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The challenge of Parkinson's disease

With varying patient responses to pharmacological and surgical therapies, treatment of Parkinson's disease presents a challenge to the GP. Major advances in the management of Parkinson's disease have recently been made and research into new therapies continues.

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Parkinson's disease is a progressive, neurodegenerative condition. Recently, major advances have been made in both the management of Parkinson's disease and the understanding of its pathogenesis. The most significant motor features of Parkinson's disease can currently be well controlled by medical and surgical therapies, which can provide patients with a reasonably good quality of life for about 10 to 15 years after diagnosis. Newer pharmacological therapies should hopefully reduce the incidence and severity of the motor complications of Parkinson's disease.

Pathophysiology

Parkinson's disease occurs when neurons in an area of the brain known as the substantia nigra degenerate. Neurons of the substantia nigra project into the striatum and produce dopamine, an important neurotransmitter. The striatum is the main source of input for the basal ganglia, which are a group of nuclei within the brain that have extensive interconnections with the cerebral cortex, thalamus and brainstem. Traditionally, the basal ganglia have been regarded as motor structures that regulate the initiation and maintenance of movement. However, the basal ganglia also regulate important nonmotor functions within anatomically distinct but linked networks.

Nonmotor functions of the basal ganglia are analogous to the motor functions. They include:

- an 'executive' loop involving the dorsolateral prefrontal cortex and part of the caudate – this may regulate the initiation and termination of cognitive processes, such as planning, working memory and attention
- a 'limbic' loop involving the cingulate cortex

IN SUMMARY

- **Parkinson's disease is the second most common neurodegenerative condition in Australia.**
- **There is no reliable diagnostic test that can distinguish Parkinson's disease from other conditions with similar presentations.**
- **The motor symptoms of Parkinson's disease are the easiest to treat with dopaminergic drug therapies.**
- **The wearing-off effect and dyskinesias are complications associated with dopaminergic drug therapies.**
- **The nonmotor symptoms of Parkinson's disease typically respond less well to dopaminergic drug therapies and often progress to overshadow the motor symptoms.**
- **Surgical therapy for Parkinson's disease involves deep brain stimulation, which has been found to be an effective therapy for selected patients.**

and the nucleus accumbens – this may regulate emotional behaviour.

Thus, dopamine in the brain has a central role in regulating not only movement but also cognitive functions and emotional behaviour.

A loss of dopamine results in abnormal patterns of neuronal firing within the basal ganglia that ultimately lead to impaired movement because of increased inhibition of thalamocortical movement control. Studies have shown that most patients with Parkinson's disease have lost 60 to 80% or more of the dopamine-producing cells in the substantia nigra by the time that motor symptoms appear.[1] Dopamine loss is accompanied by the microscopic appearance of Lewy bodies within neurons. Lewy bodies are abnormal aggregates of proteins, including alpha-synuclein. Research on the staging of Lewy body pathology in Parkinson's disease indicates that the disease begins in the medulla and olfactory complex, and ascends in a predictable sequence to involve the entire neocortex.[2]

Recent studies have shown that people with Parkinson's disease also have loss of the nerve endings that produce the neurotransmitters noradrenaline and serotonin. These chemical messengers are related to dopamine, and are involved in parts of the nervous system controlling many automatic functions of the body, such as pulse and blood pressure. The loss of these messengers might help explain several of the nonmotor features of Parkinson's disease, including fatigue and blood pressure regulation abnormalities.

Prevalence and risk factors

In Australia, Parkinson's disease is the second most common neurodegenerative condition (after Alzheimer's disease), and in 2007 about 60,000 people were estimated to be affected by the disease.[3] The average age of onset is between 60 and 70 years but about 10% of cases are young onset, beginning before the age of 55 years. The lifetime risk of being affected by Parkinson's disease is estimated to be one in 40 to 50. Age, male gender and rural residence are risk factors. Tobacco use, caffeine intake, NSAID use and hyperuricaemia have been associated with a possible lower relative risk of Parkinson's disease, but causality for these has never been shown.[4] Moreover, these factors should not be prescribed as therapy in Parkinson's disease because, for example, taking up smoking may increase the risk of dementia without slowing the progression of Parkinson's disease.

