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ARTICLE

Management of Parkinson's disease

SUMMARY

Parkinson's disease has a wide variety of motor and non-motor symptoms.

Treatment aims to control the patient's symptoms by replenishing the dopaminergic system with levodopa or dopamine agonists. Monoamine oxidase B inhibitors are also effective first-line drugs.

Keeping symptoms under continual control early in the course of the disease may have beneficial effects as Parkinson's disease progresses.

Therapy is tailored to each patient's response to the drugs and their ability to tolerate them. Limited responses of motor and many non-motor symptoms may require the addition of other treatments.

The adverse effects of drugs used in the treatment of Parkinson's disease are usually reversible.

Symptom fluctuations in response to regular medication are an indication for specialist referral.

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Introduction

Parkinson's disease is a common neurodegenerative disorder, which particularly involves the loss of nigral dopaminergic neurons. The cardinal motor features are rigidity, bradykinesis, rest tremor and postural instability. Non-motor features are common both early and late in the disease course and include autonomic, neuropsychiatric and cognitive disturbances. Parkinson's disease has manifestations beyond the nigrostriatal system so it is not surprising that some motor features (such as postural instability) and many non-motor features have a limited response to dopaminergic drugs.

Non-pharmacological management

Non-drug therapies have a significant role in the treatment of Parkinson's disease and include counselling and education for both patients and carers. This includes providing information about which commonly prescribed drugs to avoid, for example dopamine-blocking drugs such as metoclopramide, prochlorperazine, haloperidol and risperidone. It is important to increase general fitness and well-being and maintain core balance and strength which may improve gait and postural stability. Physiotherapy with large amplitude physical training improves motor function[1] and allied health professionals can provide specific strategies to overcome disabilities such as start hesitancy, freezing of gait, festination and falls. Lee Silverman voice training is an established technique which has been proven to improve voice quality and audibility when patients adhere to the long-term strategy.[2] Nutrition should be considered in all stages of Parkinson's disease.

Supportive care is vital in very advanced phases of Parkinson's disease as drugs become poorly tolerated, motor fluctuations increase and non-levodopa responsive symptoms dominate. Counselling is part of the management of non-motor symptoms such as anxiety and depression, cognitive dysfunction and dementia.

Pharmacological management

There are no proven neuroprotective treatments for Parkinson's disease, but drugs are effective in symptom control, particularly in the early stages of the disorder. Treatment is then increased as required.

When to start treatment

Deciding when to start drug therapy for Parkinson's disease should be individually tailored to a patient's symptoms, circumstances and comorbidities. Treatment is indicated when symptoms impact on quality of life. When treatment is needed there is no evidence to support undue delay because of concerns about levodopa toxicity or the development of treatment resistance.[3] The aim is to control symptoms and maintain an 'on' state.

Some drugs with good symptomatic benefit are speculated to have a role in neuroprotection and some specialists advocate their use from the time of diagnosis.[4] Delayed start trials have been used to try and differentiate symptomatic from disease-modifying effects. A recent delayed start study of rasagiline, a monoamine oxidase B inhibitor, in treatment-naïve patients with mild Parkinson's disease showed a small benefit in the low-dose (1 mg) treatment group. This was not seen with the 2 mg dose and a clear explanation for this has not been established.[5] Further studies are needed before such treatments are considered truly disease modifying. Until a drug is unequivocally proven to slow disease progression, the time to commence treatment will remain contentious.

What to start

Motor features of early Parkinson's disease typically respond well to dopamine replacement therapies. The choice of drug therapy (Table 1) includes levodopa in combination with a dopa-decarboxylase inhibitor, a dopamine agonist or a monoamine oxidase B inhibitor. Rasagiline would be an appropriate first-line drug to consider for those with mild symptoms.

