Current concepts in the management of Parkinson disease

Michael W Hayes, Victor S Fung, Thomas E Kimber and John D O'Sullivan

ABSTRACT

- Parkinson disease (PD) is a multisystem neurodegenerative disorder that affects about 1% of the population over the age of 55 years and has mean age of onset of about 60 years.
- The Braak hypothesis proposes that the earliest pathological evidence of PD is found in the enteric nervous system, medulla and olfactory bulb, and only subsequently progresses (over years) to the substantia nigra and cortex.
- Non-motor symptoms, such as constipation, hyposmia and sleep disorders, may precede typical motor features of PD by several years.
- No treatment has been convincingly shown to slow PD progression (ie, a neuroprotective drug remains elusive).
- Symptomatic benefit from dopaminergic therapy is usually maintained throughout the course of the disease.
- The decision as to whether to commence treatment with either levodopa or a dopamine agonist needs to be individually tailored, but long-term outcomes appear to be equivalent.
- Advanced PD is complicated by the loss of non-dopaminergic neurones, resulting in symptoms that are largely unresponsive to dopaminergic therapy.
- Treatment with apomorphine, Duodopa or deep-brain stimulation surgery may be beneficial for selected patients with advanced PD.
- Non-motor symptoms, such as mood disorders, cognitive impairment, autonomic dysfunction and sleep disorders, are responsible for significant morbidity. Management often requires a multidisciplinary approach.

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Parkinson disease (PD) is a heterogeneous multisystem neurodegenerative disorder with a selective vulnerability of dopaminergic neurones.[1] It is a common condition, affecting about 1% of the population aged over 55 years. An estimated 60 000 Australians have PD, and about 10% of cases are diagnosed in people under the age of 50 years. The total economic cost of PD in Australia was estimated to be $6.8 billion in 2005.[2]

Recent advances in molecular biology have increased our understanding of pathogenesis. The discovery, in 1997, of an alpha-synuclein gene mutation in familial PD[3] provided a "proof of principle" of a genetic contribution to PD, as it turned out that the encoded protein was a major component of the Lewy body, a pathological hallmark of PD.[4] Although abnormal cellular protein aggregation and misfolding are common precursors to neuronal death, the function of the six identified familial PD genes indicates that this process may result from a wide range of cellular disorders.[5] The cause of the much commoner sporadic or idiopathic PD is even less clear, but there is evidence that some monogenic variants or polymorphisms may represent susceptibility genes, conferring increased risk of PD. Many environmental risk factors for PD have been proposed, but epidemiological evidence suggests that the effects are relatively small.[6]

Detailed postmortem studies support the hypothesis of Braak and colleagues that the earliest pathological evidence of PD, as defined by the presence of Lewy bodies, starts in the enteric (gut) nervous system, medulla and olfactory bulb and spreads transneuronally to the midbrain (substantia nigra) and then the cortex.[7] This may explain why non-motor symptoms of PD, such as constipation, hyposmia and rapid-eye-movement sleep disorder, often precede the typical motor symptoms by several years and why cognitive impairment is nearly always found in people with longstanding PD.[8] Advancing PD is further complicated by the loss of non-dopaminergic neurones, contributing to disturbances of gait, posture, autonomic function, speech, cognitive function and sleep that may become unresponsive to dopamine.[1] These developments underscore the difficulty of providing effective pharmacotherapy for patients with advanced PD and imply that dopamine replacement alone is ultimately inadequate.

Clinical features

Dopamine loss in the substantia nigra, which serves to modify motor control, results in the recognisable core signs of asymmetrical bradykinesia and hypokinesia (slowness and reduced amplitude of movement), muscle rigidity (stiffness) and rest tremor. Rest tremor, prominent asymmetry and a good response to levodopa (LD) are the features that most accurately predict PD pathology.[9] The tremor-dominant form of PD tends to run a more benign course than typical PD. Early falls or autonomic symptoms and a questionable response to LD should raise doubts about the diagnosis (Box 1).[10] Drug-induced parkinsonism due to commonly prescribed dopamine-blocking medications, such as antipsychotics (eg, haloperidol, risperidone) and antiemetics (eg, metoclopramide, prochlorperazine), should be excluded. Functional imaging of the dopaminergic system using cerebral single photon emission computed tomography or positron emission tomography can be useful in diagnosis of early or atypical PD (Box 2), but is unavailable in Australia. Positron emission tomography studies examining the rate of decline in dopamine-producing cells suggest that humans have already lost 50%–70% of their nigral neurones before they develop motor symptoms,[11] and it has been estimated that the duration of this "presymptomatic" phase is

Abbreviations

DA	Dopamine agonist
DBS	Deep brain stimulation
DDI	Dopa-decarboxylase inhibitor
LD	Levodopa
MAO-B	Monoamine oxidase type B
PBS	Pharmaceutical Benefits Scheme
PD	Parkinson disease

about 5 years (Box 3). Early diagnosis will become a critical issue if effective neuroprotective drugs become available.

