

Drugs for Parkinson's disease

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SYNOPSIS

Levodopa is the most effective drug available for treating the motor symptoms of idiopathic Parkinson's disease. It is usually combined with a peripheral dopa decarboxylase inhibitor. Early treatment with dopamine agonists can reduce the risk of developing dyskinesia. Dopamine agonists and catechol-O-methyltransferase inhibitors can significantly reduce motor fluctuations. Amantadine reduces the severity of dyskinesia in some patients. No treatment has been proven to delay disease progression.

Index words: amantadine, dopamine, entacapone, levodopa, selegiline.

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Introduction

Motor dysfunction in idiopathic Parkinson's disease is caused predominantly by degeneration of dopamine-producing neurons in the substantia nigra of the midbrain. Symptomatic treatment of idiopathic Parkinson's disease is therefore aimed at restoring dopaminergic stimulation of the striatal neurons which are involved in controlling movement. These striatal neurons are preserved in idiopathic Parkinson's disease, but degenerate in the atypical parkinsonian syndromes, which explains their variable and usually poor response to therapy.

Mechanism of action of available drugs

The major classes of drugs currently available for the treatment of idiopathic Parkinson's disease are shown in Table 1. Many aim to increase dopamine in the brain, by increasing its production or altering its metabolism (Fig. 1).

Levodopa

Levodopa is absorbed from the small intestine and transported into the brain where it is converted to dopamine. (Dopamine cannot cross the blood-brain barrier.) Levodopa has a short plasma half-life of about one hour. Early in Parkinson's disease, levodopa has a long duration of action (lasting days) which is independent of plasma concentration, but as the disease progresses, the duration of the effect reduces. The short-duration effect is strongly linked to plasma concentration and lasts, at most, hours.

Slow-release preparations are gradually absorbed, resulting in more sustained plasma concentrations. They have reduced bioavailability; higher doses are required to match the benefit of an equivalent strength of a standard preparation. Rapid release preparations are taken in liquid form to enhance passage through the stomach and absorption from the small intestine.

Levodopa commonly causes nausea, especially when treatment begins. This nausea results from the conversion of levodopa to dopamine which stimulates the dopamine receptors in the area postrema ('vomiting centre') in the brainstem, a structure which lies outside the blood-brain barrier. The nausea is minimised by introducing levodopa slowly, starting with a low dose, taking it with food and giving it in combination with a peripheral dopa decarboxylase inhibitor such as carbidopa or benserazide. A minimum daily dose of 75 mg is necessary to adequately inhibit the production of dopamine outside the blood-brain barrier. Metoclopramide and prochlorperazine should be avoided as they are dopamine antagonists and make parkinsonism worse. If an antiemetic is required, domperidone 10-20 mg three times daily is the drug of choice as it is a dopamine antagonist which does not cross the blood-brain barrier.

Dopamine agonists

The oral dopamine agonists directly stimulate striatal neurons. They have a longer plasma half-life than levodopa, and thus provide a more continuous dopaminergic stimulation. In the doses tolerated by most patients, they usually do not provide the same degree of motor improvement as levodopa. They do not work if levodopa has failed to benefit the patient. The efficacy of the available dopamine agonists is similar. Equivalent daily doses of bromocriptine, pergolide and cabergoline are 10 mg, 1 mg and 1 mg respectively.