Table 1 **Drugs to manage motor symptoms of Parkinson's disease**

Class of drug	Name	Adverse effects	Comments
Levodopa/dopa-decarboxylase inhibitors	Levodopa/carbidopa Levodopa/benserazide	Nausea, constipation, postural hypotension, hypersomnolence, sudden sleep episodes, impulse control disorders, hypersexuality, confusion, hallucinations	Most effective symptomatic treatment Generally well tolerated and lower adverse effect profile than other drugs Minimum of 3 times daily dosing Used in early and advanced Parkinson's disease
	Controlled-release formulations	As above	Reduced and variable absorption leads to variable efficacy Main role is in stabilising nocturnal symptoms
	Short-acting formulations	As above	Used as rescue therapy in advanced Parkinson's disease Avoid use in early Parkinson's disease – may increase risk of motor fluctuations
	Enteral levodopa/carbidopa gel suspension	As above plus complications relating to percutaneous enteral tube	Consider in advanced Parkinson's disease where oral therapies have failed to control severe motor fluctuations
Dopamine agonists	Non-ergot derived: Pramipexole Rotigotine patch (TGA approved, not PBS listed) Ropinirole (TGA approved, not PBS listed for Parkinson's disease)	Nausea, constipation, postural hypotension, hypersomnolence, sudden sleep episodes, impulse control disorders, hypersexuality, confusion, hallucinations, peripheral oedema	Good symptomatic therapy Less dyskinesias/motor fluctuations compared to levodopa Higher incidence of adverse effects, especially impulse control disorders, hypersexuality and neuropsychiatric effects Available as once-daily dosing in oral and topical forms (rotigotine not currently PBS listed)
	Ergot derived: Cabergoline Bromocriptine Pergolide	As above plus cardiac valvular disease and pleuropulmonary/retroperitoneal fibrosis	Have been superseded by non-ergot drugs due to risk of fibrotic complications Monitoring essential (interval echocardiograms, respiratory function and chest X-ray) for those unable to switch from ergot preparations
	Apomorphine (injection)	As above plus skin nodules, skin necrosis	Used as subcutaneous bolus doses for rescue therapy in advanced Parkinson's disease with motor fluctuations Used as continuous infusion for advanced Parkinson's disease with motor fluctuations Often requires concomitant domperidone to manage nausea Requires high level of patient/carer support and education
Catechol-O-methyltransferase inhibitor	Entacapone	Diarrhoea, nausea, abdominal pain, discolouration of urine and sweat	Reduces 'wearing off' symptoms by prolonging the effect of levodopa May induce dyskinesia
Monoamine oxidase type B inhibitors	Selegiline Rasagiline	Nausea, hallucinations	Both drugs have a putative role in neuroprotection, although no conclusive evidence to date
Anticholinergics	Benzhexol Benztropine	Confusion, hallucinations, memory disturbance, dry mouth, constipation, urinary retention, glaucoma	Consider for treatment of levodopa-resistant tremor in younger patients No benefit for other motor symptoms Poorly tolerated in older people
N-methyl-D-aspartate antagonist	Amantadine	Hallucinations, confusion, livedo reticularis	Main role is in treatment of dyskinesia Small symptomatic benefit Tolerability problems

PBS Pharmaceutical Benefits Scheme TGA Therapeutic Goods Administration

Levodopa/dopa-decarboxylase inhibitors have the highest efficacy for motor symptoms and tend to have slightly better tolerability, particularly when started in low doses. The simplest dosing regimen is to commence a set dose at a set time and thereafter monitor the efficacy in terms of the dose required for symptom relief and the duration of that response. Box 1 shows a typical levodopa dosing regimen. A three-times daily starting frequency is required due to the short half-life of levodopa.

As the disease progresses it is important to establish the dose that relieves the increasing symptoms. This usually requires increasing the frequency of dosing from three to four (and often five) times a day (Box 2) with the addition of a long-acting preparation at bedtime.

Dopamine agonists are also effective first-line drugs and may be associated with less dyskinesia than levodopa/dopa-decarboxylase inhibitors. They are available in once-daily preparations. Long-term data suggest no significant difference in outcomes between patients started on levodopa/dopa-decarboxylase inhibitors and those given dopamine agonists.[6] It is common as time progresses to use a combination of these drugs.[4]

Adverse effects

All patients should be appropriately counselled before treatment and monitored for adverse effects throughout their lifelong treatment course. Most adverse effects are reversible. Cardiac valvular fibrosis and pulmonary fibrosis from the ergot-derived dopamine agonists such as cabergoline and pergolide may be irrreversible and some cases require surgical intervention. This risk seems most apparent amongst patients who have had more than six months duration of treatment and in those on higher doses of ergot-dopamine agonists, although individual susceptibility factors are not yet known.[7] Patients taking these drugs require constant monitoring and where possible switching to a non-ergot derived dopamine agonist such as pramipexole, ropinirole or rotigotine is desirable.

