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PHARMACOLOGICAL MANAGEMENT OF PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease (PD) is a disease that involves neurodegeneration and is characterised by the motor symptoms which include muscle rigidity, tremor, and bradykinesia. Other non-motor symptoms include pain, depression, anxiety, and psychosis. This disease affects up to ten million people worldwide. The pathophysiology behind PD is due to the neurodegeneration of the nigrostriatal pathway. There are many conventional drugs used in the treatment of PD. However, there are limitations associated with conventional drugs. For instance, levodopa is associated with the on-off phenomenon, and it may induce wearing off as time progresses. PD is a neurodegenerative illness and has a common onset between the ages of 55 and 65 years. There is progressive development of both motor and non-motor symptoms, greatly affecting one's overall quality of life. While there is no cure, various treatments have been developed to help manage the symptoms of PD. Management of PD is a growing field and targets new treatment methods, as well as improvements to old ones. Pharmacological, surgical, and therapeutic treatments have allowed physicians to treat not only the main motor symptoms of PD, but target patient-specific problems as they arise. This review discusses both the established and new possibilities for PD treatment that can provide patient-specific care and mitigate side effects for common treatments.

KEYWORDS: Neurodegeneration, bradykinesia,nigrostriatal pathway,levodopa,on-off phenomenon,quality of life.

INTRODUCTION

Parkinson's disease is a progressive disorder that affects the nervous system and the parts of the body controlled by the nerves. Symptoms start slowly. The first symptom may be a barely noticeable tremor in just one hand. Tremors are common, but the disorder may also cause stiffness or slowing of movement.

In the early stages of Parkinson's disease, your face may show little or no expression. Your arms may not swing when you walk. Your speech may become soft or slurred. Parkinson's disease symptoms worsen as your condition progresses over time.

Although Parkinson's disease can't be cured, medications might significantly improve your symptoms. Occasionally, your health care provider may suggest surgery to regulate certain regions of your brain and improve your symptoms. Symptoms.

Parkinson's disease signs and symptoms can be different for everyone. Early signs may be mild and go unnoticed. Symptoms often begin on one side of the body and usually remain worse on that side, even after symptoms begin to affect the limbs on both sides.

Parkinson's signs and symptoms may include

- **Tremor.** A tremor, or rhythmic shaking, usually begins in a limb, often your hand or fingers. You may rub your thumb and forefinger back and forth. This is known as a pill-rolling tremor. Your hand may tremble when it's at rest. The shaking may decrease when you are performing tasks.
- **Slowed movement (bradykinesia).** Over time, Parkinson's disease may slow your movement, making simple tasks difficult and time-consuming. Your steps may become shorter when you walk. It may be difficult to get out of a chair. You may drag or shuffle your feet as you try to walk.
- **Rigid muscles.** Muscle stiffness may occur in any part of your body. The stiff muscles can be painful and limit your range of motion.
- **Impaired posture and balance.** Your posture may become stooped. Or you may fall or have balance problems as a result of Parkinson's disease.
- **Loss of automatic movements.** You may have a decreased ability to perform unconscious movements, including blinking, smiling or swinging your arms when you walk.
- **Speech changes.** You may speak softly, quickly, slur or hesitate before talking. Your speech may be

more of a monotone rather than have the usual speech patterns.
- **Writing changes.** It may become hard to write, and your writing may appear small.

Causes

In Parkinson's disease, certain nerve cells (neurons) in the brain gradually break down or die. Many of the symptoms are due to a loss of neurons that produce a chemical messenger in your brain called dopamine. When dopamine levels decrease, it causes atypical brain activity, leading to impaired movement and other symptoms of Parkinson's disease.

