The management of Parkinson's disease:

Which treatments to start and when?

The treatment of patients with Parkinson's disease usually involves a multidisciplinary approach to care. The role of the general practice team is to co-ordinate an individualised treatment plan, according to the progression of the patient's condition. A combination of levodopa with carbidopa or benserazide is generally the first-line pharmacological treatment for functional disability in patients with Parkinson's disease. A crucial aspect of management is the optimisation of treatment as new symptoms develop. Dopamine agonists, e.g. ropinirole and pramipexole, and other medicines may be required to reduce motor symptoms and to minimise the adverse effects of levodopa treatment. Non-motor symptoms, e.g. pain, depression and fatigue, are very common in patients with Parkinson's disease and their management becomes increasingly important as the patient's condition progresses.

The natural history of Parkinson's disease

Parkinson's disease is a neurodegenerative disorder characterised by the cardinal symptoms of stiffness, resting tremor, slowness (bradykinesia) and reduction of movement (hypokinesia).[1] Often the symptoms are asymmetric and insidious; serious problems may not develop until several years after onset of symptoms.[2]

When patients with Parkinson's disease are examined they generally display:

- Rigidity on passive movement at major joints, e.g. when the patient's arm is moved by the clinician, sometimes with a superimposed ratchet-like sensation known as the "cogwheel" phenomenon
- Resting tremor, most commonly 4 hertz (four cycles per second), typically affecting the upper limbs
- Impairment of dextrous upper limb movements and facial expression due to bradykinesia affecting the small muscle groups of the face and hands, which is usually seen in the early phases of the condition

Bradykinesia in people with Parkinson's disease often causes a deterioration of handwriting in which the script typically slopes upwards and the writing is crabbed and becomes progressively smaller. Gait abnormalities typically manifest later in the course of the disease. However, a lack of spontaneous arm swing when walking is an early sign. Turning *en bloc*, where the whole body turns when changing direction, and a festinating gait, with small steps and tendency to shuffle as if the patient is chasing their centre of gravity are seen in patients with more advanced disease. Falls, partly due to slow activation of postural reflexes, occur in people with Parkinson's disease.

Non-motor symptoms are very common in patients with Parkinson's disease and may include hypotension, cognitive impairment, disorders of excessive sweating, depression and a reduced sense of smell (hyposmia).[3, 4] In some patients with Parkinson's disease non-motor symptoms can precede the classical motor symptoms by several years (see: "The Braak theory of Parkinson's disease progression", over page). However, non-motor symptoms are not useful for diagnosing Parkinson's disease as they have limited specificity. Early onset of prominent non-motor symptoms such as orthostatic hypotension and cognitive impairment are also consistent with alternative diagnoses such as multi-system atrophy and Lewy body dementia. Non-motor symptoms in patients with Parkinson's disease can become more troublesome than motor symptoms and their management becomes increasingly important as the condition progresses.

Parkinson's disease pathophysiology

The pathological characteristic of Parkinson's disease is a severe loss of pigmented dopaminergic neurons in the substantia nigra of the midbrain (a brain area involved in movement). These neurons project to the corpus striatum and loss of these projections leads to an overall decrease in cortical motor activity. This process also causes the positive symptoms of Parkinson's disease, such as tremor, by reducing the normal inhibitory neuronal control of movement; known as the release phenomenon.

Loss of dopaminergic neurons in patients with Parkinson's disease is accompanied by the development of intracellular protein aggregates within surviving pigmented neurons, known as Lewy bodies.[4] Lewy bodies in patients with Parkinson's disease are pathologically indistinguishable from Lewy bodies in patients with Lewy body dementia.[4] Long-term

The Braak theory of Parkinson's disease progression

The Braak theory of Parkinson's disease postulates that pathology first starts in the enteric nervous system of the gut and in the medulla and olfactory bulb. From here it spreads through neurons to the substantia nigra.[2, 4] This theory is supported by post-mortem studies and provides an explanation for the constellation of symptoms that can precede classical motor symptoms by several years, including:[2, 4]

- Constipation and other autonomic symptoms, e.g. sweating, drooling at night or erectile dysfunction
- Hyposmia (reduced sense of smell)
- Rapid-eye-movement (REM) sleep disorder
- Severe depressive illness
- Fatigue and/or mental inflexibility
- Lower back pain

The Braak theory of a spreading neurological disease is also thought to explain why cognitive impairment, caused by pathology in other brain areas, is routinely encountered in people with long-term Parkinson's disease.[2]

studies have shown that nearly all patients with Parkinson's disease eventually develop cognitive impairment and it seems likely that Parkinson's disease and Lewy body dementia represent a similar or overlapping neurodegenerative disorder.[5] However, early cognitive impairment in a patient suggests a diagnosis other than Parkinson's disease.

As Parkinson's disease advances, more widespread loss of neurons occurs, which is the likely cause of symptoms that are not controlled by the dopaminergic treatments that are used in the earlier stages of the disease.[3]

Parkinson's disease itself is not thought to be directly fatal, but falls, fractures and chest infections related to swallowing disorders increase the mortality rate in people with Parkinson's disease.

