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Parkinson's Disease: Traditional and Emerging Approaches to Therapy

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Parkinson's Disease

Parkinson's disease (PD) is a prevalent neurodegenerative movement disorder, effecting patients all over the world (Burchum & Rosenthal, 2022). Copious research has evaluated the most effective and safest treatment modalities. Pharmacological therapy has advanced tremendously over the past few decades, but overall management of PD revolves around delaying progression and symptomatic management. There is currently no cure or neuroprotective approach within PD therapy. As a result, there has been novel research evolving in the realm of non-pharmacological therapies targeted towards the main areas of physiological struggle and decline for patients with PD (Feisher, 2023). Thus, these new approaches to PD care need to be examined in light of traditional pharmacological treatment regimens to inform future clinical practice guidelines and ongoing support of patients with PD.

Pathophysiology Overview of Parkinson's Disease

The fundamental pathological basis for PD involves an imbalance between dopamine and acetylcholine (Burchum & Rosenthal, 2022). These two neurotransmitters are responsible for coordinating the function of the brain's striatum, and when they fail to regulate this system, a series of dyskinesias occur. These physiological impacts include tremors, rigidity, bradykinesia, and postural instability. As current research literature indicates, there is no clear, definable cause for PD. Whatever the direct etiological factor is, PD is characterized by a defect in the neurons responsible for dopamine production in the substantia nigra. A lack of this inhibitory neurotransmitter allows acetylcholine to be produced and circulate unchecked and unregulated. This excess in acetylcholine results in the increased synthesis and release of gamma-aminobutyric acid (GABA), one of the main mechanisms responsible for PD motor symptoms.

One theorized cause of PD involves the build up of alpha-synuclein within the brain cells (Koch et al., 2023). Normally, this protein is broken down by two proteins, parkin and ubiquitin (Burchum & Rosenthal, 2022). When there is systemic deficiency of these proteins, toxic amounts of alpha-synuclein accumulate in the brain, forming a structure known as Lewy bodies. These cytoplasmic filamentous aggregates are identifiable only after death via an autopsy. The main reasons one might develop Lewy bodies involves either a genetic defect or exposure to environmental toxins. These two factors would predispose the individual to a lack of parkin and ubiquitin. Regardless of the exact pathophysiological cause, the hinderance of dopamine production and release in the striatum of the central nervous system (CNS) results in a myriad of extrapyramidal side effects, one of the targets of PD treatment.

Traditional Pharmacological Therapy

Carbidopa-Levodopa

There is no current drug regimen that can reverse or completely cease neurological decline associated with PD (Burchum & Rosenthal, 2022). However, there are medications that can help mitigate the effects of PD induced dyskinesia, resulting in an improved and prolonged quality of life. The hallmark of PD pharmacotherapy is carbidopa-levodopa (Spindler, 2023). Unfortunately, this combination medication, while proven to slow cognitive and physical decline, eventually loses its efficacy resulting in a return to the patient's previous baseline or aggravated Parkinson's symptoms. For this reason, carbidopa-levodopa may not be initiated immediately following a PD diagnosis (Koch et al., 2023). If the patient is not experiencing any motor symptoms that impact their quality of life, pharmacotherapy may be reserved for later in the disease course. This would approach seeks to align the efficacy period of carbidopa-levodopa with the onset of the patient's persistent PD symptoms.

Relating to the pathophysiology of PD, one might assume that treatment and cure of PD could be attained with direct dopamine administration (Burchum & Rosenthal, 2022). However, dopamine is unable to cross the blood brain barrier (BBB), preventing it from reaching CNS. Levodopa, conversely, is able to access the CNS via the BBB by utilizing an active transport system. This allows levodopa to enhance the production of dopamine in the striatum by stimulating the nerve terminals still alive and operating in the substantia nigra. An enzyme, decarboxylase, converts this medication into its active form, dopamine, by removing a carboxyl group from the levodopa molecule. Therefore, after this conversion, dopamine can travel into the synaptic space and latch onto GABA receptors. This attachment then provides for regulation of GABA activity, decreasing Parkinson's induced symptoms.