Most cases of Parkinson's disease are 'sporadic' – that is, the disease does not seem to be inherited. However, first-degree relatives of patients with Parkinson's disease are 1.5 to 9.5 times more likely to develop Parkinson's disease and some cases of Parkinson's disease can be traced to specific genetic mutations. The first gene to be identified was *alpha-synuclein* in 1997 (Table 1). Subsequent

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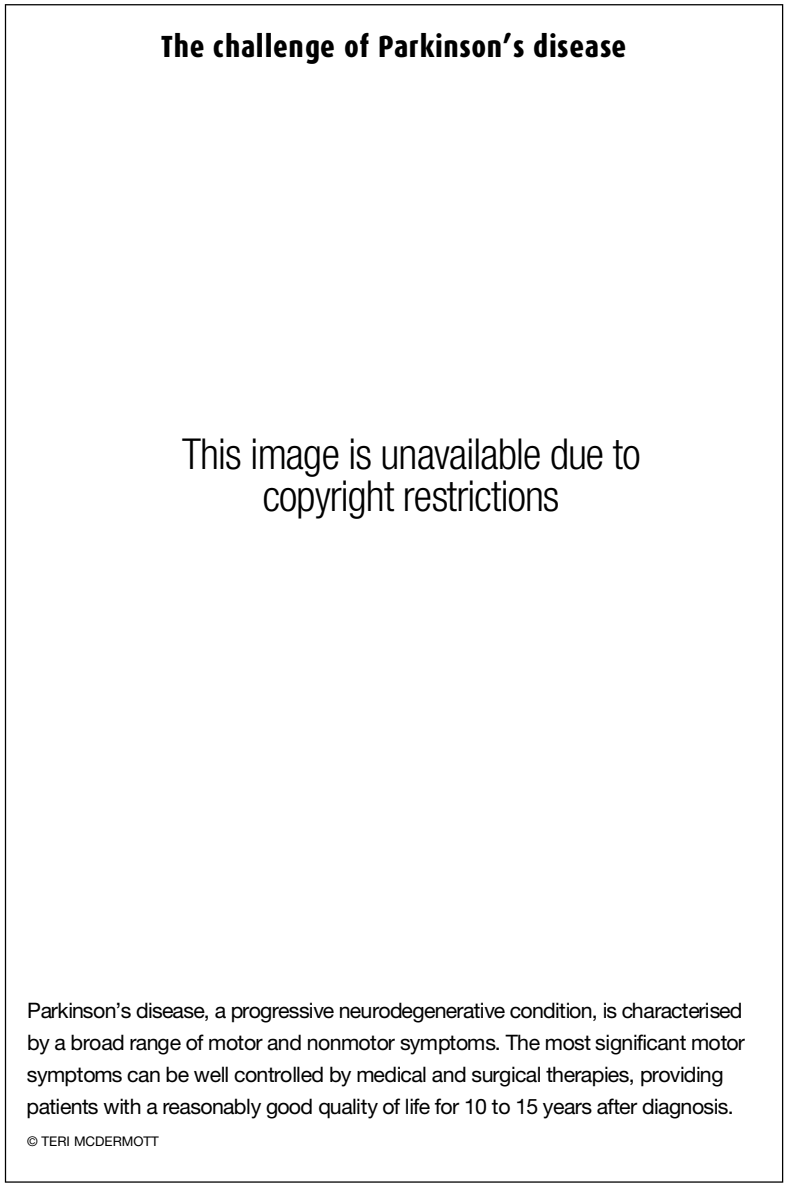

Parkinson's disease, a progressive neurodegenerative condition, is characterised by a broad range of motor and nonmotor symptoms. The most significant motor symptoms can be well controlled by medical and surgical therapies, providing patients with a reasonably good quality of life for 10 to 15 years after diagnosis.

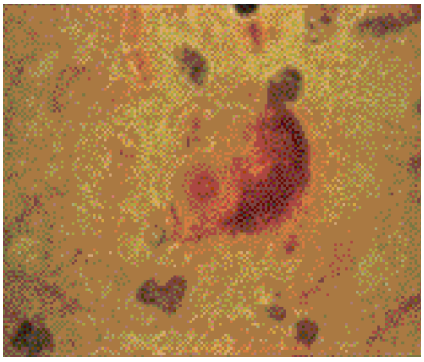

Figure 1. Lewy body within a neuron (H & E stain). A Lewy body is an eosinophilic inclusion comprising a dense core surrounded by a halo of radiating fibrils.

studies of the role of *alpha-synuclein* in Parkinson's disease led to the discovery that Lewy bodies (Figure 1) from people with the sporadic form of Parkinson's disease contained clumps of alpha-synuclein protein. The most commonly found mutation in familial Parkinson's disease is the *LRRK2* mutation. This accounts for 5 to 15% of cases when two or more first-degree relatives have the disease. The discovery of this and other genes has revealed important links between hereditary and sporadic forms of Parkinson's disease.

