



Therapeutic Progress in Parkinson's Disease

Pharmacological dopamine replacement is the most effective form of treatment for patients with early Parkinson's disease. However, it is only a symptomatic therapy. Future therapeutic strategies should therefore focus not only on ameliorating the symptoms of Parkinson's disease, but on neuroprotective or neurorescue therapies.

Symptomatic therapies for Parkinson's disease remain the most effective means for control of Parkinson's motor symptoms. However, there are several limitations associated with their use. After taking their Parkinson's disease medication for a while, patients usually notice that after each medication dose their symptoms go away for hours at a time (ON times) and then return (OFF times). Symptoms also return during the 'wearing-off' period, when Parkinson's treatments become less effective. The challenge of currently available symptomatic therapies is to maintain optimal ON time and reduce OFF time without causing disabling medication-induced abnormal involuntary movements (dyskinesias). This article discusses the limitations of current treatments for Parkinson's motor symptoms and future therapeutic strategies.

Current treatment strategies

The dopamine precursor levodopa is the most effective drug available for treating the motor symptoms of Parkinson's

About the authors

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disease. However, chronic use of the drug is limited by several factors, including:

- 'Wearing-off' (the re-emergence of motor fluctuations before the next scheduled dose or a shortened response to each dose).
- Dyskinesias (levodopa-induced abnormal involuntary movements).
- A potential to exacerbate some non-motor symptoms of hypotension.
- Failure to prevent the progression of Parkinson motor symptoms.

Other treatment options include dopamine agonists, which activate dopamine receptors, and monoamine oxidase B inhibitors, which increase dopamine levels by blocking its metabolism. Such agents can result in the continuous stimulation of brain dopamine receptors to prevent or diminish the emergence of 'wearing-off' and dyskinesias, but are not as effective as levodopa at improving the symptoms of Parkinson's disease.

Levodopa Extending the half-life of levodopa

Medium to long-term therapy with levodopa can result in an individual's response to this drug becoming unstable due to a combination of deteriorating peripheral levodopa pharmacokinetics and progressive degeneration of the substantia nigra. The emergence of motor fluctuations associated with levodopa is

aggravated by:

- The short plasma half-life of levodopa.
- The primary absorption of levodopa in the duodenum after oral administration.
- Interference in absorption of levodopa by the presence of food in the stomach.

Levodopa administered orally alone is rapidly decarboxylated to dopamine in peripheral tissues such that only a small amount of each dose reaches the central nervous system, and the high peripheral levels of dopamine contribute to its side effects, eg, nausea. The major route of peripheral metabolism of levodopa is via the dopa-decarboxylase pathway, with a smaller proportion through the catechol-O-methyltransferase (COMT) pathway. When levodopa is administered with a peripheral dopa-decarboxylase inhibitor (DDCI; carbidopa or benserazide), the peripheral formation of dopamine is blocked, extending the half-life of levodopa and allowing more to reach the central nervous system.

The addition of a COMT inhibitor to the levodopa/DDCI combination can further extend the peripheral half-life of levodopa and increase brain bio-availability. Adding the COMT inhibitor at the onset of the 'wearing-off' symptoms,

Future therapeutic approaches

Pharmacological approaches

- Novel longer-acting dopaminergic drugs
- Antidyskinetic therapies

Restorative approaches

- Neuroprotective strategies
- Neural growth factors
- Cellular replacement



TABLE

The Parkinson's disease drug pipeline

Compound	Mechanism of action	Comments
Rotigotine	A nonergolinic dopamine receptor agonist formulated as a transdermal delivery system designed for once-daily application.	Safe and effective in early Parkinson's disease. ⁵ In patients with Parkinson's disease and early-morning motor dysfunction, significantly benefits control of motor function and nocturnal sleep disturbances. ⁶
Rasagiline	A novel, highly potent irreversible monoamine oxidase B inhibitor, anti-Parkinsonian drug.	Effective as monotherapy or adjunct to levodopa for patients with early and late Parkinson's disease. ⁷ Demonstrates possible neuroprotective effects.
Preladenant	A highly selective nonmethylxanthine adenosine A2A receptor antagonist (A2A receptors are highly enriched in the striatum, and their blocking results in a reduction of the postsynaptic effects of dopamine depletion).	Phase II studies suggest a modest reduction in the OFF time, with no significant worsening of dyskinesias. ⁸
IPX066	A novel levodopa/carbidopa formulation that rapidly attains and maintains therapeutic plasma concentrations for a more prolonged duration compared with regular immediate-release levodopa/carbidopa.	Shows promise in increasing ON time compared to standard levodopa formulations. ⁹
AFQ056	A glutamate receptor 5 antagonist aimed at reducing levodopa-induced dyskinesias. ⁸	Phase II studies show an antidyskinetic effect without a worsening in parkinsonism. ¹⁰
VR040	An inhaled form of apomorphine (traditionally a rapidly acting dopamine agonist that can be given only subcutaneously).	Shows promise as a novel rescue therapy in patients with unpredictable ON/OFF fluctuations.
Safinamide	A monoamine oxidase B inhibitor that also inhibits glutamate release.	Shows promise in improving motor ON time without worsening dyskinesias. ¹¹
L-dihydroxyphenylserine	A prodrug of noradrenaline.	Shows promise in improving the symptoms of orthostatic hypotension. ¹²

achieves a more continuous stimulation of brain dopamine receptors and thus reduces the 'wearing-off' effect.