Unfortunately, since levodopa is given orally, this process is impeded by the rapid conversion of levodopa within the periphery (Burchum & Rosenthal, 2022). This results in only 2% of oral levodopa reaching the CNS, with the remaining systemic dopamine having no beneficial effects in treating PD. To enhance levodopa's transport through the BBB, this medication is only administered in combination with carbidopa. When given together, carbidopa acts against decarboxylases in the periphery, facilitating more drug passage of levodopa into the CNS. Carbidopa has no medicinal effects on its own. Rather, it simply acts as the transporter and protector of levodopa until reaching the BBB, enabling 10% of levodopa to reach the striatum. This combination medication also allows for levodopa dosage reduction by as much as 75%.

While Carbidopa-Levodopa is highly effective for a period of time, there are other medications that can be used as monotherapy or adjuvant therapy in traditional PD management (Koch et al., 2023). These drugs can either delay the initiation of carbidopa-levodopa, enhance the effects of carbidopa-levodopa, or target adverse effects and phenomena associated with

carbidopa-levodopa. This combination drug can induce dyskinesias, on-off cycles, and a wearing off phenomenon that can interfere with control of Parkinson's symptoms and progression. Additional pharmacologic administration may be useful in addressing these adverse impacts.

NMDA Receptor Antagonists

Levodopa, while used to treat PD dyskinesias, can also contribute to the development of drug induced dyskinesias (Burchum & Rosenthal, 2022). Amantadine is an antiviral medication that can block N-methyl-D-aspartate receptors. These receptors facilitate the movement of calcium into neurons, regulating the stimulatory effects of glutamate. Amantadine therefore assists with balancing intra-neuronal and extra-neuronal ions, like magnesium and calcium. By controlling this transportation process, this medication can help calm the overstimulated nerve impulses and prevent neurodegeneration. Adding amantadine therefore helps mitigate levodopa induced dyskinesias. However, this rapidly effective medication's benefits are short lived, lasting only three to six months. For this reason, amantadine is never used as monotherapy or as first line, long-term treatment.

Dopamine Agonists

There are two main categories of dopamine agonists, ergot derivatives and non-ergot derivatives (Burchum & Rosenthal, 2022). Ergot derivatives are not commonly used in the management of PD due to the numerous adverse effects associated with them. They are poorly tolerated because they alter the balance of serotonin and block some alpha-adrenergic receptors, while also activating dopamine production. As a result, non-ergot derivatives, like pramipexole, are included in first line therapy for PD. Pramipexole can be used independently during the early stages of disease management or can be added to carbidopa-levodopa at a further point in the

disease progression. When used as monotherapy or concurrently with carbidopa-levodopa, non-ergot derivatives have a tremendous effect on stabilizing Parkinson's motor symptoms.

Pramipexole works by binding to and activating dopamine-2 and dopamine-3 receptors (Koch et al., 2023). However, it is the stimulation of dopamine-2 receptors that allows for an increase in dopamine production. Unfortunately, there are many side effects that can develop with the use of non-ergot derivatives. Pramipexole has been associated with somnolence, hallucinations, impulsive behavior, sleep attacks, orthostatic hypotension, and dyskinesias. Since there is no cure for Parkinson's a risk versus benefit assessment must be made regarding the continuation of a dopamine agonist when there is evidence of these adverse effects.

COMT Inhibitors

When there is preemptive wearing-off of levodopa, signaled by a return of symptoms before its duration of action has lapsed, the addition of a catechol-O-methyltransferase (COMT) inhibitor may improve levodopa efficacy (Burchum & Rosenthal, 2022). Just like carbidopa has no independent action when combined with levodopa, COMT inhibitors merely prevent the breakdown of levodopa in the periphery. Entacapone prolongs the half life of levodopa by blocking COMT, a class of specific enzymes. This allows for increased transport of levodopa through the BBB by preventing levodopa metabolites. One important consideration with combining carbidopa-levodopa is the consequence of increasing the concentration of levodopa. Some of the adverse effects of levodopa may reappear, or be worsened, with the addition of entacapone. This implication might warrant a reduction in the dosage of levodopa.