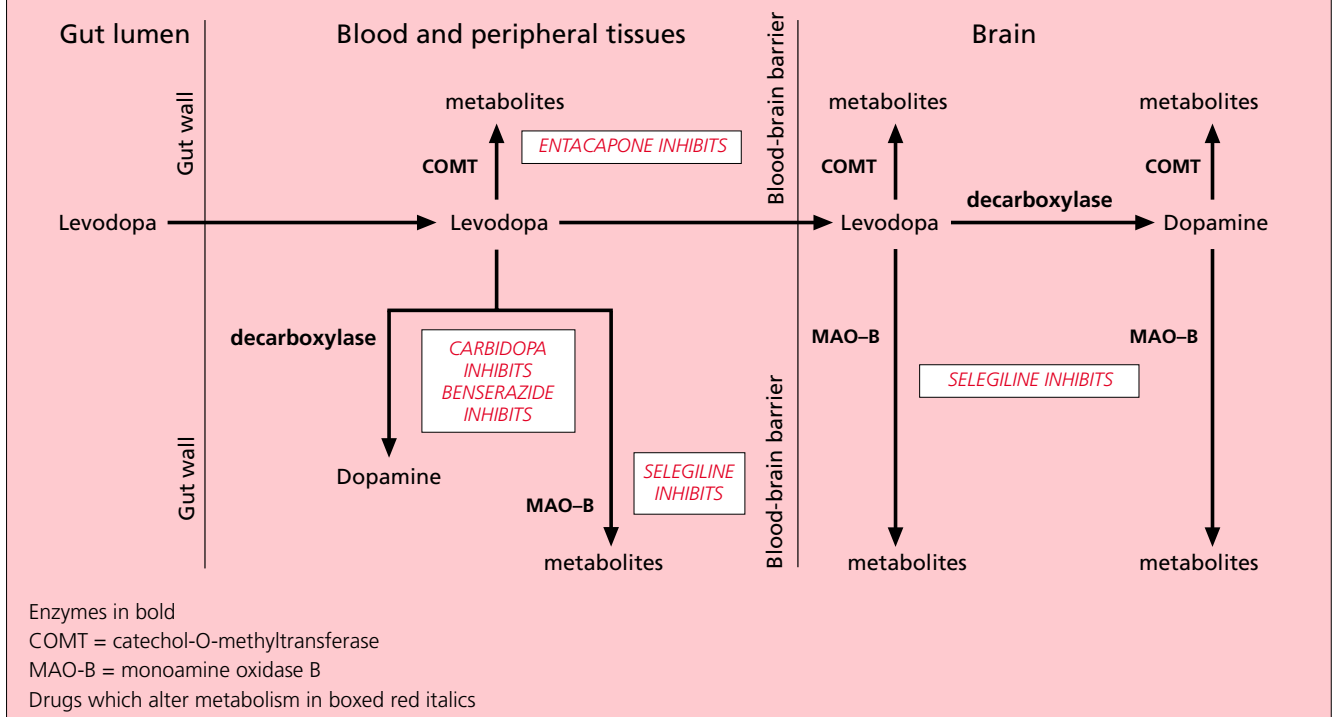
Table 1

The major classes of drugs currently available for the treatment of Parkinson's disease

Levodopa preparations	Standard release	Levodopa/benserazide Levodopa/carbidopa
	Slow release	Levodopa/benserazide Levodopa/carbidopa
	Rapid release	Levodopa/benserazide
Dopamine agonists	Ergot	Bromocriptine Cabergoline Pergolide
	Non-ergot	Pramipexole Ropinerole Apomorphine
Catechol-O-methyltransferase inhibitors		Entacapone Tolcapone
Monoamine oxidase B inhibitors		Selegiline
Other	NMDA antagonist	Amantadine
	Anticholinergics	Benzhexol Benztropine Biperiden Orphenedrine Procyclidine

Fig. 1

Drugs affecting the metabolism of levodopa



The newer agonists are probably better tolerated than bromocriptine, although there have been few comparative studies.¹ The long half-life of cabergoline (65 hours) allows a once daily dosage, whereas the shorter half-life of bromocriptine and pergolide can make it easier to tailor therapy. Pramipexole and ropinirole are non-ergoline derived preparations which are not available on the Pharmaceutical Benefits Scheme in Australia but are used extensively overseas.

Dopamine agonists commonly cause nausea and postural hypotension, and must be introduced slowly over a few weeks. Some patients require the use of domperidone when starting treatment to reduce the peripheral adverse effects. Dopamine agonists should be avoided in all patients with hallucinations or cognitive impairment because of the risk of confusion and prolonged delirium. Ergoline-derived dopamine agonists (bromocriptine, cabergoline and pergolide) can cause pulmonary and retroperitoneal fibrosis and other ergot adverse effects such as digital vasospasm and erythromelalgia. The fibrosis is reversible if diagnosed early. Patients should be monitored with regular chest auscultation and measurement of the erythrocyte sedimentation rate, although even with these measures detection can be difficult. Patients treated with pramipexole and ropinirole, can experience 'sleep attacks' severe enough to cause motor vehicle accidents.

Apomorphine is a short-acting dopamine agonist which is given by subcutaneous injection. It is used as 'rescue' medication (where a dose of levodopa has failed to take effect) for severe fluctuations in younger patients because of its rapid and reliable onset of action within 5–10 minutes. Patients need to be admitted to a specialised clinic or hospital in order to establish the effective dose and to be educated about its administration.

Apomorphine is a potent emetic so patients must be pre-treated with domperidone 20 mg three times daily orally for at least 48 hours before the first injection. Domperidone should be continued for at least a few weeks once regular intermittent treatment has commenced. The dose can then be tapered slowly as tolerance to the emetic effects of apomorphine (but not its anti-parkinsonian action) usually develops.

Catechol-O-methyltransferase (COMT) inhibitors

If dopa decarboxylase is inhibited, peripheral levodopa is predominantly metabolised by catechol-O-methyltransferase (COMT). COMT inhibitors prolong the plasma half-life of levodopa and therefore reduce motor fluctuations. Dopaminergic adverse effects can result, including increased peak-dose dyskinesia and confusion. Class-related adverse effects include urine discoloration, diarrhoea and abdominal pain.