The cause of Parkinson's disease is unknown, but several factors appear to play a role, including:

- **Genes.** Researchers have identified specific genetic changes that can cause Parkinson's disease. But these are uncommon except in rare cases with many family members affected by Parkinson's disease.
- However, certain gene variations appear to increase the risk of Parkinson's disease but with a relatively small risk of Parkinson's disease for each of these genetic markers.
- **Environmental triggers.** Exposure to certain toxins or environmental factors may increase the risk of later Parkinson's disease, but the risk is small.
- Researchers have also noted that many changes occur in the brains of people with Parkinson's disease, although it's not clear why these changes occur. These changes include:
- **The presence of Lewy bodies.** Clumps of specific substances within brain cells are microscopic markers of Parkinson's disease. These are called Lewy bodies, and researchers believe these Lewy bodies hold an important clue to the cause of Parkinson's disease.
- **Alpha-synuclein found within Lewy bodies.** Although many substances are found within Lewy bodies, scientists believe an important one is the natural and widespread protein called alpha-synuclein (a-synuclein). It's found in all Lewy bodies in a clumped form that cells can't break down. This is currently an important focus among Parkinson's disease researchers.

Risk factors

Risk factors for Parkinson's disease include

- **Age.** Young adults rarely experience Parkinson's disease. It ordinarily begins in middle or late life, and the risk increases with age. People usually develop the disease around age 60 or older. If a young person does have Parkinson's disease, genetic counseling might be helpful in making family planning decisions. Work, social situations and medication side effects are also different from those of an older person with Parkinson's disease and require special considerations.
- **Heredity.** Having a close relative with Parkinson's disease increases the chances that you'll develop the disease. However, your risks are still small unless you have many relatives in your family with Parkinson's disease.
- **Sex.** Men are more likely to develop Parkinson's disease than women.
- **Exposure to toxins.** Ongoing exposure to herbicides and pesticides may slightly increase your risk of Parkinson's disease.
- Complications
- Parkinson's disease is often accompanied by these additional problems, which may be treatable:
- **Thinking difficulties.** You may experience cognitive problems (dementia) and thinking difficulties. These usually occur in the later stages of Parkinson's disease. Such cognitive problems aren't usually helped by medications.
- **Depression and emotional changes.** You may experience depression, sometimes in the very early stages. Receiving treatment for depression can make it easier to handle the other challenges of Parkinson's disease.
- You may also experience other emotional changes, such as fear, anxiety or loss of motivation. Health care providers may give you medication to treat these symptoms.
- **Swallowing problems.** You may develop difficulties with swallowing as your condition progresses. Saliva may accumulate in your mouth due to slowed swallowing, leading to drooling.
- **Chewing and eating problems.** Late-stage Parkinson's disease affects the muscles in the mouth, making chewing difficult. This can lead to choking and poor nutrition.
- **Sleep problems and sleep disorders.** People with Parkinson's disease often have sleep problems, including waking up frequently throughout the night, waking up early or falling asleep during the day.
- People may also experience rapid eye movement sleep behavior disorder, which involves acting out your dreams. Medications may improve your sleep.
- **Bladder problems.** Parkinson's disease may cause bladder problems, including being unable to control urine or having difficulty in urinating.
- **Constipation.** Many people with Parkinson's disease develop constipation, mainly due to a slower digestive tract.

You may also experience

- **Blood pressure changes.** You may feel dizzy or lightheaded when you stand due to a sudden drop in blood pressure (orthostatic hypotension).
- **Smell dysfunction.** You may experience problems with your sense of smell. You may have difficulty identifying certain odors or the difference between odors.
- **Fatigue.** Many people with Parkinson's disease lose energy and experience fatigue, especially later in the day. The cause isn't always known.

- **Pain.** Some people with Parkinson's disease experience pain, either in specific areas of their bodies or throughout their bodies.
- **Sexual dysfunction.** Some people with Parkinson's disease notice a decrease in sexual desire or performance.

Treatment

Neuroderm recently announced positive results from its Phase III trial on ND0612, a liquid levodopa/carbidopa. Levodopa temporarily replaces the dopamine brain chemical, which decreases in Parkinson's, to ease motor symptoms, like tremor, slowness and stiffness. It's currently available as a pill (to take by mouth), inhaler or gel (for infusion into the small intestine).

ND0612 is a liquid that's infused continuously, under the skin. Like the available gel and inhaled formulations of levodopa, this drug bypasses the stomach, which can empty slowly or irregularly in Parkinson's, interfering with medication absorption. The 24-hour-a-day infusion aims to provide consistent medication levels for consistent symptom relief. This may be particularly beneficial for people who experience ups and downs in symptom control throughout the day — motor fluctuations — which cannot be adequately controlled with oral medications. Motor fluctuations can happen after living with Parkinson's and taking medication for many years.

