Research Review™
EDUCATIONAL SERIES
Parkinson's Disease

Making Education Easy 2018

Independent commentary by Dr Andrew Evans

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Abbreviations used in this issue:

COMT = catechol-O-methyl transferase; **NMDA** = N-methyl-D-aspartate; **MAO-B** = monoamine oxidase B; **MDS** = Movement Disorder Society; **PD** = Parkinson's disease.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, following Alzheimer's disease, in developed societies.[1-4] Its prevalence increases with age, and it is estimated to affect up to 3% of the population aged ≥65 years of age.[5] In Australia, conservative estimates indicate that one in every 340 people (approximately 70,000 people) live with PD, with over 11,500 new PD cases being diagnosed each year.[6]

PD is a progressive disease, with the onset generally being gradual and early symptoms remaining undetected or unnoticed.[7] However, the pattern of progression varies, with some patients being reasonably active and independent for up to 20 years after diagnosis.[8] Nevertheless, most patients progress to the advanced palliative stage by about 15 years after the initial diagnosis of motor symptoms (**Figure 1**).[9]

PD results in significant disability and a reduced quality of life for the patient, and indirectly may reduce the quality of life of their family and carers.[5, 7, 10] PD is also associated with significant costs to both the individual and to society, with the burden to Australian society likely to increase as the population ages.[11] The total economic cost of PD to the Australian community was estimated to be approximately $9.9 billion per annum (year of costing 2014).[12]

Diagnosis

There is no definitive diagnostic test for PD and the diagnosis of PD is based on clinical history and examination.[10] According to a commonly used criteria (The United Kingdom Parkinson's Disease Society Brain Bank), PD is diagnosed based on the presence of bradykinesia; and at least one of the following: muscular rigidity, 4 to 6 Hz rest tremor, and postural instability (not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction).[10]

Dopaminergic and non-dopaminergic pathways

PD is a multisystem, multi-neurotransmitter dysfunction-related, heterogeneous disorder.[13]

PD is characterised by neuropathological changes in the brain,[14] including the loss of dopaminergic neurons in specific areas of the substantia nigra and widespread intracellular protein (α-synuclein) accumulation.[5, 14] Lewy bodies, the pathological hallmark of PD, are largely made up of aggregated α-synuclein.[5]

When deficiency of dopamine within the substantia nigra reaches approximately 60%, the individual develops motor symptoms consisting of bradykinesia, tremor, rigidity and gait difficulty.[2, 14] The onset of motor symptoms is usually unilateral, with asymmetry persisting as the disease progresses.[5]

Although motor disturbances are required for the diagnosis of PD and tend to predominate, non-motor symptoms (**Table 1**) are invariably present and average from four to 19 in number.[2, 5, 7, 9, 10, 14-16] The presence of non-motor symptoms reflects degeneration of neurons beyond the substantia nigra.[15, 16] The peripheral and enteric nervous systems, the spinal cord, multiple viscera and skin may be involved.[9] Deposition of α-synuclein has been reported in peripheral organs such as the heart, gastrointestinal tract, submandibular glands and skin, indicating the widespread involvement of the peripheral nervous system.[9] In the later stages of the disease, people often report increasing pain and autonomic disturbances (e.g. orthostatic hypotension, erectile dysfunction, urinary incontinence and constipation; **Table 1**).[10]

Some of the non-motor symptoms may be present before the onset of classic motor symptoms by years or even decades.[5, 15] The phase in which the early symptoms or signs of PD neurodegeneration are present, but when the classic clinical diagnosis based on motor symptoms is not yet possible, has been called the prodromal period (**Figure 1**).[17] As PD progresses, non-motor symptoms become increasingly prevalent over time and are a major determinant of the patient's quality of life, progression of overall disability and need for nursing home care.[5]