Entacapone has a short half-life (90 minutes) and must be taken concurrently with each dose of levodopa. It does not have a central effect as it does not cross the blood-brain barrier. Tolcapone has a longer half-life but has been withdrawn in Australia because of rare severe or fatal hepatic toxicity. It can be obtained under the restricted conditions of the Special Access Scheme.

Monoamine oxidase B inhibitors

Levodopa and dopamine are metabolised in the brain by monoamine oxidase B (MAO-B) and COMT. Selegiline selectively inhibits MAO-B and prolongs the duration of effect of levodopa. It also provides mild symptomatic benefit when used as monotherapy. The most common significant adverse effect is confusion or delirium. Patients should be warned about the possibility of a tyramine-induced

hypertension if a selective monoamine oxidase A inhibitor (e.g. the antidepressant moclobemide) is also prescribed.

Anticholinergics

Although anticholinergics were the mainstay of treatment prior to the advent of dopaminergic drugs, their current role is limited because of their relative lack of efficacy and the frequent occurrence of unacceptable adverse effects such as memory impairment, confusion and psychosis, dry mouth, difficulty with micturition and constipation. Anticholinergics can occasionally be of benefit when tremor is prominent and poorly responsive to dopaminergic therapy. Withdrawal of long-term therapy with anticholinergics can be difficult and should be done slowly to avoid precipitating a cholinergic crisis.

An approach to the treatment of Parkinson's disease

No treatment can arrest or slow neurodegeneration in Parkinson's disease. The aim is to relieve symptoms and avoid the complications of therapy.

Early Parkinson's disease

Many studies have shown that early treatment with dopamine agonists reduces the incidence of dyskinesia.¹ Fewer motor fluctuations were shown in some but not all of the studies. We recommend a dopamine agonist as the first treatment in younger patients (under 50 years old) who have mild disease and no cognitive deficit. It is necessary to add levodopa within 1–5 years in most patients. In more severe disease, treatment begins with levodopa but a dopamine agonist may be added to keep the daily dose of levodopa in the lower range (300–600 mg) if there is no cognitive deficit. Dopamine agonists are used infrequently and with caution in patients more than 70 years old because of the risk of neuropsychiatric adverse effects and postural hypotension. They are contraindicated in the presence of dementia.

Isolated resting tremor is rarely disabling, but if it interferes with function it can usually be managed with levodopa. When this is ineffective at low to moderate doses, the addition of an anticholinergic can sometimes be useful.

Patients with motor fluctuations

Patients' mobility may fluctuate throughout the day. It is important to determine whether these motor fluctuations are occurring because of inadequate dopaminergic stimulation ('off-periods') or excessive dopaminergic stimulation. Common off-period fluctuations include 'end of dose failure', in which the benefit of levodopa wears off before the next dose, and painful twisting and cramping of the feet or legs at the end of a dose cycle ('end of dose dystonia') or early in the morning. Dyskinesia (involuntary movements of the limbs or trunk) usually occurs when the plasma levels of levodopa are maximal ('peak dose dyskinesia'). Dyskinesias may also occur before and after an 'on-period' ('diphasic dyskinesias').

Off-periods and diphasic dyskinesias are managed by attempting to maintain the level of dopaminergic stimulation above the critical threshold for motor benefit. This can be achieved by

giving levodopa more frequently or adding a COMT inhibitor or a dopamine agonist. The latter is preferable in younger patients. Selegiline has been disappointing in this situation.

Failure of a dose to induce an 'on' period is often due to delayed gastric emptying and can be reduced by taking tablets on an empty stomach 30 minutes before meals, or by using a dispersible formulation of levodopa. Slow-release preparations are useful for nocturnal off-periods or early morning akinesia. They are less effective in treating daytime motor fluctuations.

Peak dose dyskinesia may be managed by reducing individual levodopa doses, but this may increase 'off' time. An alternative is to gradually introduce, or increase, a dopamine agonist while reducing the dose of levodopa by about 25%. In many patients amantadine 100 mg two or three times daily is effective in reducing dyskinesia. Amantadine can cause nightmares, anticholinergic adverse effects and livedo reticularis. It should be avoided in patients with hallucinations or dementia and the last dose should not be given after mid-afternoon.

Role of physical therapy and surgery

Medical treatment with dopaminergic drugs is the mainstay of therapy, however, physical therapies have an important adjunctive role. Early in the course of the disease, patients should be advised to exercise regularly in order to maintain good muscle tone and to shed excess weight. This reduces impediments to movement, other than those caused by the disease. Later in the course of the disease, specific treatments by allied health professionals can be extremely helpful. Involvement of the carer in these therapies is crucial.