Non-motor adverse effects of dopaminergic therapy include nausea, postural hypotension, cognitive symptoms, hallucinations, psychosis, hypersomnolence, sudden sleep episodes and impulse control disorders (gambling, compulsive behaviours and hypersexuality). Such adverse effects can occur with all dopaminergic therapies, although are more common with dopamine agonists, which can also cause peripheral oedema. The risk of impulse control disorders is significantly higher with dopamine agonists. Pretreatment counselling and sustained clinical vigilance for these disorders is essential. A reduced dose of pramipexole is needed in patients with impaired renal function and doses should be increased cautiously in older people.

Dopaminergic drugs sometimes increase the non-motor symptoms of Parkinson's disease. Many of the drugs cause gastrointestinal adverse effects. If drug treatment is required for nausea or vomiting, metoclopramide and prochlorperazine should be avoided due to their dopamine blocking effects. Domperidone is the preferred treatment for these symptoms.

Inadequate response

If the patient's symptoms are not controlled it is important to exclude other diseases. As Parkinson's disease progresses slowly, any sudden deterioration is an indicator of a co-existent medical condition, such as a urinary tract infection, or problems with compliance. Adherence can be a particular problem given the frequent dosing schedule of levodopa preparations, but may be helped by providing the medicines in a multidose pack.

Box 1 Typical regimen for starting levodopa *

Step 1: Start at 50 mg 3 times a day for 2 weeks

Step 2: Increase to 100 mg 3 times a day. Continue until there is a clinical need for a change in dose. This will vary between individuals depending on the severity of their Parkinson's disease (e.g. could range from weeks to years).

Step 3: Increase to 150 mg 3 times a day if not coming 'on'

or

change to 100 mg 4 times a day if coming 'on' but not making it from dose to dose

or

change to 100 mg 3 times a day with entacapone if not coming 'on' or not making it from dose to dose

or

add pramipexole extended-release once daily if not coming 'on' or not making it from dose to dose

* Strength refers to levodopa dose alone, regardless of whether in combination with a dopa-decarboxylase inhibitor/catechol-O-methyltransferase inhibitor

Box 2 Typical levodopa dosing times

3 times a day – 6 am/12 pm/6 pm

4 times a day – 6 am/10 am/2 pm/6 pm

5 times a day – 6 am/9 am/12 pm/3 pm/6 pm

A prolonged-release formulation can be used at bedtime

Sustained failure to achieve adequate symptom control with a particular levodopa or dopamine agonist regimen should prompt an increase in the dose of that drug or consideration of combination therapy.

A fluctuating or erratic treatment response in early Parkinson's disease may reflect variable absorption of oral therapy. Separating levodopa therapy from meals can improve absorption. Consideration of drugs which provide more continuous dopaminergic stimulation such as once-daily pramipexole or the rotigotine patch may be helpful.

Nocturnal symptoms are often improved with the addition of long-acting dopamine agonists (particularly if the patient has restless legs) or controlled release levodopa/dopa-decarboxylase inhibitors. Non-motor symptoms such as nocturia may also need to be addressed (Table 2).

Some patients with tremor refractory to levodopa therapy may respond to dopamine agonists. Anticholinergic drugs can cautiously be tried in younger patients and are occasionally useful in reducing saliva production. However, they can have significant cognitive adverse effects such as hallucinations, particularly in older people.

Treatment of motor fluctuations and dyskinesia

Motor and non-motor fluctuations occur as Parkinson's disease progresses. This can make drug therapy challenging.[10] Fluctuations include the return of symptoms at the end of the dose interval ('wearing off'), failed symptom relief and sudden and unpredictable 'offs' of both motor and non-motor type. Increased dosing is also associated with so-called drug-induced dyskinesias resembling choreiform movements which occasionally can be localised, but generalise as the disorder progresses. These can occur in peak dose and diphasic* patterns.