Many researchers now believe that most cases of sporadic Parkinson's disease result from a combination of genetic susceptibility and exposure to one or more environmental factors that trigger the disease. Genetic testing for the genetic causes of Parkinson's disease, even though they are uncommon, is available in some specialised Australian centres.

Motor symptoms and diagnosis

There is no reliable diagnostic test that can distinguish Parkinson's disease from other conditions that have similar clinical presentations – such as distinguishing an essential tremor from a tremor due to Parkinson's disease or atypical Parkinson syndromes such as progressive supranuclear palsy. Evaluation of patients by a movement disorders specialist is the best way to reach a diagnosis quickly. In older patients, Parkinson's disease can present with general functional decline and non-specific symptoms.

Tremor of the fingers, hands, arms or jaw affects about 75% of patients with Parkinson's disease. It is unilateral at onset, occurs at rest and improves with purposeful movement. Rigidity makes movement difficult and may cause pain and cramps. Akinesia affects small and precise movements first (such as writing or fastening buttons). Later involvement of larger muscles, such as those in the legs, leads to difficulty getting out of a chair or starting to walk. Postural instability causes unsteadiness when walking, turning or rising from a chair. This can lead to falls and may necessitate the use of walking aids. Predictive factors for more rapid motor progression, nursing home placement and shorter survival time in patients with Parkinson's disease include:

- older age at onset of Parkinson's disease
- associated comorbidities
- presentation with rigidity and akinesia
- reduced responsiveness to dopamine.[5]

The motor symptoms of Parkinson's disease are the easiest to treat with dopaminergic drug therapies. Rigidity and akinesia almost always respond (sometimes dramatically) to treatment with drugs containing levodopa, and diagnostic support can be achieved from a trial of levodopa plus a dopa-decarboxylase inhibitor. However, other than Parkinson's disease, parkinsonian syndromes (for example, drug-induced parkinsonism, multiple system atrophy or autosomal recessive juvenile parkinsonism) may also improve significantly with the use of dopaminergic drugs.

In specific situations, investigations can be useful – for example, MRI of the brain may show subtle signs of an atypical parkinsonian disorder (such as multiple system atrophy, progressive supranuclear palsy, vascular parkinsonism or

Table 1. Loci and genes linked to and associated with Parkinson's disease

PD locus	Chromosome	Gene	Mode of inheritance	Clinical features
PARK1	4q21.3	*α-synuclein*	AD	Early onset
PARK2	6q25.2-27	*Parkin*	AR	Early onset
PARK3	2p13	Unknown	AD	Late onset
PARK5	4p14	*UCHL-1*	AD	Late onset
PARK6	1p35-36	*PINK1*	AR	Early onset
PARK7	1p36	*DJ1*	AR	Early onset
PARK8	12q12-q13.1	*LRRK2*	AD	Late onset
PARK9	1p36	*ATP13A2*	AR	Early onset
PARK10	1p32	Possibly *ELAVL4*	Complex	Late onset
PARK11	2q36-37	*GIGYF2*	AD	Early onset
PARK12	Xq21-q25	Unknown	Complex	Unknown
PARK13	2p12	*HTRA2*	Possibly AD	Typical

Polymorphisms or mutations in the *NR4A2*, *NDUFV2*, *ADH3*, *FGF20*, *GBA* and *MAPT* genes have also been associated with susceptibility to Parkinson's disease.
Abbreviations: PD = Parkinson's disease, AD = autosomal dominant inheritance, AR = autosomal recessive.