Physiotherapists and occupational therapists can provide gait and balance retraining and instruction about compensatory strategies which emphasise the use of external cues to help initiate movement, or how to break down complex movements into simpler sequences. Speech therapy can improve speech clarity and volume, and swallowing difficulties also necessitate careful assessment and treatment. Dietary advice, especially regarding the effects of meals and protein intake on drug pharmacokinetics, should be offered.

In younger patients without obvious cognitive impairment, who have severe motor fluctuations that are poorly controlled with medical therapy, stereotactic functional neurosurgery or deep brain stimulation can be extremely effective. Assessment by a movement disorder specialist, with or without neuropsychological assessment, is recommended prior to referral to the neurosurgeon.

Treatment of late stage complications of Parkinson's disease

Postural hypotension

Levodopa and dopamine agonists worsen postural hypotension and it may be necessary to lower the dose of levodopa or withdraw the agonist. Treatment is difficult, but patients should be advised to sleep with the head of the bed raised by one or two bricks and to add salt to their diet. Fludrocortisone

can then be added at a dose of 0.1 mg in the morning, increasing if necessary up to 0.5 mg in the morning. If these measures are ineffective, the alpha agonist midodrine 10–20 mg four hourly can be useful but it is experimental and only available via the Special Access Scheme. Patients treated for postural hypotension need to have electrolytes, renal function and supine blood pressures closely monitored.

Parkinsonian psychosis, depression and dementia

Psychotic symptoms such as visual hallucinations and persecutory delusions occur most commonly in the setting of dementia, which may be mild and therefore easily missed. Most drugs for Parkinson's disease make these symptoms worse. Depression is also common and requires treatment in its own right.

Occasional visual hallucinations with retained insight do not require treatment. Acute psychosis is a medical emergency. It can be triggered by a change of environment, treatment or intercurrent illness. Apart from levodopa all the drugs for Parkinson's disease should be ceased. If possible stop the drugs over a few days rather than abruptly to avoid provoking neuroleptic malignant syndrome from dopaminergic withdrawal, or a cholinergic crisis from withdrawal of anticholinergics.

If psychotic symptoms persist it may be necessary to introduce a neuroleptic drug. This is always a difficult decision because neuroleptics are dopamine antagonists which can cause profound worsening of parkinsonism. The role of the new atypical neuroleptic drugs, including clozapine, olanzapine, quetiapine and risperidone, is still being assessed.² At present they have only been approved in Australia for the treatment of schizophrenia. If the patient is aggressive and potentially violent, the most suitable way to achieve immediate control is

to withhold one to two doses of levodopa until control is achieved. Sometimes benzodiazepines, orally or parenterally, may be required. This will sedate the patient and allow oral neuroleptic medication to be given if needed.

Summary

For patients moderately affected by Parkinson's disease the first-line treatment is levodopa with a peripheral dopa decarboxylase inhibitor. A dopamine agonist may be added to minimise the dose of levodopa. Anticholinergic drugs may help patients with tremor. Physical therapy is an important adjunct to drugs. Patients with more severe disease may require injections of apomorphine. All the drugs have unpleasant adverse effects, so therapy should aim to minimise the complications of treatment.

REFERENCES

1. Hely MA, Fung VSC, Morris JGL. Treatment of Parkinson's disease. *J Clin Neurosci* 2000;7:484-94.
2. Friedman JH, Factor SA. Atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease. *Mov Disord* 2000;15:201-11.

Self-test questions

The following statements are either true or false (answers)

7. Metoclopramide is the drug of choice for treating the nausea caused by levodopa.
8. If levodopa has failed to benefit the patient they are unlikely to respond to a dopamine agonist.

Parkinson's disease: a personal experience

Editor's note:

Kay Messiter is a 47-year-old single mother who has had Parkinson's disease for 13 years.

AP: *When did you develop Parkinson's disease?*

KM: It was around Christmas 1987 that I noticed a tremor in the top part of my right arm. There was nothing to see at that stage, but I could feel it when I did things like picking up the telephone. The tremor gradually increased.

The neurologists were uncertain of the diagnosis at that stage. There was nothing that could be done anyway because I was three months pregnant. I did not do anything until after my second child was born four years later.

AP: *How was the diagnosis made?*

KM: I diagnosed myself. My general practitioner had mentioned Parkinson's disease as a possible cause of my tremor so I got some information from the Parkinson's Association. As soon as I read that information I knew I had Parkinson's disease.

AP: *How did you react when you realised the diagnosis?*

KM: I remember my flesh beginning to crawl when I read that Parkinson's disease was incurable, but it was a relief to know what I had. I decided I was not going to take tablets so I waited about two years before seeing a neurologist to confirm the diagnosis.

AP: *What treatment were you given?*

KM: I avoided treatment for a few years, but I was having problems with bumping into things, and everyday tasks