'Wearing off' between doses can be managed by increasing the dose, reducing the dose interval (if using levodopa/dopa-decarboxylase inhibitors) or adding other drugs. Entacapone is a further inhibitor of levodopa breakdown and in combination with levodopa/dopa-decarboxylase inhibitors reduces 'wearing off' and increases the potency of an individual dose of levodopa. Often a dose reduction of approximately 25% is needed when entacapone is added. Dopamine agonists are also useful in smoothing out the end-of-dose 'wearing off' effect by reducing the severity of the 'off' period. Monoamine oxidase B inhibitors can also be considered in this situation. Dose failures may respond to oral rescue therapy with short-acting levodopa/dopa-decarboxylase inhibitors.

Involuntary motor movements or dyskinesias are often not troubling to patients, so they do not always require a change of treatment if good 'on' time is maintained. Disabling dyskinesias may require dose reduction at the risk of loss of efficacy. Amantadine has a mild to modest benefit in controlling motor symptoms and can reduce dyskinesia, however it has potential adverse effects including confusion, peripheral oedema and livedo reticularis.

Treatment options for motor complications refractory to oral therapies

Specialist referral and co-management of patients as time progresses is needed to manage the more challenging aspects of motor fluctuations. Non-oral therapies including apomorphine, intestinal levodopa infusion and deep brain stimulation can be considered when standard drug therapy fails to effectively manage motor fluctuations. All these treatments require ongoing involvement of a multidisciplinary team experienced in managing advanced Parkinson's disease.

Apomorphine

Apomorphine is an injectable dopamine agonist which can be given as intermittent bolus doses or by continuous subcutaneous infusion. Intermittent boluses are effective rescue therapy for disabling motor 'off' symptoms, while continuous infusion can reduce daily 'off' time and reduce the required doses of oral drugs.[11] Apomorphine has the same potential adverse effects as oral dopamine agonists and may cause injection site reactions and skin nodules. Patients may need domperidone to prevent vomiting.

Intestinal levodopa infusion

Continuous administration of levodopa/dopa-decarboxylase inhibitors in gel form via a percutaneous enteral tube is available for advanced Parkinson's disease with severe motor fluctuations refractory to oral therapy. Typically, patients carry an infusion pump around the waist or across the shoulder allowing continuous infusion during waking hours, with the option to extend to a 24-hour infusion to cover nocturnal symptoms if required. It overcomes complications relating to variable absorption of levodopa secondary to delayed gastric emptying and protein consumption. Usually, oral therapy can be withdrawn. Several studies, including some small randomised controlled trials have shown improvement in motor function, motor fluctuations and quality of life. Complications include all those seen in standard