Treatment principles in early Parkinson disease

The early management of PD is based on the following principles:

- The main aim of treatment is to preserve quality of life, which can be adversely affected by motor or non-motor symptoms;
- There are many effective symptomatic treatments for PD;
- No treatment has been convincingly shown to slow or hasten disease progression;[13] and
- A symptomatic response to dopaminergic therapy is usually maintained throughout the disease.

Note that the levels of evidence referred to here are determined by the American Academy of Neurology and the European Federation of Neurological Societies (A = established as effective, B = probably effective, C = possibly effective) (Box 4).[10,14,15,17,18]

1 Features *not* typical of primary or idiopathic Parkinson disease (PD)[10]

- Acute onset
- Rapid progression
- Early falls
- Poor response to levodopa*
- Symmetrical clinical signs
- Early autonomic symptoms
- Vertical gaze palsy
- Early cognitive impairment

* Of the cardinal features of PD, tremor is normally the least responsive to levodopa. ◆

2 Clinical hallmarks of some atypical parkinsonian syndromes

Progressive supranuclear palsy

- Early falls
- Axial rigidity
- Supranuclear gaze palsy
- Blepharospasm
- Frontalis muscle overactivity ("startled" appearance)
- Usually symmetrical limb signs
- No response or poor response to levodopa

Multiple system atrophy

- Prominent dystonia
- Antecollis (dropped neck)
- Urinary incontinence
- Orthostatic hypotension
- Variable response to levodopa

Corticobasal degeneration

- Markedly asymmetrical limb onset (usually beginning in arm)
- Progressive limb rigidity
- Focal cortical deficits, typically apraxia and/or speech and cognition deficits
- Alien limb syndrome
- Myoclonus (brief, jerky movements, predominantly of the limbs) ◆

Treatment of motor symptoms in early Parkinson disease

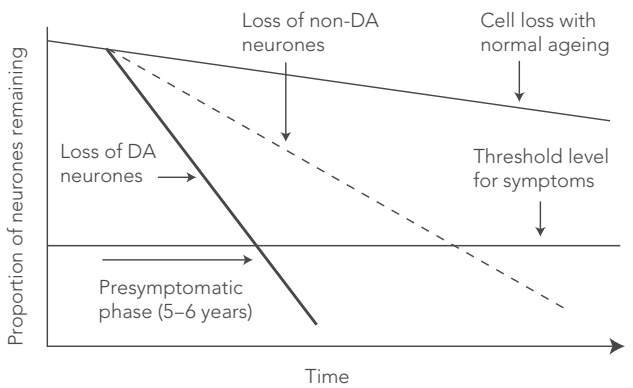
Although PD is a progressive disorder, deterioration is typically very slow, with considerable individual variability. Satisfaction with the explanation of the diagnosis has been shown to have a favourable impact on the quality of life of people with PD in the long term.[19] The time to commence drug treatment for motor symptoms is when they are causing physical or psychological disability. It is a misconception that PD treatment is only effective for a limited time and should be deferred for as long as possible to reserve that benefit. Most movement disorder specialists also believe that physical therapy is important, although there is limited evidence to support this.[20]

Levodopa versus a dopamine agonist as first-line therapy

LD combined with a dopa-decarboxylase inhibitor (LD/DDI) remains the most potent drug therapy for reversing motor impairment (Level A). Despite its short half-life of about 90 minutes, dosing with LD/DDI three times daily usually provides a stable response without symptom fluctuations in early PD. At this stage, LD has a long-duration (pharmacodynamic) effect in the brain that is independent of plasma levels. A higher maintenance dose of LD (eg, 200 mg three times daily compared with an initial dose of 100 mg three times daily) provides slightly greater benefit for reducing motor symptoms, but at the cost of earlier wearing-off symptoms and dyskinesias (see below).