Table 2. The nonmotor symptom complex of Parkinson's disease

Neuropsychiatric symptoms
- Depression
- Apathy
- Anxiety
- Anhedonia
- Attention deficit disorder
- Hallucinations, illusions or delusions
- Dementia
- Drug-induced compulsive behaviours
- Delirium
- Panic attacks

Sleep disorders
- Restless legs syndrome and periodic limb movements
- REM sleep behaviour disorder
- Daytime sleepiness
- Vivid dreaming
- Insomnia
- Sleep-disordered breathing

Autonomic symptoms
- Nocturia, urinary urgency and frequency
- Sweating
- Orthostatic hypotension
- Impotence
- Dry eyes

Gastrointestinal symptoms
- Dribbling of saliva
- Choking
- Reflux
- Vomiting
- Nausea
- Constipation

Sensory symptoms
- Pain
- Paraesthesia
- Loss of sense of smell

Other symptoms
- Fatigue
- Blurred vision
- Weight changes

normal pressure hydrocephalus). Use of ^{123}I metaiodobenzylguanidine (MIBG) cardiac single photon emission computed tomography (SPECT) may show cardiac sympathetic denervation in Parkinson's disease but not in other parkinsonian disorders, and normal quantitative smell testing makes a diagnosis of Parkinson's disease less likely. The interpretation of these investigations is difficult and requires subspecialty interest in the field.

Specific features, such as early falls, poor response to levodopa, symmetry of motor manifestations, lack of tremor and early autonomic dysfunction, may also suggest an alternative diagnosis.

Motor response complications

Wearing-off effect

Dopaminergic drug therapies are very successful at reducing the handicap of the motor symptoms of Parkinson's disease. These treatments allow the majority of people with Parkinson's disease to extend the period of time when they can lead relatively normal, productive lives. However, with long-term treatment, patients typically begin to notice that their symptoms resolve for hours at a time (on times) and then return (off times). These motor fluctuations occur in about 50% of patients after five years of levodopa therapy; at this time the motor symptoms usually affect patients for up to 25% of their waking hours. The proportion of patients affected increases to about 70% among those treated for more than 15 years, and off periods can increase to up to 50% of the waking day.

Alternating between on and off times is a frequent problem for patients with Parkinson's disease. Off times may be accompanied by muscle spasms, pain and worsening motor function. Reduction of the period of effectiveness after each drug dose with the transient re-emergence of parkinsonian symptoms is called the wearing-off effect. The emergence of wearing-off symptoms marks a crucial point in the disease because it is often at this stage that patients start to report increased difficulties with daily living, a reduced quality of life and increased disability and dependence on others.

Dyskinesias

Dyskinesias or abnormal involuntary movements are clinically and pharmacologically heterogeneous. Dystonic posturing caused by sustained muscular spasm of a limb may coincide with low levels of dopaminergic stimulation, such as occurs in the off periods. On times can also be accompanied by chorea – sudden jerky or uncontrolled movements of the limbs and neck – usually seen with the peak concentration of levodopa. These movements may be either mild (and the patient may be unaware of them) or severe and either very rapid or very slow. Less commonly, a proportion of younger patients are affected by onset and end of dose (biphasic) dyskinesias that are frequently very transient (lasting for 10 to 15 minutes at a time) and painful.

Nonmotor symptoms

Although Parkinson's disease is predominantly a movement disorder, other impairments such as neuropsychiatric, autonomic and sensory symptoms frequently develop with advancing disease (Table 2). Nonmotor symptoms may be the most difficult to treat: they typically respond less well to dopaminergic therapies and may even be exacerbated by drug treatments. Nonmotor symptoms often progress to overshadow the motor symptoms of Parkinson's disease.

Some nonmotor features may precede the motor symptoms of Parkinson's disease by many years and relate to the underlying degenerative process. In particular, REM sleep-behaviour disorder, constipation, orthostatic hypotension, urinary urgency, impotence, depression, daytime sleepiness and a loss of sense of smell may precede motor symptoms. However, many behavioural disorders, such as compulsive gambling, have

been directly linked to the use of dopamine agonists – medications that directly stimulate brain dopamine receptors.

Prognosis

The Sydney multicentre study showed that after 20 years of follow up, 74% of a cohort of patients with newly diagnosed Parkinson's disease had died.[6] The average life expectancy of a patient with Parkinson's disease is slightly reduced compared with people who do not have the disease.[6] Although disease progression is quite variable, it is possible, to some extent, to predict the future course of Parkinson's disease. Patients who are younger at disease onset progress more slowly but tend to develop more motor response complications to levodopa treatment. Patients with tremor-dominant symptoms may also have a more benign course, although dementia more commonly complicates Parkinson's disease in older patients. Within each individual, the rate of progression tends to be approximately constant through the disease course and a rapid deterioration makes it necessary to consider comorbid conditions.