In a Phase III trial, researchers randomly assigned people with Parkinson's to take either levodopa/carbidopa pills or ND0612 for 12 weeks. Those on ND0612 had nearly one and three-quarters hours more "on" time per day, without significant symptoms, like tremor, slowness or stiffness or dyskinesia (involuntary movement). The most common potential side effects included infusion site reactions, like bruising, swelling and bleeding.

The Michael J. Fox Foundation funded earlier studies of this therapy, a critical step toward gathering additional data, support and momentum on the path to this current late stage of drug development.

The next step on the path to potential approval is for the company to submit an application to the FDA. If approved, this therapy would offer another treatment option for people with progressing Parkinson's who are unable to achieve optimal symptom control with oral medications.

Stay tuned for updates on this and other new potential medications in the pipeline.

Management of Parkinson's disease and Its Associated Psychosis

There are conventional drugs used in treating PD such as levodopa, dopamine agonists, anticholinergics, catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase-B (MAO-B) inhibitors, and amantadine. Other drugs used in treating PD related psychosis include antipsychotics. During this review period, three drugs were newly approved by the FDA for the treatment of PD symptoms and PDP, which were safinamide, istradefylline, and pimavanserin. Their mechanism of action, efficacy, and safety will be discussed below.

Mechanism of Action

The mechainsm of action of drugs that are commonly used for the treatment of PD and its symptoms are describe below.

1. Levodopa

The mode of action of levodopa involves absorption from the gastrointestinal tract, crossing through the blood-brain barrier (BBB), uptake by neurons, enzymatic action of the aromatic amino acid decarboxylase to be converted into dopamine and the synaptic release of dopamine. The disruption of the nigrostriatal pathway reduces dopamine levels and produces the symptoms of PD. Hence, the dopamine from exogenous levodopa will activate the central dopamine receptors, thus improving the symptoms of PD. Since aromatic-L-amino-acid decarboxylase (AADC) and COMT are responsible for the metabolism of levodopa peripherally, it is usually in combination with AADC inhibitors such as carbidopa and benserazide or COMT inhibitors such as entacapone and tolcapone. Levodopa has to be administered multiple times daily since it has a short half-life of about 36–96 min which will cause the fluctuation in plasma levels. Treatment with Levodopa alleviates bradykinesia and other typical motor manifestations of PD. Long-term Levodopa treatment, on the other hand, is associated with complications such as motor fluctuations and dyskinesia, which severely impair quality of life. The combination of levodopa and carbidopa is most widely used to treat PD and Parkinson-like symptoms that may develop after encephalitis (brain swelling), or nervous system injury caused by carbon monoxide or manganese poisoning.

2. Dopamine Agonists

Dopamine agonists can be categorized into two classes, which are ergot and non-ergot dopamine agonists. They have antiparkinsonian activity due to the direct-acting effect on dopamine receptors which mimic the neurotransmitter. Bromocriptine, cabergoline, pergolide, and lisuride are examples of ergot dopamine agonists whereas non-ergot dopamine agonists include ropinirole and pramipexole. Ergot dopamine agonists act primarily on the D2-like dopamine receptors including D2, D3, and D4. On the other hand, non-ergot dopamine agonist ropinirole is a potent and selective agonist of the D2 dopamine receptors while pramipexole has a higher affinity towards D3 receptors.

3. Anticholinergics

In PD patients, it has been theorized that a lesion is formed in the nigra striatum. This results in the reduction

of intranigral dopamine concentrations. Imbalances of the dopaminergic and cholinergic neurological pathway lead to more cholinergic firing. The stimulation causes dyskinesia and tremors. Thus, the mechanism of anticholinergics is to block the cholinergic receptors from the activation of acetylcholine. They act to counteract the imbalance of neurotransmitters in the nigra striatal pathway. Specifically, M4 receptor is targeted for the block by anticholinergics. This eventually will reduce the tremor and dyskinesia conditions of the patient.