Initiating treatment with a dopamine agonist (DA) (a synthetic dopamine receptor agonist with a longer plasma half-life than LD/DDI) reduces the risk of dyskinesias and wearing-off fluctuations in the first few years of therapy (Level A evidence for cabergoline and pramipexole; Level B for pergolide and bromocriptine).

3 Loss of neurones with progression of Parkinson disease (PD)*



DA = dopaminergic. * This conceptual figure assumes that loss of DA and non-DA neurones begins at the same time. However, there is evidence of selective vulnerability of DA neurones in PD, and hence more rapid loss of these cells and a predominance of DA symptoms (eg, motor impairment) in early PD. Neuroprotective or restorative treatments aimed at DA neurone loss alone are unlikely to have much impact on non-DA symptoms (eg, cognitive impairment), which tend to predominate in advanced PD. Neuroprotective strategies targeting primary neurodegenerative mechanisms as well as vulnerable DA neurones may be required. (Figure adapted, with permission, from Lang.[12]) ◆

However, DAs are less potent than LD for ameliorating motor symptoms, and most people require the addition of LD/DDI within 2 years. At that stage, there is still a rationale for ongoing combination therapy, as DAs may serve as an LD dose-sparing agent as well as offering pharmacokinetic advantages. Rotigotine, a non-ergoline (non-ergot-derived) DA delivered by transdermal

4 Pharmacological and non-pharmacological treatments for Parkinson disease (PD): regulatory status and evidence for use

Treatment	Drug type	Side effects	TGA status*	PBS status	EFNS (i) (symptomatic PD)†	EFNS (ii) (delay motor symptoms)†	EFNS (iii) (reduce off time)†	AAN (reduce off time)‡
Drugs								
LD/DDI combination	LD	GI effects, hypotension	Yes	General	A			
Slow-release LD/DDI combination	LD	GI effects, hypotension	Yes	General (Madopar HBS); Authority (Sinemet CR)	A	A (ineffective)	C	C (no benefit over LD/DDI)
Entacapone	LD + COMT	GI effects, discoloured urine	Yes	Authority			A	A
Duodopa	LD (infusion)	Device-related GI effects	Yes	Not approved			B	
Bromocriptine	Ergoline DA	Fibrosis, effusions	Yes	Restricted	B	B	B	
Cabergoline	Ergoline DA	Fibrosis, including valvular	Yes	Restricted	B	A	B	C
Pergolide	Ergoline DA	Fibrosis, including valvular	Yes	Restricted	A	B	A	B
Pramipexole	Non-ergoline DA	GI effects, somnolence, oedema	Yes	Restricted	A	A	A	B
Ropinirole	Non-ergoline DA	GI effects, somnolence, oedema	Yes	Not approved for PD	A	A	A	B
Apomorphine	Non-ergoline DA	Skin nodules, sedation	Yes	S100			A (penject), C (pump)	C
Rotigotine	Non-ergoline DA	GI effects, somnolence, oedema	Yes	Not approved				
Amantadine	NMDA antagonist	Cognitive effects, oedema	Yes	Restricted	B		A (less dyskinesia)	C (less dyskinesia)
Selegiline	MAO-B inhibitor	Cognitive and psychiatric effects	Yes	Restricted	A	A (ineffective)		C
Rasagiline	MAO-B inhibitor	Cognitive effects, insomnia	No	Not approved	A		A	A
Benztropine	Anticholinergic	GI and cognitive effects	Yes	General	B			
Other treatments								
Physical therapy					B			C (symptomatic benefit)
Speech therapy					C			C (symptomatic benefit)
DBS		Surgery risks, cognitive effects	Yes	na			B	C (motor complications)

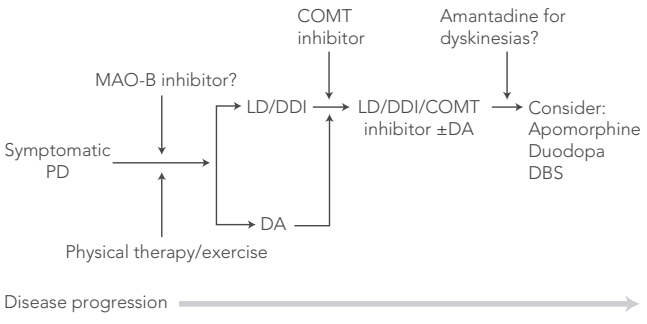
AAN = American Academy of Neurology. COMT = catechol-O-methyltransferase. DA = dopamine agonist. DBS = deep brain stimulation. DDI = dopa-decarboxylase inhibitor. EFNS = European Federation of Neurological Societies. GI = gastrointestinal. LD = levodopa. MAO-B = monoamine oxidase type B. na = not applicable. NMDA = N-methyl-D-aspartate. PBS = Pharmaceutical Benefits Scheme. TGA = Therapeutic Goods Administration.