The epidemiology and genetics of Parkinson's disease

Parkinson's disease affects an estimated 1% of people aged over 65 years.[4] A General Practitioner in New Zealand can expect to have approximately three patients with Parkinson's disease per 1000 patients, although this will vary depending on practice characteristics.[6] The median age of onset is 60 years and life expectancy is on average 15 years following diagnosis.[4]

The cause of Parkinson's disease is unknown. Some rare autosomal dominant genes for Parkinson's disease have been identified, but account for only a few cases. In people diagnosed after age 60 years, there is a negligible increased risk of their children developing the condition, if there is no other family history of Parkinson's disease.[4] However, in people with Parkinson's disease, who also have an affected parent or other affected first degree relative, the likelihood of one of the rare genes for Parkinson's disease being present may be as high as 5%.[4]

Environmental toxins, e.g. industrial waste and pesticides, may be a causative factor in the development of Parkinson's disease, however, mitochondrial dysfunction, oxidative damage and abnormal protein processing have also been implicated.[7] Non-smokers are twice as likely to develop Parkinson's disease as people who smoke; it is not known why.[4]

An expert opinion is recommended for diagnosis

Diagnosing patients with Parkinson's disease is challenging and it is important that all patients suspected of having the condition are examined by an experienced Neurologist or Geriatrician before treatment is initiated.[8] A specialist second

opinion will improve the likelihood of a good outcome and provide reassurance that an alternative diagnosis does not better fit the patient's presentation.

A response to levodopa is a key criterion for the diagnosis of Parkinson's disease. Common alternative diagnoses include medicine-induced parkinsonism, essential tremor and multiple cerebral infarctions.

Managing the motor symptoms of Parkinson's disease

Although there is no cure for Parkinson's disease, patients can achieve good symptom control during the first few years of treatment, unlike in other neurodegenerative conditions. It is reasonable to expect treatment to provide functional benefit for at least ten years.[4]

Non-pharmacological treatment

A multidisciplinary approach is usually recommended in the treatment of patients with Parkinson's disease, although there is a lack of robust evidence to support the usefulness of this approach. Physiotherapists, Occupational Therapists, Speech Therapists and Nurse Specialists may all be involved in the care of a patient with Parkinson's disease, in addition to a Neurologist or a Geriatrician and a General Practitioner.

Exercise should be encouraged and formal exercise rehabilitation is likely to benefit patients with Parkinson's disease. Physiotherapists experienced in the treatment of people with Parkinson's disease may be able to provide specific interventions for overcoming disabilities such as start hesitancy, freezing of gait, festination and falls. The results of clinical trials suggest three broad physical therapy strategies may be useful:[9]

1. Strategy training, e.g. instruction with reinforcement to use longer stride length
2. Management of musculoskeletal issues, e.g. weakness and loss of range of movement
3. General promotion of physical activity with specific interventions for falls prevention

A systematic review of physiotherapy interventions in patients with Parkinson's disease found a wide-range of techniques introduced for a period of up to three months improved gait speed and balance as well as improving measures of the impact of Parkinson's disease, e.g. the Unified Parkinson's Disease Rating Scale (UPRDS).[10] There was no evidence that one particular approach was better than any other, although the quality of the comparisons was poor. A more recent review provides some inconsistent evidence that more intensive and longer duration interventions provide greater benefits.[11]

Occupational therapy may assist people with Parkinson's disease to safely maintain activity and employment. Continued activity and employment is likely to improve self-esteem as well as maintaining the patient's role within their family.[12] Patients may also be referred to occupational therapists specially trained in assessing driving performance to determine if they are medically fit to drive (see: "Driving a motor vehicle", Page 30).

Speech therapy may be appropriate; soft speech (hypophonia) is a particular problem for patients with Parkinson's disease. Voice training can improve voice quality and audibility.[3] Some speech therapists run intensive exercise programmes in which the patient focuses on increasing the volume of their speech. Speech therapists are also able to assess dysphagia in patients with Parkinson's disease which can affect speech and may also be a contributor to poor dietary intake.

Weight loss may be an issue for some people with Parkinson's disease, although it is not clear if this is part of the process of Parkinson's disease, i.e. extra energy expenditure due to tremor or rigidity, altered swallowing, changes to satiety, or due to the appetite reducing affect of dopaminergic treatment. Patients who are underweight may benefit from dietary supplements but there is little evidence of a strong effect. Some patients with Parkinson's disease experience constipation and dietary changes may alleviate this, although, pharmacological treatments are more likely to be reliable for management. However, be aware that for some patients with Parkinson's disease the timing and protein content of meals can affect levodopa absorption.

The support and shared experiences of other people of a similar age with the same condition is important. The Parkinson's New Zealand website provides information on local services and support for people diagnosed with Parkinson's disease, and their families. The fifth edition of "Parkinson's: A guide for the newly diagnosed" was published in October, 2013.

