkinson's disease.[9] It may also be given with levodopa therapy during the later stages of Parkinson's disease to help control dyskinesia induced by levodopa.[9] Amantadine is available in a short-acting and extended-release formulation.[8] Side effects

may include insomnia, anxiety, and hallucinations.[9]

Depression, dementia, and psychosis are common psychiatric problems associated with Parkinson's disease.[3] Depressed patients currently receiving levodopa are usually treated with a selective serotonin reuptake inhibitor (SSRI).[3] Tricyclic antidepressants should be used with caution in patients with Parkinson's disease as it can exacerbate anticholinergic adverse effects.[3] Psychosis in patients with Parkinson's disease is usually drug induced.[3] It can be managed by decreasing doses of anticholinergics or dopamine agonists and by using the lowest possible dose of levodopa.[3] However in more severe psychosis, clozapine and quetiapine are commonly prescribed.[11] Clozapine can cause potentially fatal agranulocytosis and requires frequent monitoring.[3] Quetiapine has not yet been proven effective for psychosis in Parkinson's.[11] About 20-40% of patients with Parkinson's disease develop dementia.[3] Cholinesterase inhibitors, like donepezil, are effective treatments for these patients.[3]

Multidisciplinary Studies:

Patients with PD face a wide variety of both physical and behavior challenges in their care. A team of multidisciplinary healthcare professionals that work together towards the overall care of a patient can help patients overcome these challenges and improve outcomes.[12] This has driven the implementation of specialized PD management centers.[13] Many different services are needed for treatment of PD such as medication management, physiotherapy, occupational therapy, speech-language therapy, dietetic therapy, and others.[13] Clinical studies have helped to establish the benefit and impact different health care professionals can have.

Clinical trials have established evidence that early involvement of a multidisciplinary team can affect overall health, quality of life, and progression of disability specifically in patients with PD.[13] In one study, 49 patients with neurologist-confirmed PD and without dementia were enrolled into a specialized program focusing on multidisciplinary care in patients with PD.[14] The primary outcome of this study was assessed using Part III Motor Examination subscale of the Unified Parkinson's Disease Rating Scale (UPDRS), a well-established tool. The 27-part test has been used in many clinical trials to assess long term outcomes in patients with PD.[14] The multidisciplinary interventions included: medication management, neurologist visits, psychiatrist visits, neuropsychological visits, functional diagnostic testing, rehabilitation therapy,

home exercise, support group, and health and wellness education.[14] At one and three year follow ups, 37 out of the 49 patients enrolled (75.5%) had unchanged or improved UPDRS motor scores.[14] The results of this study suggest that multidisciplinary interventions can not only slow progression of motor dysfunction but may also potentially improve it.

Next, a study in Canada compared treatment of patients with PD with intensive, multidisciplinary care versus standard care.[15] Patients with PD and without dementia were referred to a specialized care center and were randomized to an intervention group or a control group.[15] The intervention group consisted of a multidisciplinary team of a movement order specialized neurologist, nurses, and a social worker.[15] The control group was provided care by a general neurologist.[15] The primary outcome was change in baseline Parkinson's Disease Questionnaire (PDQ-39) after 8 months.[15] 122 patients were randomized in a 1:1 ratio and followed up after 8 months.[15] At follow up, the PDQ-39 score of the intervention group improved from 22.2 to 19.7 while the control group score worsened from 19.1 to 20.2 which was significantly different (95% CI [0.5-6.2]).[15] This study also provides evidence that a multidisciplinary approach can have positive impacts on patient outcomes.

Another study randomized 44 patients with idiopathic PD to receive either specialized care in the intervention group or standard care in the control group.[16] The intervention group received group education from several specialists. These included neurologists who specialize in movement disorders, physical and occupational therapists, dieticians, and a psychologist.[16] Health education was the primary focus as the intervention and each professional had a pre-specified role in the care of the patient.[16] Individualized rehabilitation was then given over the course of 8 weeks to the intervention group.[16] The primary outcome was assessed using the Health-related quality of life tool (HR-QOL) tool.[16] After an 8-week period, patients in the intervention group had a significantly higher HR-QOL score compared to the standard group ($p<0.001$).[16] The study showed that group education in combination with standard rehabilitation improved patient quality of life and complemented current medical treatment.