Treatment update

Neuroprotection and cellular therapies

No treatment has been shown to be neuroprotective and no vitamins or supplements have been found to improve motor function in patients with Parkinson's disease. Cellular therapies are mooted to potentially limit disease progression; however, two recent clinical trials of fetal nigral transplantation for advanced Parkinson's disease failed to meet the primary endpoints of improved quality of life or reduced off-time. Phase 2 studies of gene transfer techniques are ongoing.

Many would argue that to be effective, cellular therapies have to do more than produce or process dopamine alone: they may also need to integrate into the neural circuitry and replenish other neuron populations. It may be some time before this can be achieved safely in humans.

First-line treatments

Levodopa

Drugs that work directly or indirectly to increase the level of dopamine in the brain are the mainstay of symptomatic treatment for Parkinson's disease. The most common drug used for Parkinson's disease is levodopa – the amino acid precursor of dopamine that crosses the blood–brain barrier and is changed into dopamine. Levodopa is usually combined with a peripheral decarboxylase inhibitor to prevent its peripheral breakdown.

There is debate about whether the initial treatment for patients with Parkinson's disease should be drugs containing levodopa or a dopamine agonist. The early use of levodopa offers the most symptomatic benefit but leads to the earlier emergence of motor response complications such as levodopa-induced abnormal involuntary movements (dyskinesias) and treatment-related motor fluctuations.

Dopamine agonists

Initiating treatment with a dopamine agonist confers the advantage of delaying motor response complications. Bromocriptine (Kripton, Parlodel), pergolide (Permax), cabergoline (Cabaser), pramipexole (Sifrol) or apomorphine (Apomine Injection, Apomine PFS) directly stimulate dopamine receptors and mimic the action of dopamine. Dopamine agonists have the advantage of a longer duration of action compared with levodopa and reduce the medium-term risk of developing motor complications. However, they are generally less effective than levodopa in controlling rigidity and akinesia.

Many of the potential side effects of dopamine agonist use are similar to those associated with the use of levodopa (i.e. nausea, vomiting and dyskinesias). Hallucinations, confusion, oedema and nightmares may occur more frequently with dopamine agonist treatment compared with levodopa. The ergot-derived dopamine agonists, bromocriptine, pergolide and cabergoline, can also cause fibrotic complications (including pleuropulmonary and retroperitoneal fibrosis and cardiac valvulopathy). The maximum recommended dose of cabergoline is 3 mg per day and patients taking ergoline agonists should be monitored for fibrosis. Fibrosis usually clears once the drugs are stopped. Pramipexole and apomorphine are the only nonergoline agonists currently available on the PBS and their use is restricted to adjunctive therapy in patients being treated with levodopa-decarboxylase inhibitors.

Doctors should counsel patients taking dopamine agonists about the small potential risk of unheralded sleep attacks and should routinely ask if they fall asleep when driving. When a patient taking a dopamine agonist complains of drowsiness, a detailed history should be elicited to determine whether or not the patient actually fell asleep, the rapidity of onset of sleep and whether sleepiness occurs during activities such as driving. Despite the potential danger when driving, sleep attacks are too infrequent to recommend that patients taking dopamine agonists for Parkinson's disease routinely stop driving.

Recently, dopamine agonists in particular have been linked to a variety of compulsive behaviours. These behaviours include pathological gambling, hypersexuality, compulsive eating and compulsive shopping and relate to aberrant or excessive dopamine receptor stimulation of the brain's reward centres. Reports of pathological gambling in patients taking dopamine agonists have received considerable attention in the media, making headlines as patients who have lost financial assets seek damages from pharmaceutical companies.[7]

Patients taking dopamine agonists may also display a range of complex repetitive behaviours called punding. Punding or compulsive 'hobbyism' is characterised by an intense fascination with repetitive manipulations of technical equipment; examining, collecting and

sorting of common objects; artistic pursuits or excessive computer use.

Studies have shown that compulsive behavioural disorders are more common in patients:

- with younger age at onset of Parkinson's disease
- with a personal or family history of an addiction
- requiring higher medication doses.[8]

About 17% of patients treated with dopamine agonists display at least one compulsive disorder, and currently most of these disorders go unrecognised by treating physicians. An understanding of these problems, their early identification and prompt management can limit financial losses, relationship breakdown and potential medicolegal consequences. Therefore, the potential for compulsive behaviours should be routinely discussed with patients, and family members should be involved in these discussions whenever feasible (some patients may only reveal these behaviours to their physician privately for fear of repercussions from family members). Patients receiving dopamine agonists should also be asked routinely whether they have any of these behaviours as the problems may only emerge after many years of treatment.