* TGA status "yes" means that drug is approved for use in Australia. † Levels of evidence for medications/therapies used to (i) treat symptomatic PD, (ii) delay the onset of motor complications, and (iii) reduce off time (ie, periods of time when PD symptoms are not adequately controlled), determined by the EFNS and the Movement Disorder Society — European section.[14,15] The EFNS ratings classification[16] is similar to that of the AAN, though less stringent. ‡ Levels of evidence for medications/therapies used to reduce off time, determined by the AAN.[10,17,18] The level of evidence is graded A, B or C based on the quality of clinical trial data (Class I-IV): A = established as effective, B = probably effective, C = possibly effective. ◆

24-hour patch, is available in Australia but is not yet funded by the Pharmaceutical Benefits Scheme (PBS). Its efficacy is similar to that of oral DAs.

All dopaminergic medications can cause nausea, gastrointestinal symptoms, hypotension, drowsiness, cognitive symptoms and impulse control disorders (see below), but these are more common with DAs than LD/DDIs. The ergoline DAs can also cause clinically significant fibrosis (cardiac valvular, pleuropulmonary and retroperitoneal), a problem avoided by the newer, non-ergoline DAs (Box 4). There is no distinctive difference between the DAs in clinical efficacy. In general, there is a trend towards initiating treatment with a DA in people with earlier-onset PD and using LD/DDI as first choice in people with later-onset PD (Box 5). Two studies comparing long-term outcomes (> 10 years) in patients initially treated with either DA or LD/DDI failed to identify any ultimate advantage of one strategy over the other.[21,22]

5 Suggested treatment algorithm for Parkinson disease (PD)



COMT = catechol-O-methyltransferase. DA = dopamine agonist. DBS = deep brain stimulation. DDI = dopa-decarboxylase inhibitor. LD = levodopa. MAO-B = monoamine oxidase type B. ◆

Disease-modifying therapy

No treatment has been proven unequivocally to slow disease progression in PD. There has been renewed interest in the role of monoamine oxidase type B (MAO-B) inhibitors (eg, selegiline), which inhibit catabolism of dopamine. A recent study using a more potent MAO-B inhibitor, rasagiline (not available in Australia), in previously untreated PD patients suggested a small, sustained benefit in patients who began treatment earlier compared with those who started the drug 9 months later.[23] Several earlier studies of MAO-B inhibitors, also using delayed-start protocols, had shown similar modest effects, but interpretation of these findings is controversial. The hypothesis that early treatment, regardless of which agent is used, may delay subsequent irreversible compensatory mechanisms in the basal ganglia is of current interest.[24]

Later treatment of Parkinson disease

Fluctuations and dyskinesias — pathogenesis

Motor fluctuations and dyskinesias are believed to be caused by progressive loss of striatal dopamine storage capacity and the pulsatile fashion in which LD is administered.[25] Fluctuations in the motor response to LD usually emerge after several years of treatment.[26] The patient may notice a decline in motor benefit several hours after the last dose of LD has been taken ("end-of-dose deterioration" or "wearing-off phenomenon"). Choreiform involuntary movements commonly emerge within 1–2 hours after LD intake (peak-dose dyskinesias). Later, dyskinesias may also occur at the onset and offset of motor benefit (diphasic dyskinesias).

Fluctuations and dyskinesias — management

Wearing-off symptoms are usually managed by combining LD with additional dopaminergic medication, such as a catechol-O-methyltransferase inhibitor (entacapone) (Level A), a DA (Level A), or an MAO-B inhibitor (selegiline) (Level C). Slow-release LD preparations (eg, Sinemet CR [Merck Sharp and Dohme, Sydney, NSW] and Madopar HBS [Roche, Sydney, NSW]) may be useful at bedtime to relieve nocturnal akinesia and early morning dystonia, but are hampered during the day by unpredictable gut absorption. Fractionating the daily LD dose into smaller, more frequent doses and administering liquid LD/DDI formulations (eg, Madopar Rapid [Roche, Sydney, NSW]) may hasten absorption and reduce "off" time (ie, periods of time when PD symptoms are not adequately controlled) (Level C). As amino acids compete with LD for transfer across the blood–brain barrier, separating the times of dietary protein and LD intake may improve drug effectiveness. Amantadine (100–300 mg daily) can help to suppress peak-dose dyskinesias (Level C).