4. COMT Inhibitors

A COMT inhibitor acts by breaking down catecholamines such as dopamine and norepinephrine by inhibiting the enzyme COMT. The enzyme COMT can be found in peripheral and central circulation and the aim is to prevent the breakdown of levodopa while travelling to the brain region and crossing through the BBB. It works in combination with levodopa to prevent methylation of levodopa to 3-O-methyldopa in peripheral circulation, thus improving the bioavailability of levodopa. Besides, low doses of levodopa in combination with COMT inhibitors may prevent dyskinesia.

5. MAO-B Inhibitors

MAO-B inhibitors (MAO-BIs) are the antiparkinsonian drugs that have the mechanism of action of preventing monoamine oxidase-B (MAO-B) from catalyzing dopamine metabolism, hence prolonging dopamine action in basal ganglia. It is considered as an adjuvant for PD, and it is usually used with L-Dopa for PD therapy. Besides PD, MAO-BIs are also the adjuvant for treating Alzheimer's disease. MAO-BIs exhibit neuroprotection which is the protective effect of neuronal structure and function. Other than that, they also exhibit antioxidant effects and can prolong neuronal death caused by apoptosis as well as protect functions of mitochondria. Current MAO-BI consists of selegiline and rasagiline. Both are selective and irreversible MAO-BIs.

6. Amantadine

The mechanism of amantadine in the brain is not well understood. Generally, amantadine works by inhibiting the N-methyl-D-aspartate (NMDA)-glutamate receptor and cholinergic muscarinic receptors, thereby increasing dopamine release, and blocking dopamine reuptake. It reduces dyskinesia in PD patients receiving levodopa, as well as extrapyramidal side effects of medications. Multiple studies showed that NMDA-blocking is the most important mechanism to explain its antidyskinetic effect.

7. Antipsychotics Used for Treating PDP

Clozapine

Clozapine is an FDA-approved tricyclic dibenzodiazepine antipsychotic drug commonly used in schizophrenia patients. It is classified as an 'atypical' antipsychotic due to the selectivity of binding towards the dopamine receptors that differ from typical antipsychotic drugs. In this review, clozapine is focused as an off-label used in psychosis in PD patients. Psychosis happens when there is excessive dopamine level while clozapine able to antagonist the dopamine receptor to control the dopamine level. It has a high affinity towards dopamine D4 receptors while also targets D1, D2, D3, and D5. In other words, clozapine is more likely to act on limbic rather than striatal dopamine receptors thus reducing the psychosis symptoms in the parkinsonian patients. In addition, clozapine is found to have an antagonistic effect on adrenergic (alpha-1), cholinergic (muscarinic M1, M2, M3, and M5), histaminergic, and serotonergic receptors. Evidence has also shown that serotonin 2A receptors neurotransmission abnormalities are associated with psychosis in PD patients. Clozapine has great efficacy in managing psychosis in PD but is underused due to its potential adverse events.

Olanzapine

Olanzapine is a second-generation antipsychotic that produces its effect on the dopamine as well as serotonin receptors. It works primarily on the mesolimbic pathway dopamine 2 receptor as a blocker. It blocks the dopamine neurotransmitter from exerting the effects on the postsynaptic receptor. Olanzapine binds to the receptor loosely and so enables the normal amount of dopamine to carry out neurotransmission. The effects of olanzapine on the dopamine 2 receptor led to the reduction in positive symptoms in the patient, which includes hallucination, delusion, and disorganized speech. As for the serotonin 5-HT2A receptors, the olanzapine works as an antagonist as well. Since serotonin 5-HT2A receptors are located in the frontal cortex, this results in reduced negative symptoms which include anhedonia, flat affect, alogia, and poor attention.

Quetiapine

Quetiapine, a dibenzothiazepine atypical antipsychotic, has a similar action to clozapine whereby it inhibits D2 receptors and serotonin 5-HT2A receptors. It also binds to serotonin 5-HT1A, D1, H1, alpha 1, and alpha 2 receptors. Nowadays, quetiapine is the most widely used antipsychotic in the treatment of PDP as monitoring for blood dyscrasias is not required and it shows the minor effect on motor symptoms.