🔗 For further information visit: **www.parkinsons.org.nz**

Counselling for the patient can assist in the development of self-management techniques for anxiety and depression. Caring for a family member with Parkinson's disease can place additional strain on relationships. Counselling may help the carer and family with coping strategies. In the final stages of

Parkinson's disease palliative care and advanced care planning may be beneficial for the patient and their family.

⌔ For further information see: "End-of-life care for patients with chronic disease: the need for a paradigm shift", BPJ 40 (Nov, 2011).

Pharmacological treatment of motor symptoms

Motor symptoms in patients with Parkinson's disease typically respond well to medicines that boost dopamine function and this response is part of the diagnostic criteria for Parkinson's disease. When motor symptoms are well controlled this is referred to as the patient's "on" state; conversely periods of poor motor symptom control are referred to as "off" states. There is little evidence that treatment with either levodopa or long-acting dopamine agonists in the early phases of Parkinson's disease results in improved long-term outcomes for the patient. However, levodopa will eventually be used in the treatment of all patients. If a patient does not respond to dopaminergic treatment then alternative diagnoses, e.g. medicine-induced Parkinsonism, essential tremor or multiple cerebral infarctions, should be strongly considered. Motor fluctuations, including dyskinesias, mainly associated with

levodopa treatment develop in all patients with Parkinson's disease. These can vary in severity from a "wearing off" phenomenon, where a patient notices an increase in stiffness and slowness after a dose of medication, to very severe fluctuations between rigid-akinetic states and severe episodes of dyskinetic (involuntary) movements (see: "Motor fluctuations and levodopa", opposite).

When to start pharmacological treatment?
Treatment for Parkinson's disease should be considered once the patient reports troubling symptoms.[14] In most cases, a Neurologist or Geriatrician with experience in diagnosing Parkinson's disease will be responsible for initiating treatment. Diagnostic trials of levodopa, e.g. for a patient with functional disabilities and a strong clinical suspicion of Parkinson's disease, should generally not be considered without discussion with a Neurologist or Geriatrician. If there will be a substantial delay in the patient's referral, case-by-case management is required involving initial telephone consultation with a Neurologist or Geriatrician, and consideration of the patient's level of disability, circumstances, e.g. living alone, co-morbidities and individual preference for treatment.

Driving a motor vehicle

People with Parkinson's disease may have a reduced ability to drive before a functional disability becomes apparent, due to cognitive impairment or as an adverse effect of dopaminergic treatment, e.g. daytime sleepiness. Limb strength, accuracy of rapid foot movements and joint proprioception should be assessed.[13] If a General Practitioner is uncertain about a patient's ability to drive then referral to an Occupational Therapist trained in driving assessment will be helpful. A Parkinson's disease Nurse Specialist, a Neurologist or Geriatrician may also be consulted before a final decision is made.

Driving should always cease if there is doubt about a person's ability to control a vehicle in an emergency situation.[13] It is reasonable to assume that if a person has trouble walking then they may not be fit to drive.[13]

Levodopa with a dopa-decarboxylase inhibitor is usually first-line

Patients with motor symptoms of Parkinson's disease will benefit from dopamine treatment. However, dopamine itself does not cross the blood brain barrier easily and causes severe nausea and vomiting when given at doses high enough to have a motor effect. Levodopa, a metabolic precursor to dopamine, is able to cross the blood brain barrier and is therefore used instead. However, levodopa is rapidly metabolised to dopamine by the enzyme decarboxylase which is present in the body's periphery as well as in the brain. In order to allow sufficient levodopa to reach the brain it must be administered with a peripheral decarboxylase inhibitor. In New Zealand carbidopa or benserazide are commonly used (Table 1, Page 34) and given in fixed combination with levodopa.

In patients aged over 40 years with Parkinson's disease, combination levodopa medicines are generally the first-line treatment (see "Levodopa treatment should not be delayed in patients aged over 40 years", over page).[14] These are available in tablets, capsules, immediate release and modified release preparations, and dispersible tablets. Preparations should be swallowed whole, and not halved or broken, unless specified. Dispersible tablets shorten the onset of effect and may be useful for patients with difficulties swallowing or when rapid effect is needed, e.g. in the early morning. Adherence to levodopa treatment may be a problem for some patients due to the frequent dosing regimen, e.g. at least three times daily. A Pharmacist may be able to provide further information about which preparation is most suitable.