For most patients with PD, motor fluctuations and dyskinesias are not disabling and can be adequately managed by manipulating the oral drug regimen. However, some patients with PD (particularly those with early-onset disease) develop severe motor fluctuations and dyskinesias, and alternative routes of medication delivery or surgical treatment may be considered. There is experimental and clinical evidence that motor fluctuations can be reduced with the use of continuous administration of dopaminergic medication.[27] Apomorphine is an injectable DA that is administered either as intermittent subcutaneous bolus injections or by subcutaneous infusion. Apomorphine treatment produces a reduction in daily off time of about 50%,[28,29] and long-term benefit can be maintained in some patients.[28] However, side effects, including skin nodules, can be problematic.

More stable plasma levels of LD, and a corresponding reduction in motor fluctuations, can be achieved by delivering LD/DDI directly into the jejunum via percutaneous gastrostomy.[30] A concentrated gel form of LD–carbidopa (Duodopa [Solvay Pharmaceuticals, Hannover, Germany]) has been developed for this purpose and successfully trialled in Europe.[31] Duodopa has been approved by the Therapeutic Goods Administration in Australia, but is expensive and not PBS-funded. Patients receiving apomorphine and Duodopa need to be managed in specialist clinics by an experienced multidisciplinary team.

Neurosurgical treatments for PD have gained increasing importance in recent years. Lesioning (eg, pallidotomy and thalamotomy) has largely been superseded by deep brain stimulation (DBS) surgery. This technique involves subcutaneous implantation of a pulse generator or pacemaker(s) below the clavicle (usually bilaterally), with a connecting lead and electrodes that are stereotactically placed in the targeted brain site(s). In appropriately selected patients with advanced PD, DBS of the subthalamic nucleus or globus pallidus interna significantly reduces off-time motor symptoms, reduces dyskinesias and improves quality of life (Level B, although there is sufficient recent evidence for Level A).[32-35] The

beneficial effects of DBS on certain motor symptoms (such as tremor, bradykinesia and dyskinesias) appear to be long-lasting.[32] However, other symptoms, including gait dysfunction and falls, do not necessarily improve after DBS and may even worsen.[35] Appropriate patient selection for DBS is critical, and Australian consensus guidelines have been recently published.[36]

Non-motor symptoms

A variety of non-motor features can contribute significantly to morbidity and may be resistant to, and even aggravated by, standard dopaminergic therapy. The tendency for dopaminergic therapy to aggravate orthostatic hypotension and visual hallucinations in advancing PD creates a common management dilemma. Disturbances of sensation (including pain perception and olfaction), autonomic function, sleep, mood, behaviour and cognition occur frequently, and are difficult to manage.

Autonomic dysfunction

Orthostatic hypotension, constipation, and disturbance of bladder function, erectile function and sweating occur frequently in PD. Although constipation can be an early feature of PD, prominent dysautonomia early in the course of parkinsonism raises the possibility of multiple system atrophy (Box 1). Management involves drug treatment and non-pharmacological strategies, but these have not been subjected to large clinical trials, particularly in patients with PD (Box 6).

Mood disturbance

Depression, apathy and anxiety can occur in the early stages of PD, possibly related to lowered serotonin levels, and treatment with antidepressants or anxiolytics may be necessary before treatment of motor symptoms.[37] An overlap between depressive and parkinsonian symptoms can delay recognition and treatment of both depression and PD. Depression has a major impact on quality of life in PD, possibly more so than motor disability.[19] Anxiety can be particularly troublesome in patients with more advanced PD, with symptoms sometimes paralleling motor fluctuations. There is some evidence that treatment with a DA may reduce depression.[14,15] Limited controlled trials have demonstrated that tricyclic antidepressants (including nortriptyline and amitriptyline [Level C]) but not selective serotonin reuptake inhibitors are effective for treating depression in patients with PD.[17,38] Nevertheless, we have found selective serotonin reuptake inhibitors to be effective in clinical practice.

