

Overview of Pharmacologic Treatment of Motor Fluctuations in Parkinson's Disease

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ABSTRACT

Parkinson's disease is a debilitating neurodegenerative disorder characterized by motor impairments such as tremors, rigidity, and gait disturbances, as well as non-motor symptoms, including sleep disorders and autonomic dysfunction. While dopamine replacement therapy remains the mainstay of treatment for managing motor symptoms, the progressive nature of the disease often necessitates complex pharmacological regimens and a multidisciplinary approach. This article provides an overview of the pathophysiology of Parkinson's disease and discusses the various pharmacological interventions available for managing complications as the disease advances.

Keywords: *Parkinson's disease, α -synuclein, Lewy bodies, dopamine replacement therapy, motor symptoms.*

INTRODUCTION

Parkinson's disease is a complex neurodegenerative disorder that extends beyond the motor systems.⁽¹⁾ The diverse range of motor, non-motor, and cognitive manifestations can collectively have a devastating impact on patients' quality of life, independence, and overall well-being.^(2,3) The cause of sporadic Parkinson's disease remains unclear but may be influenced by both genetic and environmental factors.⁽⁴⁾ Cell model studies suggest that Parkinson's disease is characterized by the loss of dopaminergic neurons, as well as the accumulation of α -synuclein-containing aggregates known as Lewy bodies in the pars compacta of the substantia nigra.⁽⁵⁾ It occurs due to the extensive damage to dopamine-producing neurons, causing dopamine deficits in the

midbrain, and altering the balance and activity of various other neurotransmitters (glutamate, GABA, serotonin, etc.), consequently disrupting motor control.^(5,6) A wide range of medical and surgical interventions are available, but dopamine replacement therapy remains the most effective treatment for motor symptoms.^(7,8) Chronic dopamine replacement treatment, however, is associated with motor complications in most patients as their disease progresses.⁽⁸⁾ Therefore, it is recommended that clinicians initiate dopamine replacement therapy with low doses in patients with Parkinson's disease and gradually titrate it, especially in younger patients and women, who are more likely to develop dyskinesia.^(8,9) If monotherapy is inadequate for motor fluctuations, trials suggest add-on drugs such as Dopamine Agonists (DAs), Monoamine Oxidase B (MAO-B) inhibitors and Catechol-O-Methyl Transferase (COMT) inhibitors as an adjuvant therapy.⁽¹⁰⁻¹³⁾ This review will provide an overview of the background and different pharmacological treatment targeting the motor symptoms of Parkinson's disease.

PATHOPHYSIOLOGY

Physiologically, Parkinson's disease is progressively characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta, as well as the abnormal aggregation of α -synuclein called Lewy bodies.^(14,15) Lewy bodies, which contain α -synuclein filaments, are thought to trap mitochondria and lysosomes, contributing to neuronal dysfunction.^(16,17) Pathogenic mutations in the α -synuclein gene lead to an accelerated formation and accumulation of the proteins at synapses, resulting in synaptic dysfunction and contributing to neurodegeneration and system atrophy.⁽¹⁸⁾

From a molecular mechanism perspective, mitochondrial dysfunction and a decline in the clearance capacity of the ubiquitin-proteasome and autophagy-lysosomal systems have been implicated in the pathobiology of Parkinson's disease (Figure 1).⁽¹⁹⁻²²⁾ Mitochondria are responsible for

Lastly, inflammation and immunity are also linked to the progression of Parkinson's disease. The cascade of inflammation can increase intestinal permeability and the leakage of inflammatory mediators into the bloodstream and through the blood-brain barrier, promoting α -synuclein aggregation.⁽²⁷⁾ For immunity,

T cells were observed in the affected brain regions of Parkinson's disease patients, leading to targeted extravasation.⁽²⁸⁾

CLINICAL MANIFESTATIONS

Parkinson's disease is progressively characterized by both motor and non-motor symptoms, and it can progress rapidly without treatment.⁽¹⁾ Motor symptoms are classified into cardinal symptoms (dopamine responsive) and