* Diphasic dyskinesia occurs as the levodopa concentration rises and then falls

Table 2 **Management of non-motor features of Parkinson's disease**

Non-motor manifestation		Management options
Cardiovascular	Postural and postprandial hypotension	Increased fluid and salt intake, frequent small meals, compression stockings (above knee) Avoid antihypertensives Domperidone +/– fludrocortisone Pyridostigmine Midodrine (Special Access Scheme only)
Gastrointestinal	Constipation	Good hydration, high fibre diet, laxatives Avoid anticholinergics
	Gastroparesis (nausea, bloating, abdominal pain, early satiety)	Postural advice, frequent small meals Domperidone
	Dysphagia and dysphonia	Speech therapy assessment, Lee Silverman voice training Dopaminergic therapy – may be partially levodopa responsive
	Drooling	Dopaminergic therapy Anticholinergics (beware adverse effects) Salivary gland botulinum toxin injections
Genitourinary	Urinary irritability (frequency, urgency, urge incontinence, nocturia)	Avoid diuretics including coffee Perform post-void bladder scan to rule out retention before starting therapy Oxybutynin, amitriptyline, tolterodine, prazosin, duloxetine
	Erectile dysfunction	Dopamine agonists Sildenafil or similar oral therapy – check for postural hypotension before prescribing Specialist referral for counselling/consideration of intracavernosal and surgical treatments
Neuropsychiatric and cognitive	Anxiety	'Off' state anxiety may respond to an increase in dopaminergic therapy Antidepressants (tricyclics or selective serotonin reuptake inhibitors) Counselling, support, psychotherapy
	Depression	Counselling, support, psychotherapy Dopamine agonists may have antidepressant properties[8] Antidepressants (tricyclics or selective serotonin reuptake inhibitors)
	Psychosis	Non-troubling hallucinations do not require drug treatment For distressing hallucinations/paranoia: • exclude treatable causes of delirium • modify Parkinson's disease drug therapies (reduce or cease anticholinergics, monoamine oxidase B inhibitors, amantadine, dopamine agonists, catechol-O-methyltransferase inhibitors) • reduce levodopa if no response • quetiapine appears to have a relatively low incidence of extrapyramidal effects (clozapine has less extrapyramidal effects but its use is limited by adverse effects and need for monitoring)
	Cognitive impairment	Manage as for distressing psychosis Cholinesterase inhibitors improve cognition and activities of daily living in Parkinson's disease dementia,[9] but are currently only approved in Australia for Alzheimer's dementia
Sleep	Excessive daytime sleepiness	Rule out other causes of ineffective sleep (e.g. sleep apnoea, depression, nocturia, inadequately controlled Parkinson's disease motor symptoms) Reduce dopaminergic therapy if possible Sleep attacks may necessitate reduction of dopaminergic therapy at expense of motor control
	Restless legs syndrome	Dopaminergic therapy
	REM sleep behaviour disorder	Clonazepam
Pain	Pain/sensory symptoms	Establish whether present during a motor 'on' or 'off' state and adjust dopaminergic therapy appropriately If unrelated to dopaminergic therapy, consider simple analgesics, drugs for neuropathic pain, antidepressants, chronic pain management strategies

oral levodopa therapy. Additional complications related to the technical aspects of the infusion system, including tube removal/dislocation, local infection, peritonitis and intestinal obstruction, are reported in 20–70% of patients.[12]

Functional neurosurgery

There are two main neurosurgical options for Parkinson's disease. The first is lesional surgery, which permanently ablates a target region to achieve either tremor control or lessen dyskinesia. The second is deep brain stimulation surgery. This is reversible and provides continuous electrical stimulation to a target from an implanted pulse generator (battery) which is adjustable via an externally applied programmer. Several randomised controlled trials have shown deep brain stimulation improves motor symptom control, reduces motor fluctuations and improves quality of life in people with advanced Parkinson's disease.[13-15] Sustained motor benefit over 10 years has been demonstrated.[16] Often dopaminergic drug therapy can be significantly reduced following deep brain stimulation which is of particular benefit when the drugs are difficult to tolerate.

Both forms of functional neurosurgery carry immediate perioperative risk and deep brain stimulation carries additional risks associated with the implanted hardware and stimulation field effect. Deep brain stimulation is not a cure, and inevitably symptoms of Parkinson's disease progress, but possibly at a slower rate.[17] Australian referral guidelines for deep brain stimulation are available.[18]

Management of non-motor symptoms

Patients with Parkinson's disease may have autonomic dysfunction, neuropsychiatric symptoms and cognitive impairment. Non-motor symptoms contribute significantly to the morbidity of Parkinson's disease. Interestingly, some of these are present as part of the 'off' phenomena and remain responsive to levodopa, but many are not and warrant management in their own right. Adverse effects of dopaminergic therapies often overlap with non-motor symptoms so the combined opinion of movement disorder specialists, neuropsychiatrists and other specialists is often important. Common non-motor problems and possible treatment options are outlined in Table 2.

Conclusion

Parkinson's disease is a progressive neurological disorder with motor and non-motor features. It has significant cost and burden of care to the community over a prolonged course. Treatment is aimed at maintaining continuous relief of motor and non-motor symptoms. Drugs may be necessary, but are not sufficient to maintain quality of life in the long term. As the disease progresses, specialist referral and allied health involvement is important. The patient will need collaborative assistance from general practitioners, movement disorder specialists, neuropsychiatrists and allied health professionals. ◀

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. Levodopa therapy should be delayed as long as possible as it is only effective for a limited time.

4. Dopaminergic therapy may exacerbate the non-motor symptoms of Parkinson's disease.

Answers on page 211

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