Sleep disturbance

Overnight motor and autonomic symptoms, including dystonia and frequent nocturia, are common in people with PD, but primary disorders of sleep may also occur. Rapid-eye-movement sleep behaviour disorder, characterised by violent limb and trunk movements and often associated with dream enactment, occurs in about 30% of patients with PD and has emerged as a marker of early PD.[37] Restless legs syndrome occurs frequently in patients with PD and often responds to dopaminergic therapy. Excessive daytime somnolence is common, and may be disease- or treatment-related.

6 Management of autonomic symptoms

Orthostatic hypotension
- Increase dietary salt, water, caffeine
- Compression stockings
- Head-up tilt in bed
- Fludrocortisone 0.1–0.3 mg daily
- Midodrine 2.5–10 mg daily
- Domperidone 10–30 mg daily
- Pyridostigmine 30–90 mg daily

Urinary frequency/nocturia/detrusor hyperreflexia
- Oxybutynin 5–15 mg daily
- Tolterodine 2–4 mg daily
- Amitriptyline or nortriptyline 10–30 mg daily (beware of orthostatic hypotension and constipation)

Constipation
- Avoid anticholinergic drugs
- Ensure adequate intake of fluid, fibre and fruit
- Add laxatives (macrogol)

Erectile dysfunction
- Sildenafil 50 mg (avoid in patients with orthostatic hypotension)
- Vardenafil 10 mg
- Tadalafil 20 mg
- Apomorphine 1–6 mg (subcutaneous) ◆

Neuropsychiatric symptoms

A range of neuropsychiatric symptoms can be triggered or aggravated by drug therapy in patients with PD. Psychotic symptoms, particularly visual hallucinations, are more common in those with cognitive decline or dementia.[37] A reduction of anti-parkinsonian medication is often necessary. Clozapine is effective for reducing psychotic symptoms (Level B), but its use is limited by side effects[14,15] and, like other antipsychotics, it is not reimbursed under the PBS for this indication. There is insufficient evidence to support the use of other atypical antipsychotics. Quetiapine is relatively safe and may help (Level C), but olanzapine and especially risperidone often aggravate parkinsonism, even at low doses.[14,15]

Impulse control disorders, including pathological gambling and hypersexual behaviour, have recently been recognised as an important side effect of dopaminergic medication in up to 15% of patients with PD.[39] DAs (both ergoline and non-ergoline) are more commonly implicated than LD, and dose reduction or cessation usually improves this behaviour. Dopamine dysregulation syndrome, a less common condition, is related to medication overuse and involves more complex and challenging behavioural problems. Dopaminergic reward pathways in the limbic region have been implicated.[39]

Cognitive symptoms and dementia

The incidence of dementia increases with duration of PD. It is characterised by fluctuating cognition and visual hallucinations. Cognitive impairment affects up to 75% of people who have had PD for at least 15 years, although the main risk factor is advancing age.[8] If cognitive symptoms emerge within 12 months of the motor symptoms, the condition is described as "dementia with Lewy bodies" rather than "PD dementia", although pathologically the two conditions are similar. Clinical trials with cholinesterase inhibitors have demonstrated benefit in treatment of cognitive symptoms (Level A) and behavioural and psychotic symptoms

(Level B) in patients with both dementia with Lewy bodies and PD dementia.[14,15,17,40] However, they are not PBS-approved for this indication in Australia.

Competing interests

Michael Hayes is on advisory boards for Novartis and Solvay; Victor Fung and John O'Sullivan are on advisory boards for Novartis, Solvay, Hospira and Boehringer Ingelheim; and Thomas Kimber is on advisory boards for Solvay and Hospira.

Author details

Michael W Hayes, MB BS, MSc, FRACP, Neurologist[1]
Victor S Fung, MB BS(Hons), PhD, FRACP, Neurologist and Director, Movement Disorders Unit,[2] and Clinical Associate Professor[3]
Thomas E Kimber, MB BS(Hons), PhD, FRACP, Neurologist[4]
John D O'Sullivan, MB BS, MD, FRACP, Neurologist,[5] and Associate Professor[6]
1 Department of Neurology, Concord Hospital, Sydney, NSW.
2 Department of Neurology, Westmead Hospital, Sydney, NSW.
3 Sydney Medical School, University of Sydney, Sydney, NSW.
4 Department of Neurology, Royal Adelaide Hospital, Adelaide, SA.
5 Department of Neurology, Royal Brisbane and Women's Hospital, Brisbane, QLD.
6 School of Medicine, University of Queensland, Brisbane, QLD.
Correspondence: hayesm@email.cs.nsw.gov.au

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