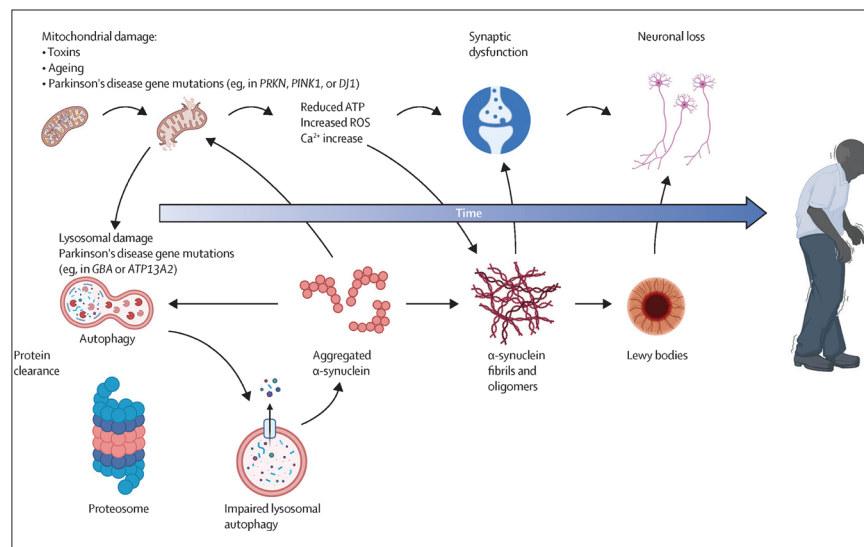


Figure 1: Molecular mechanisms contributing to Parkinson's disease⁽²⁵⁾

generating the chemical energy needed for the cell's biochemical reactions, including cell signaling in dopaminergic neurons.⁽²⁰⁾ Dysfunctional mitochondria can lead to high intracellular calcium levels and low ATP production, which facilitate the formation of soluble α -synuclein oligomers and insoluble fibrils to compose the core of intraneuronal Lewy bodies and Lewy neurites.⁽¹⁹⁻²¹⁾ Furthermore, the concentration of α -synuclein is linked to the lysosomal clearance of abnormal and accumulated proteins. Impaired lysosomes can reduce the turnover of α -synuclein, leading to its aggregation.⁽²³⁾

The cause of Parkinson's disease is believed to be multifactorial, involving the interaction of host susceptibility and environmental factors.⁽⁴⁾ Although the cause of sporadic Parkinson's disease is unclear, it is believed that idiopathic Parkinson's disease is influenced genetically.⁽²⁴⁻²⁶⁾ For example, pathogenic mutation of VPS35 can induce phosphorylation of Rab proteins, proteins that are involved in endocytosis and lysosomal trafficking, which consequently reduces lysosomal function and increases α -synuclein aggregation.⁽²⁶⁾

axial symptoms (non-dopamine responsive).⁽²⁹⁾ Non-motor symptoms are subdivided into neuropsychiatric and autonomic dysfunction. These non-motor symptoms may precede motor symptoms by five years or more, and they contribute significantly to the disability and worsening quality of life compared to motor symptoms.⁽³⁰⁾ Parkinson's disease is typically staged using various classification systems, with the most common being the five-stage system proposed by Margaret Hoehn and Melvin Yahr, although the progression is not uniform in all patients.⁽³¹⁾ Stage 1 consists of unilateral movements, including tremor, rigidity, a clumsy leg or facial weakness. Stage 2 involves motor symptoms occurring on both sides of the body or at the midline, together with speech abnormalities and rigidity in the trunk muscles. Stage 3 is characterized by slowness of movement, early signs of postural instability, and difficulty making automatic and involuntary adjustments. Stages 4 and 5 are considered advanced Parkinson's disease, in which individuals suffer from severe symptoms and are unable to walk unassisted or live independently.⁽³¹⁾ Apart from motor symptoms, non-motor symptoms can also be debilitating for patients, such as excessive daytime sleepiness, rapid eye movement, drooling, constipation, dementia, anxiety, and depression.⁽³⁰⁾