Over time there is often a need to increase the doses of levodopa or to add dopamine agonists or other medicines that inhibit the metabolism of dopamine. The patient's treatment should be adjusted according to the level of disability experienced in the performance of everyday activities.[14] The severity of a patient's dyskinesias will often determine the maximum dose and length of time that levodopa treatment can be tolerated.[14] Modified release levodopa does not reduce motor fluctuations related to the absorption of levodopa but may be useful for patients whose symptom control is insufficient between doses.[3]

In patients aged under 40 years with Parkinson's disease a dopamine agonist (over page) is generally the first-line treatment, rather than levodopa. This is because in these patients the likelihood of developing motor fluctuations within five years of beginning levodopa treatment is effectively 100%.[14] Levodopa monotherapy is also associated with earlier and more severe motor fluctuations compared with using dopamine agonists for initial treatment.[14]

Motor fluctuations and levodopa

The cause of motor fluctuations in patients with Parkinson's disease is unknown. In normal physiology, dopamine is stored in pre-synaptic terminals. As people with Parkinson's disease lose dopaminergic neurons the dopamine storage capacity of the brain is reduced. The length of time that levodopa doses are able to provide benefit then decreases because dopamine in the blood is metabolised more quickly than it is in synaptic terminals.[14]

In patients with more advanced Parkinson's disease, symptomatic "off" periods can begin when levodopa blood levels drop below therapeutic levels. When this occurs dosing of levodopa needs to be more frequent.[14] However, the adverse effect of more frequent levodopa dosing is the occurrence of peaks of dopamine concentration which cause dyskinesias. Altered dopamine receptor function in the corpus striatum may also cause "supersensitivity" to blood dopamine. Disabling dyskinesias may require a reduction in levodopa dosing and other dopaminergic medicines, e.g. dopamine agonists, may become more useful.[3]

Dopamine agonists are an alternative first-line treatment

Dopamine agonists, e.g. ropinirole or pramipexole (Table 1), may be considered as an alternative first-line treatment for motor symptoms in patients with Parkinson's disease, particularly in those aged under 40 years.[14] Dopamine agonists are also frequently used in combination with levodopa for patients who have not achieved adequate symptom control and may "smooth-out" motor fluctuations (see: "Motor fluctuations and levodopa", previous page).[3] Patients taking dopamine agonists may experience fewer motor complications than patients taking levodopa treatment.[3] However, compared to levodopa, dopamine agonists cause more sleepiness, oedema and hallucinations, and are reported to be associated with higher "dropout" rates in clinical trials.[16] The development of impulse control disorders, e.g. binge-eating, compulsive shopping, gambling or hypersexuality is associated with dopamine agonists, and levodopa, and these possible adverse effects should be discussed with the patient and their family. Modified release preparations of dopamine agonists are not available in New Zealand.

Ergot-derived dopamine agonists, e.g. bromocriptine and pergolide, are generally no longer prescribed for patients with Parkinson's disease due to the possibility of cardiac valvular fibrosis, pulmonary fibrosis or retroperitoneal fibrosis developing.[3] Patients who are still being treated with these medicines should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness.[17] If long-term treatment is expected lung-function tests may be helpful, or consider switching to a non-ergot derived dopamine agonist, i.e. ropinirole or pramipexole.[17]

A monoamine oxidase type B inhibitor may be appropriate for mild symptoms

Selegiline (Table 1) may be appropriate for patients with Parkinson's disease who have mild motor symptoms and early treatment with selegiline can delay the need for levodopa treatment.[17] Selegiline can be prescribed alone or in combination with a levodopa-dopa-carboxylase inhibitor combination. Selegiline inhibits the catabolism of dopamine and may also be combined with levodopa treatment to reduce

Levodopa treatment should not be delayed in patients aged over 40 years

Patients aged over 40 years should be considered for levodopa treatment as soon as they display significant symptoms.[14] Historically there was a concern that early treatment with levodopa resulted in patients developing premature dyskinesias.[14] This idea was supported by two observations. Firstly, as many as 90% of patients treated with levodopa for ten years develop dyskinesias.[14] Secondly, the younger the age of onset of Parkinson's disease, the more likely it is that dyskinesia will occur.[14] However, the benefit of levodopa treatment is greatest earlier in the course of Parkinson's disease.[14] An Australian study of 149 people with Parkinson's disease found that at fifteen-year follow-up there was no difference in outcomes for motor complications and mortality for patients whose treatment was initiated with either dopamine agonists or levodopa.[15]