The non-motor symptoms have both dopaminergic and non-dopaminergic origins and vary widely in their nature, range and presentation. Disruptions of non-dopaminergic systems (including glutamatergic, adrenergic, adenosine, serotonergic, histaminic, opioid and cholinergic pathways) occur.[18-20] These pathways may also have a role in maintaining smooth motor function via their interaction with the dopaminergic system.[18] The targeting of non-dopaminergic systems may thus be a complementary approach to improving and controlling motor complications of PD, removing the need for further increases in levodopa.[19]

Table 1. Non-motor symptoms of PD[2, 5, 14-16, 21]

Neuropsychiatric symptoms
Depression and depressive symptoms, apathy, anxiety and anxiety symptoms, psychosis, impulse control and related disorders, dementia, cognitive impairment
Autonomic dysfunction
Sialorrhoea, urinary dysfunction, orthostatic hypotension, erectile dysfunction, gastrointestinal dysfunction (dysphagia, achalasia, delayed gastric emptying, small intestinal bacterial overgrowth, constipation), excessive sweating
Sleep disorders
Sleep fragmentation and insomnia, rapid eye movement sleep behaviour disorder, excessive daytime sleepiness
Other symptoms
Pain, fatigue, olfactory dysfunction, ophthalmologic dysfunction, non-motor fluctuations

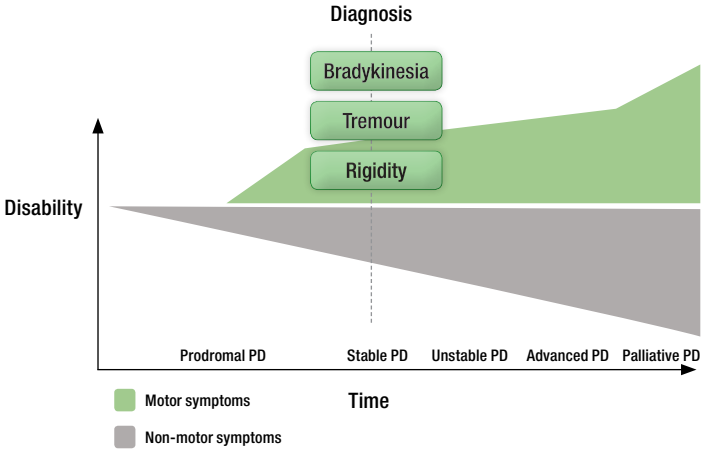

Figure 1. Development of symptoms associated with Parkinson's disease (PD)[5, 9, 15]

Unmet needs in PD

There are many unmet areas of need relating to the diagnosis and treatment of PD.[22]

Despite available treatment strategies, the disease continues to progress, with patients suffering various motor and non-motor symptoms.[22] Thus, a critical unmet clinical need in PD is for a therapy that can slow or halt progression of PD, provide reversal of the disease and/or neuroprotection.

Research is also needed to identify biomarkers (imaging, genetic, clinical or other modality) for early identification and tracking of PD.[23] Sleep and imaging measures, and to some extent non-motor symptoms, assessed using adequate scales, may have value to quantify progression and inform holistic management strategies.[24] However, clinicians must bear in mind that there can be significant overlap of the symptoms of PD with those of other chronic illnesses of the aged.[24]

There is also need for the improved 24-h control of motor fluctuations in patients with moderate to advanced PD.[15] Circadian rhythm disorders, nocturnal symptoms and early morning fluctuations (motor and non-motor symptoms) often remain untreated.[23]

Non-motor symptoms often go under-recognised and undertreated and their management represents an important unmet need in PD.[15] Patients often do not recognise the link between non-motor symptoms and PD. Contrary to the evidence, clinicians often regard the management of non-motor symptoms as less important than motor symptom control.[22] Future research needs to develop therapies that treat non-motor symptoms and target non-dopaminergic degeneration in PD.