Risperidone

Risperidone is a benzisoxazole atypical antipsychotic which has high antagonistic activity on the 5-HT2A and D2 receptors. Thus, it can cause a harmful effect on dopamine replacement therapy and can aggravate motor symptoms. Unlike clozapine, risperidone does not cause seizures, and hematologic and antimuscarinic side effects. In people with schizophrenia, risperidone does not cause more extrapyramidal symptoms at doses less than 6 mg/day compared to placebo as serotonin antagonism will be predominant at low doses. Furthermore, low doses of risperidone cause progressive occupancy of dopamine D2 receptor in comparison to

typical neuroleptics, modulation of the dopamine system by serotonin 5-HT2 antagonism, and selective mesolimbic blockage instead of striatal dopamine receptors.

Ziprasidone

Ziprasidone is a second-generation atypical antipsychotic with the chemical structure of benzylisothiazolylpiperazine. It has inhibitory effects on D2, 5-HT2A, and 5-HT1D receptors as well as agonistic effects to 5-HT1A receptors. The inhibitory effect for the reuptake of norepinephrine and serotonin is moderate. Among PDP medications, it is deemed to be efficacious and safe due to its profile of efficacy and safety.

8. Safinamide

Safinamide is an FDA newly approved drug used in treating PD. It is a derivative of benzylamino which has various modes of action. The main mode of action of safinamide is that it inhibits MAO-B selectively and reversibly. Moreover, safinamide has the non-dopaminergic mechanism of action which includes the state-dependent block of voltage-gated sodium channels in the inactivated state. Furthermore, safinamide also has antiglutamatergic activity. These actions may be responsible for its pain mitigating effects. Safinamide also prevents the formation of free radicals through the inhibition of MAO-B

9. Istradefylline

Istradefylline is known as the selective adenosine A2A receptor antagonist. Adenosine A2A receptors are demonstrated to suppress the activity of GP projection by suppressing GABA which is transmitted and released in the striatum. This will lead to the enhancement of GABA in the GP. Therefore, when istradefylline blocks A2A receptors, it can reduce outrageous excitability of the indirect output pathway, thereby minimizing the occurrence of the motor symptoms in PD patients. In addition, istradefylline is considered as nondopaminergic due to the lack of effects on dopamine receptors and dopamine-metabolizing enzymes. It does not have the inhibitory activity toward enzymes such as COMT, MAO-A, and MAO-B which metabolize dopamine or levodopa. It also has a low affinity for receptors such as dopamine (D1, D2), serotonin (5-HT1A, 5-HT2, 5-HT3), and noradrenaline receptors.

10. Pimavanserin

Pimavanserin is known as the selective antagonist or inverse agonist of 5-hydroxytryptamine (HT) 2A receptor. This is because of its ability to reduce 5-HT2 receptor activity without acting on other receptors. Thus, it does not induce a pharmacological reaction to agonists on other receptors. Pimavanserin has a 40 folds higher affinity towards 5-HT2A receptors compared to 5-HT2C receptors. However, it has a low affinity towards dopaminergic, muscarinic, histaminergic, or adrenergic receptors and has a low ability in blocking D2 receptors. Therefore, the deleterious effect of pimavanserin on dopamine replacement therapy will not be the same as atypical psychotic drugs and it does not worsen motor symptoms. Thus, pimavanserin is the first medication licensed in the United States for the treatment of Parkinson's disease psychosis (PDP)-related hallucinations and delusions, eventually making pimavanserin the first agent approved by FDA in 2016 for treatment of PDP.

Efficacy and safety of the newly approved drugs for treatment of PD.