Conversely, in patients aged under 40 years, treatment with levodopa is delayed and initiated when symptoms become more severe.[14]
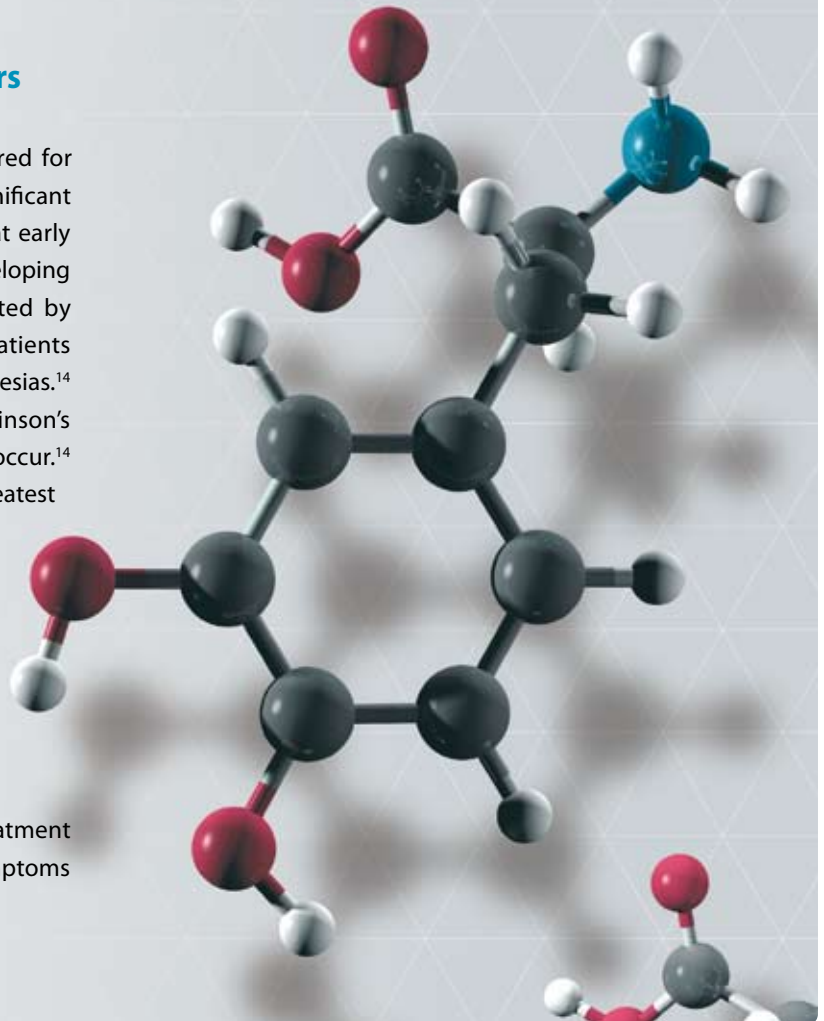
symptoms in patients with advanced Parkinson's disease. However, in patients who have postural hypotension selegiline together with levodopa should be avoided or used with extreme caution.[17] Currently there are issues surrounding the supply of selegiline and therefore this medicine is unapproved by Medsafe in New Zealand, although this is likely to change in the near future.

Amantadine can be used to treat dyskinesia
Amantadine (Table 1) is a weak dopamine agonist and is a possible treatment option for people with early onset Parkinson's disease, but should not be considered as a first-line treatment.[8] Amantadine may be used in conjunction with other treatment, usually levodopa, to control dyskinesias once patients have begun to display motor fluctuations.[8] The effect of amantadine is thought to be modest and to last less than eight months.[16] However, a recent trial suggests that amantadine may help control dyskinesias for several years.[18]

Catechol-O-methyltransferase inhibitors may be added later in treatment
When patients with advanced Parkinson's disease begin to experience "end-of-dose" deterioration that cannot be stabilised by adjusting the regimen of current medicines, catechol-O-methyltransferase (COMT) inhibitors, i.e. entacapone and tolcapone (Table 1), may be used as adjunctive treatment with levodopa and dopa-decarboxylase inhibitors. COMT inhibitors, like dopa-decarboxylase inhibitors, prevent the peripheral conversion of levodopa to dopamine.

Antimuscarinic medicines are less effective than dopaminergic treatments
Antimuscarinic medicines, e.g. benztropine, procyclidine and orphenadrine hydrochloride, reduce medicine-induced Parkinsonian symptoms in patients being treated with antipsychotics, but are generally not used in patients with Parkinson's disease.[17] However, benztropine may be considered for the treatment of levodopa-resistant tremor in younger patients.[3] Antimuscarinic medicines are poorly tolerated by older patients and are associated with cognitive impairment and sedation.[3] Tardive (slow onset) dyskinesia is not improved by this treatment and may be worsened.[17]

Alternative treatments are not supported by evidence
There is no robust evidence that any herbal medicine or supplement is effective in the treatment of patients with Parkinson's disease.[16] In particular, vitamin E should not be used as a neuroprotective agent as there is good evidence that it does not slow the progression of Parkinson's disease.[16]

Managing the non-motor symptoms of Parkinson's disease

Patients with Parkinson's disease may display autonomic dysfunction, psychiatric symptoms and cognitive impairment (Table 2, Page 36). These non-motor symptoms are a substantial component of Parkinson's disease morbidity. Some non-motor symptoms can be associated with the patient's "off" state and optimisation of dopaminergic treatment may provide symptom relief. Therefore attempting to increase "on" time should be considered first in the management of non-motor symptoms. For example, musculoskeletal and visceral pain, is experienced by over 80% of patients with Parkinson's disease and can be associated with "off" states.[3]

Treatment of non-motor symptoms may involve additional medicines

Parkinson's disease involves pathology beyond the nigrostriatal connections of the brain, therefore many of the non-motor symptoms of Parkinson's disease do not respond to dopaminergic medicines and other treatment options may be necessary. Autonomic dysfunction resulting in orthostatic hypotension, erectile dysfunction, urinary incontinence and constipation is present in most patients with advanced Parkinson's disease (Table 2). Discussion with other members of the multidisciplinary team is recommended to provide individualised treatment plans.