MAO-B Inhibitors

If a patient is experiencing a premature wearing off from their levodopa, a monoamine oxidase B (MAO-B) inhibitor can be utilized (Burchum & Rosenthal, 2022). Two MAO-B

inhibitor prototypes include selegiline and rasagiline. Both agents can be used either independently or in combination with carbidopa-levodopa. Administration of a MAO-B inhibitor increases the lifespan of dopamine created by levodopa within the CNS. Selegiline and rasagiline inhibit the enzyme that destroys dopamine in the substantia nigra, and their effect is permanent until new monoamine oxidase enzymes are created. The main difference between these two agents is their end metabolic products. Selegiline is broken down into methamphetamine and amphetamine within the brain, both of which are neuronal stimulators. Because of this, rasagiline is often used over selegiline to prevent insomnia and overexcitation of the CNS.

Anticholinergics

The final pharmacologic category of drugs used in PD includes anticholinergics (Burchum & Rosenthal, 2022). Specifically, benztropine works on the CNS by antagonizing muscarinic receptors in the striatum, increasing the concentration of dopamine in relation to acetylcholine. Benztropine used to be considered a first line agent but has since been demoted to a second line medication, targeted towards addressing Parkinsonian tremors. These agents are only effective in reducing tremors, and they do not benefit the patient regarding any other PD symptoms. In addition, they are not well tolerated in older adults due to the incidental blockade of peripheral muscarinic receptors, leading to urinary retention, tachycardia, dry mouth, photophobia, blurred vision, constipation, and potential aggravation of glaucoma (Koch et al., 2023). Therefore, even when tremors return after efficacy of levodopa dissipates, benztropine is not an ideal treatment in older populations, those who PD disproportionately affects.

Non-Pharmacological Approaches

Since current pharmacologic therapy only staves off inevitable neurological and neuromuscular decline, there is research pointing to possible nonpharmacologic treatment

modalities that may be able to improve patients with Parkinson's quality of life (Spindler, 2023). By preserving the patient's ability to perform activities of daily living (ADL) both functionally and independently, both physical and mental health can be sustained. Providing holistic health care involves all aspects of a person's wellbeing, and nonpharmacologic interventions can be specified to meet each patient's needs in a manner that is enjoyable and noninvasive (Feisher, 2023). Current literature points to beneficial usage of targeted vibration, peripheral nerve stimulation, and various methods of physiotherapy.

Physiotherapy

Physiotherapy is a non-pharmacologic approach to treatment that involves many different modalities of physical activity (Radder et al., 2020). A meta-analysis by the American Society of Neurorehabilitation found that physiotherapy, in general, helps to decrease the severity and frequency of Parkinson's related motor symptoms. In their review, they researched the benefits of conventional physiotherapy, treadmill training, dance, martial arts, Nordic walking, aerobic exercises, balance and gait training, and hydrotherapy. Traditional physiotherapy was shown to alleviate motor symptoms, enhance gait, and improve overall quality of life. Treadmill training was the most effective intervention for stabilizing and strengthening gait. Pertaining to motor symptoms, dancing significantly improved overall physical function in the patients with PD that participated in this intervention. Finally, martial arts and hydrotherapy resulted in statistically significant improvement of physical function.

Research is showing how impactful non-pharmacologic interventions can be regarding quality of life and slowing of disease progression for these patients (Radder et al., 2020). Another essential component that contributes to the success of these interventions is the aspect of community. For example, participating in a dance class geared specifically towards patients with

PD provides a setting in which patients from the same clinical background can rally together, and support each other physically and emotionally. A state of wellbeing and health involves more than simply the absence or reduction of physical ailments. Physiotherapy is a safe, easy, noninvasive approach to holistic care for patients with PD. Furthermore, the chosen method of physiotherapy can be targeted towards each patient's needs, abilities, and interests. Health care professionals can and should educate their patients about the importance of participating in physical activity as one aspect of their Parkinson's treatment regimen.

Peripheral Nerve Stimulation

A more modern and developing approach to reducing Parkinson's motor symptoms involves the application of electrical pulses directed at the median nerve of hands affected by tremors (Arruda et al., 2021). In a recent study published by the Journal of Neuro-Engineering and Rehabilitation, peripheral nerve stimulation was applied using an external device. This study concluded that these electrical pulses directly altered the frequency and severity of tremors. Depending on the timing of electrotherapy, the stimulation could either improve or worsen the tremors.