Drug Name	Author, Year, Reference Number	Study Design	Population Characteristics	Interventions	Primary Outcome Measured	Efficacy	Safety
Safinamide	Schapira A., et al., 2013	Randomized, placebo-controlled, double-blind international Phase III trial.	Patients who had mid-to-late-stage idiopathic PD (>3 years of disease) and were treated with optimized, stable doses of L-dopa and DA, catechol-O-methyltransferase inhibitor, anticholinergic, and/or amantadine.	Safinamide 50 mg, Safinamide 100 mg, placebo.	Change in daily on time with no or non-troublesome dyskinesia.	Improved on time (without worsening the troublesome dyskinesia), off time, UPDRS part III, CGI-S, CGI-C, PDQ-39 and off time following the first morning L-dopa dose.	Major AEs: Back pain, headache, falls, dyskinesias, nausea, and urinary tract infections
	Borgohain R., et al., 2014	Randomized, placebo-controlled, double-blind	Patients aged 30–80 years, had been diagnosed with PD ≥3	Safinamide 50 mg, Safinamide 100 mg,	Change in mean daily on time with no or non-	Improved UPDRS part III in both safinamide 50 mg (p = 0.0138) and 100	Major AEs: Back pain, headache, dyskinesia,

		Phase III trial. (Study 016)	years, had the presence of motor fluctuations with 1.5 h off a day.	placebo.	troublesome dyskinesias in the 18-h recording period.	mg (p = 0.0006) groups. Significant improvement in off time, CGI-C and CGI-S in both safinamide groups following the morning dose of levodopa.	depression, and hypertension
	Borgohain R., et al., 2014	Randomized, double-blind, placebo-controlled, 18-month extension study. (Study 018)	Patients who had completed the 016 study or patients who had completed efficacy evaluation at weeks 12 and 24 of Study 016.	Safinamide 50 mg, Safinamide 100 mg, placebo.	Mean change from baseline at Study 016 to endpoint of the DRS score during on time.	Improved total daily on time without troublesome dyskinesia from baseline for safinamide 50 mg (p = 0.0031) and safinamide 100 mg (p = 0.0002). Improved off time, CGI-S, CGI-C (for SAF 50 mg), UPDRS part II, part III and part IV total scores and PDQ-39.	Major AEs: Back pain, insomnia, headache, and dyskinesia
	Stocchi F., et al., 2004	Randomized, placebo-controlled, double-blind, Phase II, dose finding study.	Early PD patients.	Safinamide 0.5 mg/kg, Safinamide 1.0 mg/kg, placebo as monotherapy or as adjunct therapy to a single DA.	Proportion of patients considered as treatment responders, for example 30% improvement in UPDRS part III compared with baseline.	Improved UPDRS part III as compared to baseline, more statistically significant between safinamide 1.0 mg/kg and placebo (p = 0.016).	Major AEs: Abdominal pain, dizziness, and musculoskeletal and connective tissue disorders
	Stocchi F., et al., 2006	Single-center, open, pilot trial.	25 PD patients with Hoehn and Yahr (H&Y) stages III–IV.	Safinamide 100 mg, Safinamide 150 mg, Safinamide 200 mg as adjunct therapy to stable single DA or LD.	Changes in UPDRS part II, part III, and part IV and CGI.	Improved motor performance (evaluated by UPDRS part III) for more than an 8-week period (p < 0.001).	

CONCLUSION

Based on the comparison of findings from all trials and studies, it was found that safinamide demonstrated the highest efficacy and safety as add-on therapy in controlling PD symptoms. The most common adverse event associated with safinamide was dyskinesia and gastrointestinal symptoms, both of which were mild and tolerable. All the other agents also demonstrated favorable efficacy in controlling PD motor complications. However, further studies and trials need to be conducted in order to prove and establish their long-term efficacy and safety profiles. L-DOPA remains the most accepted form of treatment for PD, as it is used as a dopamine replacement for this neurodegenerative disease. While other dopamine agonists are successful at controlling symptoms of PD early on in the onset of the disease, L-DOPA is the most effective pharmaceutical at helping to improve QoL, especially once symptoms become more unmanageable with other anti-parkinsonian medications. There is no known cure for PD, but alternative drug, surgical and behavioral therapies exist for the treatment of PD, and new therapies are being

developed to help mitigate the side effects and symptoms of this progressive disease. Physical, occupational, and speech therapies provide non-drug alternatives that can be used in adjunct with medications, or separately for those who prefer more natural approaches. They can help treat individual symptoms as they arise. There is still a need to further explore other treatments, and more studies can delve into the under-researched therapies for PD, but the future of PD treatment is promising for patient-specific care that is more effective and with minimal side effects.

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