Robust animal models are required for future research into the non-motor symptoms associated with PD.[9, 22] Currently, there are no models that can appropriately assist in understanding the pathophysiology of non-motor symptoms in PD. This is another key unmet need.[9, 22]

Role of the clinician in managing motor and non-motor symptoms

Given the ageing Australian population, clinicians will be increasingly involved in managing PD. The treatment of people with PD usually involves a multidisciplinary approach.[22] To manage the complex needs of people with PD, a broad understanding of the range of non-motor and motor symptoms is necessary and this will enable a more effective integration and use of health services.[22] In addition to neurologists, movement disorder specialists, geriatricians, general practitioners (GPs) or PD nurse specialists, allied health professions (e.g. physiotherapists, exercise physiologists, occupational therapists, and speech therapists) are able to assist in the management of the symptoms of PD.[6]

While neurologists, movement disorder specialists, geriatricians or PD nurse specialists will have specialist knowledge regarding the diagnosis and treatment of PD, non-specialist clinicians also need a working knowledge of both motor and non-motor symptoms of PD. Non-motor symptoms of PD are frequently missed or undeclared during routine consultations.[25] The Movement Disorder Society (MDS) recommend clinical assessment of non-motor symptoms using the various scales and questionnaires,[26] such as the NMS Questionnaire (completed by patients)[27] and NMS Scale.[28]

However, studies have shown that non-specialist clinicians may not always possess the necessary knowledge or experience of managing patients with PD.[29, 30] A study conducted in Australia found that the majority of the GPs surveyed lacked confidence in their ability to treat early PD, and manage the late stages of the disease.[29] Another study involving Australian GPs from New South Wales and the Australian Capital Territory identified a clear need for further education and training in the management of both motor and non-motor symptoms of PD.[30] The researchers of the study concluded that continuing education of GPs would help to ensure they were better equipped to accurately diagnose and manage PD patients.[30]

In more isolated rural communities, the GP team may be primarily involved in managing patients with PD. In order to improve the knowledge-base of GPs, Parkinsons NSW and the Australian College of Rural and Remote Medicine have produced an online educational course designed to help these clinicians address the issues of most concern when they are confronted with a patient who may have PD. Click to view.

Expert comment

The prevalence of PD may be increasing beyond the expected effects of our ageing community and provides a significant challenge to clinicians working with the elderly. It can be difficult to accurately diagnose PD, especially in patients with other comorbidities such as arthritis and other diseases of ageing.[31] In patients presenting with Parkinsonism or tremor disorders, specific enquiry about the presence of REM sleep disorder (acting out of dreams), daytime sleepiness, impaired sense of smell, mood disturbances, or constipation are important. The presence of these non-motor features can increase clinical suspicion of PD, aid timely diagnosis and help tie in a seemingly disparate group of non-motor and motor symptoms under the same diagnostic banner. Treatment of these non-motor symptoms commonly needs to be undertaken concurrently with initiation of dopaminergic therapies.

Treatment

There is currently no cure for PD, and available therapies only treat the symptoms of the disease.[7, 14] Although no specific Australian PD treatment guidelines have been written, various other international and national guidelines provide recommendations for the treatment and management of PD symptoms.[10, 32, 33]

Any form of therapy for PD should be personalised and take into account the patient's unique lifestyle, circumstances, preferences, needs and goals (**Figure 2**).[9, 10, 13, 32]

Pharmacotherapy is usually initiated when symptoms impair functionality, quality of life or employment, or lead to embarrassment in social situations.[10, 32] Pharmacotherapy requires careful implementation and monitoring to maintain a balance between clinical efficacy and the minimisation of adverse events.[34] Dose adjustments and the appropriate use of combination therapies are usually required. Extreme caution is advised if PD medication is to be withdrawn or reduced abruptly as it may cause serious symptoms, such as worsening tremor, rigidity and bradykinesia.[10] Abrupt withdrawal may also trigger neuroleptic malignant syndrome.[10] From a pharmacological point of view, treatment should involve both dopaminergic and non-dopaminergic strategies. The preferred first-line therapy for PD is levodopa. Most patients with PD on levodopa therapy eventually develop motor complications.[10, 32, 33]

Figure 2. Personalised management of PD[13]
Adapted from Titova N, Chaudhuri KR. Mov Disord. 2017;32(8):1147-1154.