Patients with Parkinson's disease usually experience a gradual worsening of motor and non-motor symptoms. If a patient's condition suddenly deteriorates then adherence to treatment and other potential causes, e.g. urinary tract infection, should be investigated. If a patient displays unstable non-motor symptoms despite regular treatment then referral to a Neurologist or Geriatrician is recommended.

Table 1: Treatment of motor symptoms associated with Parkinson's disease[17]

Medicine	Treatment	Adverse effects
Levodopa with a dopa-decarboxylase inhibitor		
Note: The dose of dopa-decarboxylase inhibitor needs to be sufficient to inhibit extracerebral conversion of levodopa to dopamine, e.g. carbidopa 70 to 100 mg daily, which can cause nausea and vomiting due to dopamine stimulation of chemoreceptors. Combination formulations of levodopa with carbidopa or benserazide are designed to provide adequate enzyme inhibition, with minimal extra adverse effects. The relative amount of carbidopa:levodopa is 1:4 or 1:10; for benserazide:levodopa the relative amount in formulations is 1:4.		
Levodopa with carbidopa i.e. Sinemet (100 mg + 25 mg, 250 mg + 25 mg), Sindopa (100 mg + 25 mg), Sinemet CR modified release (200 mg + 50 mg), Kinson (100 mg + 25 mg, unfunded)	Initiated at 100 mg levodopa (with 25 mg carbidopa), three times daily, e.g. 6 am, 12 pm and 6 pm.[3] Can be increased by 100 mg, daily, or on alternate days, according to the patient's response and tolerance, up to 800 mg levodopa (with carbidopa 200 mg, i.e. eight tablets of 100 mg/25 mg each), daily, in divided doses. If higher doses of levodopa are required, and tolerated, a 250 mg levodopa (with carbidopa 25 mg) tablet is used. Levodopa can then be increased by 250 mg, daily or on alternate days, to a maximum of 2 g levodopa (with 200 mg carbidopa, i.e. ten tablets of 200 mg/25 mg each).	Dyskinesias, if severe, may be managed by reducing the levodopa dose and adding a dopamine agonist to "smooth out" motor fluctuations. Both forms of levodopa are contraindicated in patients who have taken a non-selective monoamine oxidase inhibitor (MAOI) within 14 days, or in patients with a history of angle closure glaucoma. When levodopa treatment is initiated, taking the medicine with food may reduce nausea, however, the presence of food and protein in the gut can reduce levodopa absorption. Low protein meals, e.g. fruit and bread, may improve levodopa absorption. Once Parkinson's disease has advanced, taking medicine 30 minutes before food may further improve absorption and produce a greater therapeutic response. Levodopa may cause dizziness or sudden onset of sleep making driving dangerous. Benign discolouration of urine may occur. Abrupt withdrawal should be avoided due to the risk of neuroleptic malignant syndrome.
Levodopa with benserazide i.e. Madopar (50 mg + 12.5 mg, 100 mg + 25 mg, 200 mg + 50 mg), Madopar Rapid dispersible (50 mg + 12.5 mg), Madopar HBS modified release (100 mg + 25 mg)	Initiated at 50 mg levodopa, three to four times daily, with or just after food, or 100 mg, three times daily, in patients with more advanced Parkinson's disease. Doses of levodopa can be increased by 100 mg (with 25 mg beserazide), daily, once or twice weekly, according to the patient's response. Older patients may be started on a reduced dose of 50 mg, once or twice daily, increased by 50 mg, daily, once or twice weekly, according to the patient's response. The usual maintenance dose of levodopa is 400 – 800 mg (with benserazide 100 – 200 mg), daily, in divided doses.	
Dopamine agonists		
Ropinirole	Initiated at 250 micrograms ropinirole, three times daily, with or just after food. Daily doses are increased by 250 micrograms, three times daily, at weekly intervals, up to 3 mg daily. Doses can be further increased according to the patient's response. Maintenance doses are often 9 – 16 mg, daily, but higher doses to a maximum of 24 mg daily, may be required if ropinirole is taken with levodopa.	Adverse effects include nausea (common) or vomiting, postural hypotension, excessive sleeping, impulse control disorders, cognitive symptoms and hallucinations. Monitor blood pressure when initiating dopamine agonists. This medicine may cause dizziness or sudden onset of sleep making driving dangerous.
Pramipexole	Initiated at 125 micrograms pramipexole, three times daily, with the dose doubled every five to seven days, if tolerated, to 500 micrograms, three times daily. Doses can be further increased by 250 micrograms, three times daily, at weekly intervals, to a maximum of 1.5 mg, three times daily.	Doses of pramipexole should be reduced in patients with renal impairment (see: NZF for further details). This medicine may cause dizziness or sudden onset of sleep making driving dangerous.