COMMON PHARMACOLOGICAL MANAGEMENT

The main goals of therapy are to maintain functional independence and preserve quality of life by decreasing symptoms. The common oral pharmacologic interventions for motor symptoms include: levodopa, DAs, COMT inhibitors, MAO-B inhibitors, adenosine A_{2a} antagonist, anticholinergics, amantadine and clozapine (**Figure 2**).⁽³²⁾

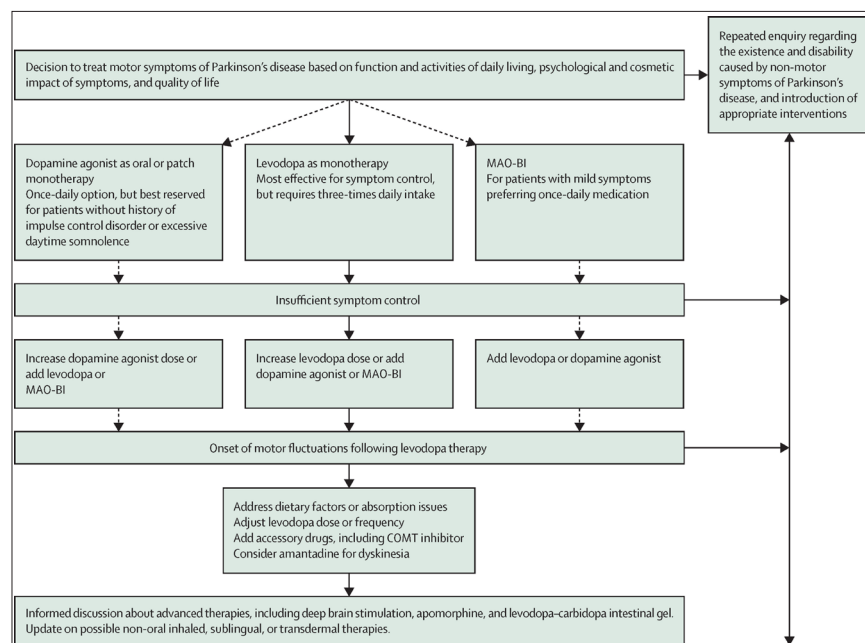


Figure 2: Algorithm for the approach to treating Parkinson's disease ⁽³²⁾

Levodopa with dopa-decarboxylase inhibitor (DDI)

Levodopa is the precursor of dopamine to relieve motor symptoms, and carbidopa is a DDI, which prevents the breakdown of levodopa in the blood-stream peripherally, allowing more of it to cross the blood-brain barrier.⁽³³⁾ It is considered as the most effective treatment to relieve motor symptoms of Parkinson's disease over DAs and MAO-B inhibitors.⁽³⁴⁾ Even though patients using levodopa as an initial treatment are more likely to develop dyskinesia, the prevalence is low with superior motor benefit.⁽⁹⁾ Hence, both the American Academy of Neurology (AAN) and National Institute for Health and Care Excellence guidelines support that levodopa should be the preferred first-line drug for symptomatic control, unless patients have additional risk factors to develop dyskinesia.^(9,34) Nausea, vomiting and orthostatic hypotension are the common acute adverse effects, whereas wearing-off phenomena, somnolence, delusions, dyskinesia, peripheral neuropathy, impulse control disorders and

psychosis are the chronic complications.⁽⁹⁾ Nausea is a common early and dose-dependent adverse effect of levodopa. Taking levodopa with meals may decrease nausea and improve compliance; however, dietary protein can decrease the entry of levodopa into the brain and lower its therapeutic efficacy.⁽³⁴⁾ It is suggested that a dosage lower than 400 mg per day reduces the risk of dyskinesia in early Parkinson's disease.⁽³⁴⁾ The timing

to initiate levodopa treatment has been controversial. While levodopa improves motor symptoms in Parkinson's disease, recent research suggests that delaying treatment with levodopa does not prevent levodopa-related motor complications.⁽³⁵⁾ In addition, chronic use of levodopa can induce elevation of plasma homocysteine levels, which are a risk factor for stroke, heart disease and dementia. Recent studies suggest routine supplementation of vitamin B12 and folic acid might minimize the promotion of homocysteine levels induced by chronic use of levodopa.⁽³⁶⁾