Rarely, addiction to anti-Parkinson's medication ('dopamine dysregulation syndrome') can occur when a person takes a higher dose of a drug than is normally required to control the symptoms of Parkinson's disease, even though it may lead to side effects such as severe abnormal involuntary movement (dyskinesia) or harmful behavioural disorders.[9] Patients with these disorders should be managed in a specialist centre.

Other medications

Monoamine oxidase-B (MAO-B) inhibitors such as selegiline (Eldepryl, Selgene) have a more modest effect on motor symptoms by reducing the breakdown of dopamine in the brain.

Anticholinergic drugs (e.g. benztropine [Benztrop, Cogentin], benzhexol [Artane]) interfere with production or uptake of the neurotransmitter acetylcholine. These drugs have a weak effect on tremors and muscle stiffness, which can result from having more acetylcholine than dopamine in the brain.

Management of advanced disease and motor complications

There are two major limitations to dopamine replacement therapies:

- the eventual emergence of nondopa-responsive symptoms, such as postural instability and decline in mental functioning, as the disease progresses
- treatment-related side effects as the patient's response to the drugs changes.

Management of wearing-off symptoms

Entacapone (Comtan; Stalevo [with carbidopa and levodopa]) and tolcapone (Tasmar; restricted to Special Access Scheme prescribing only) are catechol-O-methyl transferase (COMT) inhibitors that are given in combination with levodopa for the treatment of Parkinson's disease. When given with levodopa, entacapone both extends the duration of action and increases the trough levels of levodopa, which result in significantly reduced off periods. Sustained-release formulations of levodopa are generally ineffective in reducing off time.

Adding selegiline or a dopamine agonist to drugs containing levodopa can also be considered to lengthen the duration of response to levodopa in patients who experience wearing-off or on–off effects.

Management of dyskinesias

The antiviral drug amantadine (Symmetrel) may be used as a mild anti-parkinson's drug in the early stages of the disease to help reduce symptoms. Used in patients with advanced disease, it can lead to a modest improvement in levodopa-induced dyskinesia. In patients who are disabled by dyskinesias the dose of levodopa is often reduced to lessen these drug-induced movements. However, symptoms of Parkinson's disease often reappear with lower doses of the medication. At this point, referral to a specialist centre is indicated as doctors and patients must work together closely to find a tolerable balance between the drug's benefits and side effects.

Conversely, in some patients with biphasic dyskinesias, medication dose reduction may only exacerbate their problems with dyskinesias. GPs should be aware of the possibility that a sudden reduction or cessation of dopaminergic therapy in patients with advanced disease has a small but serious risk of an akinetic crisis, similar to neuroleptic malignant syndrome.

Continuous dopaminergic stimulation

Apomorphine is a potent injectable dopamine agonist with a similar efficacy to levodopa. Apomorphine injections can be used in appropriate individuals as a 'rescue therapy' in conjunction with oral treatment for intermittent disabling off periods. Several studies have shown a significant reduction in off time after introducing apomorphine injections.

Apomorphine solution can be given as an infusion, thus providing continuous stimulation of the dopamine receptors in the brain. This type of treatment may be beneficial for those individuals who:

- experience long off periods during the day
- have a short oral medication benefit time
- have severe involuntary movements due to levodopa therapy.

Continuous infusion is given via a small pump device through a butterfly needle placed under the skin. Apomorphine infusions usually substantially reduce the need for oral medications and it may be given as monotherapy. Continuous subcutaneous infusions of apomorphine lead to an improvement in motor function with about a 60% reduction in daily