Medicine	Treatment	Adverse effects
Monoamine oxidase type B inhibitors (MAOBI)		
Selegiline (currently a section 29, unapproved medicine)	Initiated at 5 mg selegiline, in the morning, increasing after two to four weeks, if tolerated, to 10 mg in the morning, or 5 mg in the morning and 5 mg at midday. Selegiline can be used alone or as an adjunct to a levodopa/dopa-decarboxylase inhibitor. When used in combination the dose of levodopa may need to be decreased.	Selegiline is contraindicated in patients with active peptic ulcers, other extrapyramidal disorders, severe psychosis or dementia. Patients may experience gastrointestinal effects, e.g. nausea, constipation, diarrhoea, or cardiovascular adverse effects, e.g. bradycardia, hypo- or hypertension.
Catechol-O-methyltransferase inhibitors		
Entacapone	Initiated at 200 mg entacapone, taken with each dose of levodopa/dopa-decarboxylase inhibitor, to a maximum of 2 g, daily. Levodopa doses may need to be reduced by 10 – 30% when prescribed with entacapone. Iron or calcium supplements or indigestion remedies should not be taken within two hours of taking entacapone.	Entacapone and tolcapone are contraindicated in patients with phaeochromocytoma, or a history of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis. Tolcapone is also contraindicated in patients with evidence of liver disease, increased liver enzymes or severe dyskinesia. These medicines may cause dizziness or sudden onset of sleep making driving dangerous. Patients should be advised to seek medical attention if they experience symptoms suggestive of liver toxicity, e.g. nausea, abdominal pain and pruritus or rhabdomyolysis, e.g. muscle pain. Benign discolouration of the urine may occur when taking these medicines which may require investigation, e.g. creatine kinase, to differentiate this from more serious adverse effects.
Tolcapone	Initiated at 100 mg tolcapone, three times daily. The first dose is taken at the same time as levodopa, with six hours between doses. The maximum dose of tolcapone is 200 mg, three times daily, which would only be prescribed to patients with severe symptoms.	
Dopamine modulating		
Amantadine	Initiated at 100 mg, once daily with food, increased after one week to 100 mg, twice daily, usually in conjunction with another treatment, e.g. levodopa. Some patients may require higher doses, to a maximum of 400 mg, daily. Patients aged over 65 years should be started at 100 mg, daily, adjusted according to the patient's response.	Amantadine is contraindicated in patients with a history of epilepsy or gastric ulceration or in patients who are pregnant. Amantadine may affect driving and other skilled tasks.

Table 2: Treatment of non-motor symptoms and complications of Parkinson's disease[3, 4, 16, 17]

Symptom	First-line	Additional pharmacological treatment
	First consider optimising dopaminergic treatment and non-pharmacological treatment	Note: treatment options include some "off-label" uses of medicines
Cardiovascular ■ Postural and postprandial hypotension	Patients can increase fluid and salt intake, eat frequent small meals to reduce postprandial hypotension and wear compression stockings that extend to above the knee. Any antihypertensive medicines should be taken with caution.	Fludrocortisone acetate, 50 micrograms, daily, increasing to 200 micrograms, daily, as needed, may be useful for patients with hypotension following discussion with a hospital specialist.
Gastrointestinal ■ Drooling (sialorrhoea) ■ Dysphagia ■ Gastroparesis, e.g. nausea, bloating, pain ■ Constipation	Drooling is reported by patients to be the most socially embarrassing symptom.[19] This is thought to be due to patients swallowing less often rather than over-secretion of saliva.[19] Dopaminergic or antimuscarinic medicines may reduce drooling, however, antimuscarinic medicines usually cause adverse effects. Dysphagia may be partially responsive to optimised dopaminergic treatment. Thickened fluids reduce the risk of aspiration occurring and are easier for patients to swallow than solid food. Speech therapy may assist patients with dysphagia. Patients with nausea can be advised to eat frequent small meals and try to improve posture while eating. Patients with constipation can increase fluid and fibre and avoid antimuscarinics, before beginning treatment with a laxative.	Drooling can be treated with 1% atropine eye drops, administered sublingually. Radiotherapy may also be useful for some patients. Gastroparesis may be alleviated in some patients with domperidone (a dopamine antagonist that does not cross the blood brain barrier), 10 – 20 mg, three to four times daily; maximum 80 mg, daily. For constipation, laxatives can be initiated for patients following dietary advice, e.g. bisacodyl (10 mg – a stimulant), glycerol suppositories (3.6 g – a softener), in the morning, or docusate sodium, 100 – 150 mg, twice daily, or 240 mg at night, up to 480 mg, daily, in divided doses. Docusate sodium with sennoside B is also available but should not be taken for prolonged periods.
Pain	First establish if the pain is present during "on" or "off" states, to decide whether adjusting dopaminergic treatment may provide benefit. Musculoskeletal pain can be caused by restricted movement or muscle spasm and patients may experience symptom relief following physiotherapy. Peripheral pain can be managed with mild analgesics, e.g. paracetamol, and physiotherapy.	Chronic neuropathic pain can be treated with: • Nortriptyline or amitriptyline, 10 – 75 mg, once daily • Carbamazepine, 100 mg, once or twice daily, increased gradually according to response, usually to 200 mg, three or four times daily • Gabapentin is available under Special Authority for patients with neuropathic pain, where the patient has tried and failed, or has been unable to tolerate treatment with a tricyclic antidepressant. Gabapentin is initiated at 300 mg, once daily, and titrated in 300 mg steps, to a maximum of 3.6 g, in three divided doses