A combination formulation comprising levodopa, carbidopa and the COMT inhibitor entacapone is currently approved for use in Parkinson's disease patients affected by motor fluctuations (indicated by the emergence of end-of-dose 'wearing off'). A patient's levodopa/DDCI doses can be switched individually for similar or slightly smaller levodopa equivalent doses of this combination product.

The recent availability of several fixed-dose combinations of levodopa/carbidopa/

pa/entacapone allows greater flexibility of individual patient dosing. A relatively common side effect of the combination is diarrhoea. This may affect about 4% of individuals, but resolves on stopping the drug.

Dopamine agonists

Dopamine agonists act directly on brain dopamine receptors and have a longer action than levodopa. Initiation of dopamine agonist treatment, such as pramipexole, in patients with early Parkinson's disease delays the emergence of 'wearing off' and dyskinesias.

Addition of a dopamine agonist to levodopa can improve motor symptoms and reduce time spent in the immobile OFF state.

Precautions and side effects

Doctors should counsel patients taking dopamine agonists about the small potential risk of unheralded sleep attacks (including when driving) and compulsive behaviours, such as gambling, hypersexuality, overeating and shopping. Confusion, paranoia, hallucinations and peripheral oedema may also be more frequent in patients being treated with dopamine agonists.



Monoamine oxidase B inhibitors

Monoamine oxidase B deactivates dopamine in the brain. Inhibitors of monoamine oxidase B therefore increase dopamine levels in the brain and are an additional therapeutic option for the treatment of Parkinson's disease. Two monoamine oxidase B inhibitors are indicated for the treatment of Parkinson's disease: selegiline and rasagiline.

Selegiline

Selegiline should be used in low doses (5mg twice daily) as higher doses may also inhibit monoamine oxidase A and result in side effects such as hypertension. Selegiline was commonly used in early-onset disease and in combination with levodopa for maintenance. However, concerns over cardiac side effects have been raised, and there is a potential risk of adverse effects when it is used in combination with selective serotonin re-uptake inhibitors and tricyclic anti-depressants. Selegiline is generally well tolerated as monotherapy, although side effects such as nausea, dizziness, headaches and dry mouth may occur.

Rasagiline

Rasagiline is indicated for the symptomatic treatment of idiopathic Parkinson's disease as monotherapy (without concomitant levodopa/DDCI therapy) or as adjunct therapy (with concomitant levodopa/DDCI therapy). In patients with Parkinson's disease receiving monotherapy with a monoamine oxidase B inhibitor, the effects on motor symptoms are modest.³ In patients with Parkinson's disease receiving treatment with levodopa/DDCI therapy, the addition of a monoamine oxidase B inhibitor has similar effects as the addition of entacapone in reducing daily OFF time.⁴

Future directions

Pharmacological dopamine replacement is generally very effective in early disease but it is only a symptomatic therapy. Future therapeutic strategies should focus not only on ameliorating the symptoms of Parkinson's disease but on neuroprotective or neurorescue therapies that can favourably modify the natural course of the disease and slow the progression of both motor and non-motor manifestations.

Strategies pursuing restorative approaches to Parkinson's disease

therapy involve attempts to replace the degenerating nigrostriatal dopaminergic network with cells. Fetal ventral mesencephalic tissue transplants are under continuing investigation and the stem cell field is advancing rapidly. However, further development and optimisation of the safety and efficacy of techniques involved in generating and manipulating these stem cells, and other cell sources, will be essential before any further clinical trials are done. Other experimental strategies currently under investigation include anti-apoptotic strategies and implantation of genetically engineered cells.

Future advances will include novel medication delivery systems such as transdermal or inhaled therapies (eg, VR040); novel levodopa/carbidopa formulations with prolonged action (eg, IPX066); enzyme inhibitors that can prolong the duration of action of levodopa (eg, safinamide); anti-Parkinson medication with novel receptor targeting (eg, preladenant); safinamide, and medications that improve non-motor symptoms (eg, L-dihydroxyphenylserine); or levodopa-induced dyskinesias (eg, AFQ056).

A list of references is available on request.

Patients Post Myocardial Infarction

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of bleeding.⁵⁷ The modern DAPT era has complicated the management of patients with concurrent acute coronary syndrome and/or recent stenting and atrial fibrillation – in these patients, the use of triple therapy (DAPT plus anticoagulation) significantly increases the risk of adverse bleeding events.⁵⁸

Should this patient be considered for device therapy?

The early implantation of an ICD in patients who have had an MI has been shown not to deliver any additional benefit.⁵⁹ Patients who have had ventricular fibrillation during the early hours of their MI do not need an ICD. Those who had an infarction more than 40 days previously and whose ejection fraction is persistently below 35% should have an ICD implanted, although there are healthcare access and economic limitations to this recommendation. Patients should be on maximal toler-

ated medical therapy prior to re-evaluation of LV function to prevent unnecessary device implantation and potential morbidity from the device.

Conclusion

Contemporary post-MI management should be tailored according to patient characteristics and local access to coronary angiography or noninvasive imaging modalities. Aggressive medical management has a proven benefit for secondary prevention. Coronary revascularisation is indicated for persisting symptoms and high-risk, extensive ischaemia. Implantable defibrillators should be considered in those patients who have persisting severe LV dysfunction (ejection fraction less than 35%).

References are available on request.