Table 3. Tips on pharmacotherapies for Parkinson's disease

Drugs that increase brain levels of dopamine Levodopa with dopa-decarboxylase inhibitors	Cornerstone of therapy for Parkinson's disease because it is the most effective in improving motor symptoms A simple chemical found naturally in plants and animals that is converted to dopamine in the brain Initial side effects include nausea, vomiting, low blood pressure and restlessness Regular use more frequently leads to medication-induced motor complications (wearing-off and dyskinesias) Dopaminergic drugs may cause drowsiness or sudden sleep onset, which can make driving and other activities dangerous
Drugs that mimic dopamine (dopamine agonists) Apomorphine, bromocriptine, pergolide, cabergoline, pramipexole	Used alone in the early stages of the disease Used later with levodopa to lengthen the duration of response in patients who experience wearing-off or 'on–off' effects Generally less effective than levodopa in controlling rigidity and akinesia May cause compulsive behaviours
Drugs that inhibit dopamine breakdown (MAO-B inhibitors) Selegiline	Use can delay the need for levodopa therapy by up to a year When given with levodopa, it prolongs the patient's response to levodopa Usually well tolerated, although side effects may include nausea, orthostatic hypotension or insomnia Should not be taken with antidepressants
Drugs that decrease the action of acetylcholine anticholinergics Benzhexol, benztropine	Only about half of patients who receive anticholinergics are helped by them, usually for a brief period and with only a 30% improvement Side effects may include dry mouth, constipation, urinary retention, hallucinations, memory loss, blurred vision and confusion
Drugs that inhibit dopamine breakdown (catechol-O-methyl transferase inhibitors [COMT]) Entacapone, tolcapone (only available in specialised centres via the Special Access Scheme)	Prolong the effects of levodopa by preventing the breakdown of dopamine COMT inhibitors can decrease the duration of off periods and usually make it possible to reduce the patient's dose of levodopa May cause diarrhoea and urine discolouration In a few rare cases, tolcapone has caused severe liver disease. Because of this, patients taking tolcapone need regular monitoring of their liver function
Drugs with an unknown mechanism of action for Parkinson's disease Amantadine	Can be used alone in the early stages of the disease May reduce levodopa-induced dyskinesias Side effects may include insomnia, mottled skin, oedema, agitation or hallucinations

off periods and a 30% reduction in dyskinesias.

Table 3 provides a summary of the currently available pharmacotherapies for the treatment of Parkinson's disease.

New and future pharmacotherapies

There is every indication that medical and surgical therapies will continue to improve. A number of products have recently been approved or are in development or available overseas that will add to the management options for Parkinson's disease in Australia. For example, rasagaline is an irreversible inhibitor of monoamine oxidase used overseas either as a monotherapy in early Parkinson's disease or as an adjunct therapy in more advanced cases and it may have neuroprotective properties. Alpha$_{2A}$ antagonists have been shown to have promising effects on dyskinesias. Recently approved, intraduodenal levodopa (Duodopa Intestinal Gel) has been shown to provide constant levodopa blood levels resulting in reduced off periods and fewer dyskinesias. In addition, rotigotine (Neupro) is a

nonergot (or nonergotamine) dopamine agonist delivered through transdermal patches that provide a slow and constant dosage in a 24-hour period.

Nonmedical treatments

Patients with Parkinson's disease can improve their physical performance and activities of daily living by regularly exercising. Allied health interventions have a role in treating specific impairments – for example, physiotherapy reduces the risk of falls and speech therapy may be helpful in improving speech volume.

Surgical treatments

Before dopaminergic therapies were available, lesioning of various brain regions was one of the earliest successful treatments employed to manage Parkinson's disease. More recently, deep brain stimulation (DBS) has been adopted as an effective therapy for selected patients with Parkinson's disease. DBS involves placing electrical leads into one (unilateral) or both (bilateral) sides of the basal ganglia of the brain. DBS aims to modulate the function of selected targets within the basal ganglia and improve motor function.

The DBS procedure is generally performed in two separate steps – implantation of leads and then implantation of the neurostimulator to which the leads are connected. One advantage of DBS over lesioning is that by adjusting the electronic parameters the clinician may be allowed to capture a satisfactory effect despite suboptimal localisation of the electrode tip. Four separate stimulation sites are present at the end of the DBS electrode, which permits substantial target variation.

The targets used for DBS are currently the thalamus, the globus pallidus internus and the subthalamic nucleus (STN). Target selection should be conducted by a specialised service and is influenced by symptoms such as tremor or dyskinesias.

Thalamic deep brain stimulation

Unilateral thalamic DBS abolishes or markedly reduces contralateral upper-limb parkinsonian tremor in about 85% of patients. It is also effective for other non-parkinsonian tremors. In patients with Parkinson's disease, rigidity may also be reduced, but other aspects of parkinsonism do not benefit. The indication for thalamic DBS among patients with Parkinson's disease is restricted to those with medication-refractory disabling tremor (unilateral or bilateral) as the predominant problem.