If motor symptoms are not manageable with the initial dosage or if the patient is experiencing motor fluctuations such as wearing off, delayed-onset, and dyskinesia, it is recommended to escalate the dose of levodopa, then add a DA, COMT inhibitor or MAO-B inhibitor.^(8,10,11,13) Recent studies suggest patients may benefit from using multiple agents with fewer side effects, rather than relying on the higher doses of a single agent.⁽³²⁾

Dopamine agonists (DAs)

This class of medications split into two groups based on the chemical structure: ergot-like derivatives, such as bromocriptine and cabergoline, and non-ergot DA. Due to its safety concerns, including the risk of peritoneal, pulmonary, and cardiac or valvular fibrosis, ergot-like derivatives have fallen out of favor for treating Parkinson's disease.⁽³⁷⁾ Non-ergot DAs include ropinirole and pramipexole as oral agents, and rotigotine as a transdermal patch. They are significantly selective to D2 and D3 receptors than D1 and D5 receptors.⁽³⁷⁾ Dopamine receptor agonists are classified

to two groups; D1-like (D1 and D5 receptor subtypes) and D2-like (D2, D3 and D4 receptor subtypes).⁽³⁷⁾ The selectivity of D2 and D3 receptors enhances the efficacy in managing motor symptoms including bradykinesia and rigidity, which allows these agents to be used as monotherapy in early Parkinson's disease or as adjunctive therapy with levodopa. While D1-like receptor activation (D1 and D5) may potentially provide motor control as demonstrated in experimental models. Currently available DAs primarily target the D2-like receptor family.⁽³⁷⁾ Pramipexole is excreted in urine by active tubular secretion, and ropinirole is metabolized in the liver and then excreted in urine; hence they require dosage adjustments in renal failure patients.⁽³⁸⁾ Whereas rotigotine patch is metabolized in the liver by cytochrome P450 and glucuronidation, with no dose adjustments required in patients with renal failure.⁽³⁹⁾ Apomorphine is a non-ergot derived DA available in both sublingual and subcutaneous injection formulations. It is favorably selective for D2, D3, and D4 receptors in comparison with D1 and D5 receptors, allowing effective management of motor symptoms with reduced risk of dyskinesias.⁽³⁷⁾ The sublingual formulation is designed as a bilayer to prevent oral irritation with rapid delivery and is considered a rescue medication for patients experiencing severe motor complications.⁽³²⁾ Subcutaneous apomorphine infusion is considered when motor fluctuations become persistent and are no longer adequately controlled by oral and transdermal medications.⁽³²⁾ Common adverse effects include nausea and vomiting, sleep attacks, orthostatic hypotension, impulse control disorder, psychosis and dyskinesia; however, impulse control disorders are the main concern with DAs.⁽⁹⁾

MAO-B inhibitors

This class of medications, including rasagiline, selegiline, and safinamide, works by selectively inhibiting MAO-B, an enzyme responsible for the degradation of dopamine to dihydroxyphenylacetic acid and hydrogen peroxide.⁽⁴⁰⁻⁴²⁾ They can be used as monotherapy or as adjuvant therapy for symptomatic patients with early Parkinson's disease, particularly for those with motor symptoms that do not significantly affect their quality of life but who still desire medication.