Symptom	First-line	Additional pharmacological treatment
Cognitive ■ Anxiety ■ Depression ■ Hallucinations ■ Dementia	Patients who experience "off" state anxiety may benefit from increased dopaminergic treatment. Assess the patient for pain or sleep disturbances which may contribute to depression. Referring patients for counselling is recommended. Patients with non-troubling hallucinations do not require treatment, however, if the patient is distressed medicines may need to be adjusted. Patients with dementia should be evaluated for other causes and consideration given to withdrawing anticholinergic or dopaminergic medicines.	Tricyclic antidepressants or selective serotonin inhibitors may be appropriate for patients with depression in addition to support and counselling. Quetiapine may be used with extreme caution, at low doses, in consultation with a Geriatrician or Neurologist to treat patients with psychosis. Other antipsychotics should not be considered for initiation in primary care due to an association with extrapyramidal symptoms. Olanzapine and typical antipsychotics, e.g. haloperidol, can worsen motor symptoms. Clozapine may be a treatment option that is suggested by a hospital specialist, but this requires weekly full blood count monitoring.
Genitourinary ■ Urgency and frequency ■ Nocturia ■ Incontinence	Patients can avoid diuretics, e.g. caffeine containing drinks. Before beginning pharmacological treatment a post-void bladder scan will exclude retention as a cause. For further information see: "Urinary incontinence in adults", BPJ 55 (Oct, 2013).	Oxybutynin should be used with caution in older patients, but can be initiated at 5 mg, two to three times daily.[3] Tolterodine is available under Special Authority for patients who have an overactive bladder and a documented intolerance of, or are non-responsive to, oxybutynin Treatment is initiated at 2 mg, twice daily. This can be reduced to 1 mg, twice daily, to reduce adverse effects. Treatment should be reviewed after six months. Nocturia can be treated with desmopressin.
Sleep ■ Excessive daytime sleepiness ■ REM sleep disorder ■ Restless legs syndrome	Fatigue is experienced by one-third of patients with Parkinson's disease, but is less common in patients taking levodopa compared to dopamine agonists.[16] For patients with daytime sleepiness sleep hygiene and other causes of altered sleep patterns should be assessed, e.g. depression, nocturia. A reduction in dopaminergic treatment, if possible, may reduce daytime sleepiness. Amantadine or selegiline for motor symptoms may also benefit patients with fatigue/daytime sleepiness. Nocturnal doses of a dopaminergic medicine may assist with insomnia. Levodopa and dopamine agonists may help patients with restless leg syndrome. For further information see: "The night time hustle: managing restless legs syndrome in adults", BPJ 49 (Dec, 2012).	Methylphenidate, 10 mg, three times daily, may be useful in treating patient fatigue.[20] A benzodiazepine may be effective for patients with REM sleep disorder, e.g. clonazepam, 1 mg, daily. For further information see: "Sleep disturbances: managing parasomnias in general practice", BPJ 48 (Nov, 2012).

Treatments for patients with advanced Parkinson's disease

As patients with Parkinson's disease develop motor fluctuations and the effectiveness of standard treatments diminishes, more invasive treatments may be recommended by a Neurologist.

Subcutaneous apomorphine, a non-selective dopamine agonist, can be used either intermittently for motor symptom control, or as a continuous subcutaneous infusion.[3] Apomorphine has the same potential to cause adverse effects as other dopamine agonists and may cause vomiting, injection site reactions and skin nodules.[3]

Deep brain stimulation is a reversible surgical procedure in which an area of the brain receives continuous electrical stimulation from an implanted battery, operated with an external controller. This may be appropriate for patients with Parkinson's disease who have motor fluctuations or tremor that does not respond to medication and for patients with adverse effects to medication.[21] Complication rates are highly variable and infection is the most frequently reported adverse effect.[21] It may take three to six months for deep brain stimulation to produce optimal results but tremor and dyskinesias are able to be reduced for five years or longer.[21]

Stereotactic lesion surgery involves ablating an area of the brain in order to control tremor or dyskinesias.

Stem cells taken from human embryonic tissue or transformed from adult tissue may, in the future, be able to replace dopaminergic neurons in patients with Parkinson's disease. There have been a number of international clinical trials involving foetal cell transplantation, the first of which began in 1987 and so far approximately 400 patients have been involved.[22] The results have been variable but some patients continued to experience significant improvements in symptoms several years after treatment. However, there are currently no treatments using stem cells available for patients with Parkinson's disease in New Zealand.

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