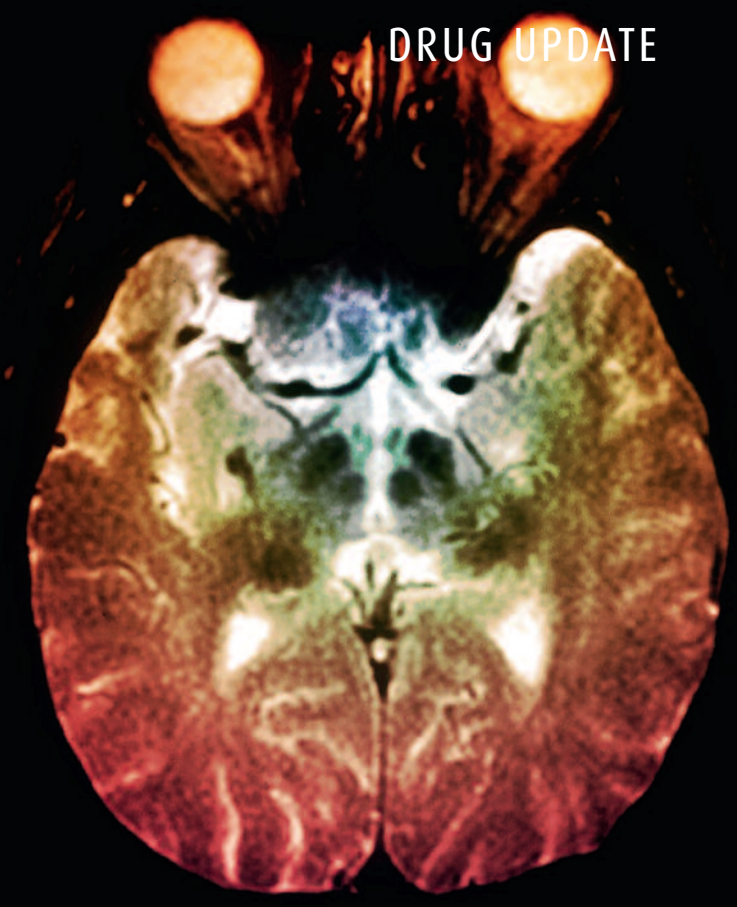

Therapeutic progress in Parkinson's disease

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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 also on neuroprotective or neurorescue therapies.

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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 some time of taking their medication for Parkinson's disease, 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 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 nonmotor symptoms of

Parkinson's disease (e.g. orthostatic 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 levodopa 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 are 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, such as 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 bioavailability. By adding the COMT inhibitor at the onset of the 'wearing-off' symptoms, a more continuous stimulation of brain dopamine receptors is achieved and thus the 'wearing-off' effect is reduced.

A combination formulation comprised of 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/entacapone allows greater flexibility of individual patient dosing. The dose combinations available are: levodopa/carbidopa/entacapone; 50/12.5/200 mg, 75/18.75/200 mg, 100/25/200 mg, 125/31.25/200 mg; 150/37.5/200 mg and 200/50/200 mg. A relatively common side effect of the combination is diarrhoea – this may affect about 4% of individuals, but resolves on stopping the drug.

Continuous levodopa delivery

The combination of levodopa with the DDCI carbidopa is now available as a gel formulation that is infused by a programmable external pump directly to the duodenum. This enables stable levodopa plasma concentrations to be achieved through continuous stimulation of the striatal dopaminergic receptors.

Clinical experience with the gel has demonstrated that continuous infusion provides sustained levodopa plasma levels, making it possible to avoid troughs in levodopa concentration. Patients being treated with the gel show significant improvement in OFF periods and, in general, ON period dyskinesia becomes mild.

The levodopa/carbidopa intestinal gel is of particular use in patients who cannot have deep brain stimulation or apomorphine infusion. Its pharmacological side effects are the same as those for other levodopa/DDCI combinations. The most frequent problems associated with the gel relate to the technical aspects of the therapy, such as dislocation of the small intestinal catheter, which occurs in 3 to 4% of patients. Rarely, bacterial peritonitis may complicate the placement of the percutaneous jejunostomy tube.[1]

Levodopa/carbidopa intestinal gel has recently been approved by the PBS as a Section 100 drug for the management of advanced Parkinson's disease in a patient with severe disabling motor fluctuations not adequately controlled by oral therapy, and as a Section 85 listing for maintenance therapy. It has also recently been made available in specialised movement disorder centres (for more information, refer to the Parkinson's Australia website, www.parkinsons.org.au).

DOPAMINE AGONISTS

Dopamine agonists act directly on brain dopamine receptors and have a longer duration of action compared with levodopa. Initiation of dopamine agonist treatment, such as pramipexole or rotigotine, 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.

Extended-release pramipexole

The recently available extended-release pramipexole requires only once-daily dosing (compared with the thrice-daily dosing of its immediate release formulation) and is available in doses of 0.375 mg, 0.75 mg, 1.5 mg, 3 mg and 4.5 mg tablets.[2] When beginning treatment with extended-release pramipexole, the dose should be increased gradually from a starting dose of 0.375 mg/day and then increased every five to seven days. The dosage should be titrated to achieve the desired therapeutic effect, provided patients do not experience intolerable side effects.

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 TGA-approved for the treatment of Parkinson's disease – selegiline and rasagiline. Only selegiline is currently available on the PBS.

Selegiline

Selegiline should be used in low doses (5 mg, 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 reuptake inhibitors and tricyclic antidepressants. Selegiline is generally well tolerated as monotherapy, although side effects such as nausea, dizziness, headaches and dry mouth may occur.

FUTURE THERAPEUTIC APPROACHES

Pharmacological approaches

- Novel longer-acting dopaminergic drugs
- Antidyskinetic therapies

Restorative approaches

- Neuroprotective strategies
- Neural growth factors
- Cellular replacement

Rasagiline

The TGA has recently approved rasagiline (1 mg tablets) 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 also on neuroprotective or neurorescue therapies that can favourably modify the natural course of the disease and slow the progression of both motor and nonmotor manifestations (see the box on this page).

Strategies pursuing restorative approaches to Parkinson's disease therapy involve attempts to replace the degenerating

TABLE. THE PARKINSON'S DISEASE DRUG PIPELINE

Compound	Mechanism of action	Comments
Rotigotine (approved by TGA but not PBS listed)	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 (approved by TGA but not PBS listed)	A novel, highly potent irreversible monoamine oxidase B inhibitor, antiParkinsonian 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	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 only be given 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]

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

A list of recently developed and investigational drugs is provided in the Table. Future advances include: novel medication delivery systems (such as transdermal or inhaled therapies [e.g. VR040]), novel levodopa/carbidopa formulations with prolonged action (e.g. IPX066), enzyme inhibitors that can prolong the duration of action of levodopa (e.g. safinamide), antiparkinson medication with novel receptor targeting (e.g. preladenant, safinamide), and medications that improve nonmotor symptoms (e.g. L-dihydroxyphenylserine) or levodopa-induced dyskinesias (e.g. AFQ056). MT

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A list of references is available on request to the editorial office.

This article is for general information purposes only, and the full product information should be consulted before prescribing any of the mentioned medications.

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