An interesting observation of this trial was that during the screening process, patients were given a survey to rank which potential health education content would be most necessary to a patient with idiopathic PD. The options were diet, mental health,

rehabilitation, and the latest advances in medicine.[16] A vast majority of patients ranked mental health and rehabilitation as first while the least ranked was latest advances in medicine.[16] The authors explained that most patients believed in rehabilitation in conjunction with current treatment as the best approach and that there was little hope for advances in anti-parkinson medicine due to adverse side-effects.[16] This further promotes the need for multidisciplinary care in patients with parkinson's especially those focusing on non-pharmacologic care.

A study in the Netherlands attempted to assess the effectiveness and costs of multidisciplinary care of patients with PD.[17] In this study, only a small benefit was seen and costs to the healthcare system were similar between the intervention and control group.[17] There were many limitations to this trial compared to previous clinical trials. Intensive care was provided to all patients with PD rather than patients that may require extra care.[17] More studies are needed to assess the true cost-benefit to patients and the health care system.

Although studies have shown positive impacts on patient outcomes, there has been difficulty implementing uniform designs. Individual studies have looked at different populations and have had different designs which makes it difficult to compare results and apply to practice. Studies looking specifically at patients with PD have become a challenge primarily due to low patient populations.[13] Research is also lacking in the use of true randomized-control design which limits the strength of the evidence that is available.[13] Multidisciplinary teamwork between different healthcare providers has shown to improve outcomes in patients with PD, but more quality research is still desired to help determine the absolute benefit, multidisciplinary design, costs, and specific interventions of most value to patients.

Conclusion:

PD is a very complex disease state that involves a wide variety of both motor and non-motor complications. Many different pharmacologic therapies have been developed which target specific mechanisms of PD pathophysiology. These treatments have shown a significant improvement in the motor symptoms these patients experience. However, they are commonly associated with many troublesome side effects that decrease quality of life and can pose a danger to the patient. This limits the effectiveness that medication alone can provide. The implementation of multidisciplinary health care teams in the care of patients with PD can help patients' quality of life when used in

combination with appropriate medication management. It is important for each health care professional to be aware of the potentials for other team members, so that an effective multidisciplinary effort can be provided. Professionals should be proactive towards implementing a multidisciplinary approach towards treatment of many disease states and especially in the treatment of patients with PD because of the positive impact it can have on patients and the health care system. Further studies and implementation may help in determining the most effective design to involve different health care professions.

Appendix

Table 1. Agents used in Parkinson's Disease

Class/Agent	MOA	Side Effects
Levodopa/carbidopa	Levodopa – dopamine precursor Carbidopa – inhibit peripheral dopa-decarboxylase	N/V, dyskinesias, orthostatic hypotension, dizziness, insomnia, confusion, behavioral changes
Dopamine agonist • **Bromocriptine** • **Pramipexole** • **Ropinirole** • **Pergolide** • **Rotigotine** • **Apomorphine**	Stimulate dopamine receptors	N/V, edema, orthostatic hypotension, drowsiness, hallucination, confusion, behavioral changes
MAO-B inhibitors · **Selegiline** · **Rasagiline** · **Safinamide**	Inhibit monoamine oxidase-B to prevent dopamine metabolism	Orthostatic hypotension, headache, confusion, hallucination
COMT inhibitors · **Tolcapone** · **Entacapone**	Inhibit catechol-O-methyltransferase to prevent levodopa metabolism	N/V/D, dyskinesias, orthostatic hypotension, confusion, hallucination

Anticholinergics · **Benztropine** · **trihexyphenidyl**	Inhibitory effect on the parasympathetic nervous system to decrease motor symptoms	Dry mouth, blurred vision, constipation, urinary retention, orthostatic hypotension, cognitive impairment
Amantadine	Noncompetitive NMDA receptor antagonist to reduce dopamine reuptake	Dizziness, insomnia, hallucination, anxiety

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