MAO-B inhibitors carry a theoretical risk of serotonin syndrome when co-administered with serotonin selective reuptake inhibitors (SSRIs). However, this occurrence is rare, and combination of SSRI and MAO-B inhibitor is generally well tolerated.⁽⁴³⁾ Overall, MAO-B inhibitors have higher tolerability than DAs, and have a lower frequency of specific adverse effects.⁽⁴⁴⁾ For selegiline, the common adverse effects are orthostatic hypotension and hallucinations, which may limit its use in patients with late-onset disease.⁽⁴⁴⁾ The safety of rasagiline is well established as monotherapy or adjunct to levodopa treatment; reported adverse effects include headache, confusion, nasopharyngitis, fall and dyskinesia.⁽⁴⁴⁾ Safinamide, the newest MAO-B inhibitor, is an orally administered α -aminoamide derivative that provides strong, selective, and reversible inhibition of MAO-B. It blocks voltage-dependent sodium and calcium channels and inhibits stimulated glutamate release.⁽⁴²⁾ Safinamide is the only MAO-B inhibitor that provides reversible inhibition, and it is safe and well-tolerated in patients with fluctuating symptoms. Due to its unique double mechanism of action, inhibiting MAO-B and blocking sodium and calcium channels, it positively provides further benefits to fluctuating Parkinson's disease patients and presents some extra benefits in both motor and non-motor symptoms.⁽⁴⁵⁾

COMT inhibitors

COMT inhibitors, such as entacapone, tolcapone and opicapone, work by maintaining dopamine concentration through decreasing the breakdown of levodopa.⁽⁴⁶⁾ They are not useful as monotherapy but are effective for treating motor fluctuations. Tolcapone, currently not registered in Hong Kong, is less commonly used due to its requirement for frequent blood tests to monitor hepatic toxicity.⁽³²⁾ Opicapone, also not registered in Hong Kong, is a third-generation, long-acting COMT inhibitor that causes fewer side effects than entacapone and has the advantage of a once-daily regimen.⁽⁴⁷⁾ Common adverse effects are related to the dopaminergic and gastrointestinal effects, such as dyskinesia, nausea, vomiting, orthostatic hypotension, sleep disorders and hallucinations.⁽⁴⁶⁾

Adenosine A_{2a} antagonist

Istradefylline, currently not registered in Hong Kong, is a selective adenosine A_{2a} receptor antagonist.⁽⁴⁸⁾ By blocking the A_{2a} receptors, it can enhance the efficacy of dopamine replacement therapy, particularly for managing motor fluctuations.⁽⁴⁹⁾ The most common adverse effect is dyskinesia, whereas gait disturbance, gastric ulcer, myocardial infarction, and hallucination are considered drug-related adverse effects.⁽⁴⁸⁾

Anticholinergics

They can be used as adjunctive therapy or monotherapy for patients with tremors who are unresponsive to levodopa replacement.⁽³²⁾ Anticholinergics, such as benztropine and trihexyphenidyl (benzhexol), act by antagonizing M1 muscarinic cholinergic receptors in the striatum.⁽⁵⁰⁾ Common side effects include dry mouth, constipation, dry eyes, blurred vision, confusion and urinary retention.⁽³²⁾

Amantadine

The exact mechanism of action in Parkinson's disease is unknown; however, it is believed to be related to its dopaminergic property, which enhances dopamine release from presynaptic neurons and inhibits dopamine reuptake.⁽⁵¹⁾ It is also a weak and non-competitive antagonist of the NMDA receptor, which influences dopaminergic activity indirectly.⁽⁵¹⁾ Amantadine can be used as monotherapy or adjuvant therapy and can be highly effective in reducing levodopa-induced dyskinesia, fatigue, and gait freezing.⁽⁵¹⁾ It is available in immediate-release and extended-release formulations, which are not interchangeable. Common side effects include CNS depression, impulse control disorders, dizziness, livedo reticularis, orthostatic hypotension and anticholinergic adverse effects.⁽³²⁾

Clozapine

It acts on multiple receptors including dopamine, serotonin, cholinergic, adrenergic, and histaminergic receptors.⁽⁵²⁾ Due to the low affinity for the D₂ receptor, it does not worsen the motor symptoms.⁽⁵²⁾ Low-dose clozapine

has beneficial effects on dyskinesia and hallucinations; however, it requires regular specialized blood count (ANC) monitoring due to the risk of agranulocytosis, as well as baseline electrocardiogram due to the risk of clozapine-induced tachycardia.⁽⁵²⁻⁵⁵⁾