Pallidal deep brain stimulation

Pallidal DBS is effective for Parkinson's disease and also benefits selected patients with dystonia. In patients with Parkinson's disease, levodopa-induced dyskinesias are markedly reduced or abolished by pallidal DBS. However, the 35 to 40% improvement in parkinsonism is primarily seen in the levodopa off state (not on drug). Oral levodopa treatment is still required after pallidal DBS surgery: in some patients the dosage can be decreased, while other patients benefit from larger doses that previously had not been tolerated because of dose-limiting dyskinesias.

Subthalamic nucleus deep brain stimulation

STN DBS generally leads to a striking improvement of 60 to 65% in mean motor scores during the levodopa off state. In contrast to pallidal DBS, levodopa dosage can usually be reduced by 50 to 60% after STN DBS. STN DBS results in a 60 to 70% reduction in both dyskinesia and daily off periods. Average improvements reported in specific Parkinson's disease quality of life scales are about 30% and after STN DBS, patients have been found to have significantly better quality of life scores than patients randomised to best medical treatment.[10] Generally, levodopa-refractory symptoms will not respond to STN DBS. The success of the procedure is predicted by the magnitude of the preoperative motor response to levodopa and poorer motor functioning at baseline.

Complication rates of deep brain stimulation

In two recent reviews, each of more than 1000 cases of DBS, the mortality rate in patients after DBS was 0.4% and causes of death were pneumonia, pulmonary embolism, hepatopathy and a case of complicated multiple sclerosis. The permanent surgical morbidity rate was 1%. The most frequently observed serious adverse events were intracranial haemorrhage (1.8 to 2.2%) and pneumonia (0.6%). Skin infection occurred in 0.4% of patients.[11,12]

In patients after STN DBS, mental status changes (often transient) were most common (18.4%) and weight gain, dysarthria and eyelid opening apraxia were the most common permanent stimulator adverse effects. Long-term follow up after STN DBS confirms that it remains effective over time and does not seem to generate functional habituation in basal ganglia circuitry. However, it does not prevent disease progression, such as the emergence of falls and development of cognitive disturbances or postural instability.

Treatment of neuropsychiatric complications

Medications that help control the non-motor symptoms of Parkinson's disease are also useful. For example, depression can complicate Parkinson's disease in up to 50% of patients, and those with Parkinson's disease-related depression may be prescribed antidepressants.

The presence of psychotic symptoms strongly correlates with the need for nursing home placement and with mortality. Up to 40% of all patients with Parkinson's disease have visual hallucinations, which are usually benign, whereas more sinister symptoms, such as delusions, paranoid ideation and delirium, become more frequent as the disease progresses. For psychosis in patients with Parkinson's disease, anticholinergic medications and amantadine should be avoided and doses of dopamine agonists should be reduced. Typical antipsychotic medications often

cause severe worsening of motor function. Atypical antipsychotics, such as quetiapine (Seroquel) or clozapine (Clopine, CloSyn, Clozaril), are best tolerated and may be considered but are not available on the PBS for this indication.

Dementia occurs in up to 40% of people with Parkinson's disease, a rate about six-times higher than that in healthy individuals. It is more likely to be present in older individuals or those with more severe or advanced disease. In the Sydney multicentre study, dementia was present in 83% of survivors at 20 years.[6] The dementia of Parkinson's disease is progressive and is clinically characterised by a dysexecutive syndrome with impairment of visuospatial abilities and memory on a background of heightened psychic sensitivity to dopaminergic drugs, including levodopa. Although a variety of pathologies may underlie the emergence of dementia in Parkinson's disease, rivastigmine (Exelon, Exelon Patch) has been shown to be effective in patients with Parkinson's disease with a Mini-Mental State Examination score of 10 to 24.[13]

Conclusion

Parkinson's disease is characterised by a broad range of motor and nonmotor symptoms. The mainstay of treatment is dopaminergic therapy. Emergence of motor complications requires adjustments to find a tolerable balance between the drug's benefits and side effects. Therapies that aim to provide more continuous stimulation of dopamine receptors have the advantage of reducing the emergence and severity of motor complications. Patients with troublesome motor complications should be considered for surgery. MT

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COMPETING INTERESTS: Dr Evans has served on advisory boards for Boehringer Ingelheim, Novartis and Hospira and has received honoraria for consultancy work and presentations from Boehringer Ingelheim and Novartis.