When timed correctly, the device could reduce the Parkinsonian tremor by as much as 36% (Arruda et al., 2021). Conversely, it could also worsen the shaking by a margin of up to 117%. These results are promising in future utilization of electrotherapy. The main limitation of this intervention stems around the variability in tremor patterns for each individual patient and each individual extremity. A method of mapping the oscillating pathways is needed before this technique can be applied with full beneficial effect. Therefore, this is an area of non-pharmacological Parkinsons' treatment that, while not employable clinically now, could be researched and refined for future use in Parkinson's therapy.

Vibration Therapy

Further research is investigating vibrational therapy for decreasing the frequency and intensity of tremors for patients with Parkinson's (Abramavicus et al., 2020). Three approaches have been clinically tested to evaluate their effectiveness. These modalities include a wearable wrist device, stimulatory glove, and the Vilim ball. Universally, the delivery of vibrational therapy attempts to match the frequency and amplitude of the Parkinsonian tremor (Faizan & Muzammil, 2020). The average frequency delivered in these trails ranged from 3-30 hertz (Hz), and the amplitude varying from 0-2 millimeters. The end goal of synchronizing tremors with mechanical stimulation is synaptic decoupling, resulting in decreased overactivity of the sensorimotor cortex.

The dual passive vibration delivered by the wearable wrist device found that this vibrational therapy reduced the amplitude and angular movement of the affected wrist by 57.25% (Faizan & Muzammil, 2020). Patients in this clinical trial demonstrated an enhanced ability to complete ADL's. Furthermore, the vibrational gloves, capable of delivering both intermittent and continuous stimulation, were shown to decrease overexcited peripheral motor neuron transmission (Pfeifer et al., 2021). The handheld Vilim ball was used on fifty-one PD patient participants (Abramavicus et al., 2020). Of this population, forty-eight testified to improved tremors and forty-nine reported improved motor and physical function. Some patients reported that there were times in which their tremors were aggravated after using the Vilim ball. However, this study reported that these occurrences were few, and the risk versus benefit profile was still very favorable.

The appeal of these devices is that they are all non-pharmacological, non-invasive, portable, and compact devices to directly target tremors (Faizan & Muzammil, 2020). This

symptom of PD is arguably the most aggravating and debilitating for patients when performing simple ADLs. One limitation identified with these devices includes potential long-term sensorimotor compensation (Pfeifer et al., 2021) Further research should be conducted to evaluate whether adjusting the frequency and amplitude of the vibrations periodically could prevent or address the issue of compensation. Nonetheless, acute therapy using these vibrational devices has shown promising benefits.

Implications for Clinical Practice

Since older patients, comprising the majority PD patients, are adversely affected by anticholinergic medications, non-pharmacologic interventions like physiotherapy, peripheral nerve stimulation, and vibrational stimulation could be beneficial in symptomatic management (Burchum & Rosenthal, 2022). Many medications for Parkinson's usually have a narrow duration of efficacy, accelerated with dose escalation. Health care professionals can advocate for the use of these non-invasive approaches to manage both drug and disease induced PD symptoms. These can also help improve patients' psychological and emotional wellbeing as many methods of physiotherapy foster community in group settings (Radder et al., 2020). Overall, a risk versus benefit assessment should be implemented to evaluate these interventions on a case-by-case basis.

Conclusion

Research is ongoing in the field of PD treatment. However, there are currently no neuroprotective or curative approaches to Parkinson's therapy (Burchum & Rosenthal, 2022). Symptomatic management is an essential component of treatment for patients with PD. Therefore, non-pharmacological interventions may assist in mitigating physical and motor effects. In combination with traditional pharmacotherapy, these non-invasive techniques seek to

improve patients' overall quality of life and delay dose escalation of already prescribed medications. While physiotherapy, peripheral nerve stimulation, and vibrational therapy are not first line interventions included in the plan of care for PD patients, these non-pharmacological approaches should be further investigated for implementation as part of evidenced based care.

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