CONCLUSION

Parkinson's disease is a common neurodegenerative disorder primarily characterized by the selective and progressive loss of dopaminergic neurons in the substantia nigra, accompanied by the accumulation of Lewy bodies. This underlying pathophysiology is the driving force behind the classic motor symptoms that define Parkinson's, which include tremor, rigidity, bradykinesia, and postural instability. Dopamine replacement therapy, particularly with levodopa, remains the mainstay of treatment for managing these motor symptoms. However, significant unmet clinical needs persist, such as the development of levodopa-induced motor complications and the lack of responsiveness to levodopa for certain symptoms. To address these challenges, a variety of adjunctive treatments have been developed, including MAO-B inhibitors, COMT inhibitors, and DAs. Incorporating these combination therapies, along with a patient-centered approach that involves pharmacists and other healthcare providers, is crucial for optimizing treatment regimens and achieving the best possible outcomes for patients with Parkinson's disease. Ongoing research and a comprehensive, multidisciplinary approach to care are essential for improving the quality of life and functional independence for individuals living with this complex neurodegenerative disorder.

Author's background

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Questions for Pharmacy Central Continuing Education Committee Program

1. Which of the following can cause Parkinson's disease?

- a. High homocysteine in plasma
- b. Loss of the brain chemical dopamine
- c. Depletion of Lewy bodies in the substantia nigra
- d. Lack of α -synuclein aggregation

2. What are Lewy bodies?

- a. Pockets of air found in the brain
- b. Microscopic crystalline matter found in the brain
- c. A build-up of salt found in the brain
- d. Protein deposits found in the brain

3. How many stages of Parkinson's disease were defined by Margaret Hoehn and Melvin Yahr?

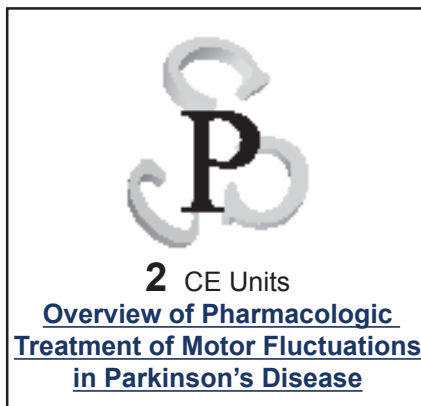
- a. 2
- b. 3
- c. 4
- d. 5

4. Which of the following is not a cause of Parkinson's disease?

- a. Genetic mutation in VPS35
- b. Dysfunctional mitochondrial causes low intracellular calcium and high ATP production, promoting autophagy-lysosomal systems
- c. Abnormal aggregation of α -synuclein in pars compacta of the substantia nigra
- d. Extensive damage of dopamine-producing neurons, followed by the alternation of various other neurotransmitters

5. Which of the following should not be used as monotherapy in managing Parkinson's disease?

- a. Levodopa with DDI
- b. MAO-B inhibitors
- c. Adenosine A2a antagonist
- d. Dopamine agonist



6. Which of the following is not a levodopa-induced complication?

- a. Somnolence
- b. Dystonia
- c. Dyskinesias
- d. Anosognosia

7. Which of the following is not a manifestation of Parkinson's disease?

- a. Gait disturbances
- b. Sleep disorders
- c. Dementia
- d. Rapid hand movements

8. Which of the following is the newest MAO-B inhibitor?

- a. Istradefylline
- b. Opicapone
- c. Safinamide
- d. Apomorphine

9. Which of the following is the main disadvantage of dopamine agonists?

- a. Hallucinations
- b. Somnolence
- c. Edema
- d. Impulse control disorders

10. Which of the following statement is incorrect?

- a. Clozapine requires specialized blood count monitoring due to the risk of hypertension, bradycardia and pericarditis
- b. Immediate release and extended release formulations of amantadine are not interchangeable.
- c. Anticholinergics can be used as monotherapy for patients with tremor but unresponsive to levodopa replacement
- d. Adenosine A2a antagonist should be used as adjunctive therapy because it enhances the efficacy of dopamine replacement therapy

Answers will be released in the next issue of HKPJ.