Treatment of motor symptoms

Non-pharmacologic therapy

Non-pharmacologic therapies for the treatment of PD include counselling and education for both patients and carers.[35] It is important that patients maintain general fitness and well-being, core balance and general strength as far as possible.[35] Physiotherapy and exercise therapy can improve motor function and allied health professionals can provide specific strategies to overcome disabilities such as start hesitancy, freezing of gait, festination and falls.[35, 36] Speech therapy may improve speech impediments associated with PD.[37]

In patients who present with increasing problems of motor response complications, including motor fluctuations and dyskinesia or tremor that is unresponsive to dopaminergic drug therapies, deep brain stimulation may also be considered.[5, 7, 38]

Pharmacotherapy

Motor symptoms in patients with PD generally respond to medicines that enhance dopamine function.[2] When motor symptoms are well controlled, the patient is described as being in an "on" state. Periods of poor motor symptom control are referred to as "off" states.

The gold standard for treatment of patients with PD and motor symptoms is dopamine replacement with levodopa (a precursor to dopamine) in combination with a dopa-decarboxylase inhibitor (carbidopa or benserazide) (**Table 2**).[2, 10, 32] Levodopa has been described in an international evidence-based systematic review as being "clinically useful" for treating motor symptoms.[32] The exact mechanism of action of levodopa is unclear, but both presynaptic and postsynaptic mechanisms are involved.[5] Decarboxylase inhibitors are added to prevent the breakdown of levodopa and to ensure it passes through the blood-brain barrier.

The preferred first-line therapy for PD is levodopa. Dopamine agonists may be used as first-line therapy in exceptional circumstances.[2, 10, 32]

Most patients with PD on levodopa therapy eventually develop motor complications. These include:

- different patterns of motor fluctuations (e.g. predictable and unpredictable 'wearing off' effect, intermittent 'dose failures', delayed or poor effect of individual doses)
- drug-induced chorea (also known as dyskinesia) or dystonia.[2, 10, 32] Dyskinesia is suspected to be the result of dysregulated striatal excitation by glutamate, a neurotransmitter acting at NMDA glutamate receptors.[39]

For patients who have developed motor fluctuations despite optimal levodopa therapy, then non-ergot-derived dopamine agonists, MAO-B inhibitors or catechol-O-methyl transferase (COMT) inhibitors are recommended as an adjunct to levodopa.[10] Amantadine, an uncompetitive antagonist of NMDA receptors, has been used in PD for the treatment of levodopa-induced dyskinesia.[2,10] In addition, another class of agents provides both MAO-B inhibition and glutamate inhibition. This class includes agents, such as safinamide, with dopaminergic and non-dopaminergic mechanism of actions. They have been used as an add-on treatment for motor fluctuations with levodopa.[10, 32]

Advanced therapies for severe motor fluctuations refractory to conventional therapy, include pump therapies, such as a continuous subcutaneous apomorphine infusion or an intraduodenal infusion of levodopa/carbidopa gel via an enterostomy tube, are also available for the treatment of advanced PD with motor fluctuations despite optimised pharmacological treatment.[35] These therapies need to be provided through specialised movement disorder units with appropriate clinical support and monitoring.

Table 2. Therapies for the treatment of motor symptoms of Parkinson's disease[5, 10, 35, 40]

Drug	Mechanism of action
Levodopa/dopa decarboxylase inhibitor	Cross the blood–brain barrier and then metabolised by L-aromatic amino acid decarboxylase (dopa decarboxylase) to dopamine. Both presynaptic and postsynaptic mechanisms are involved
Dopamine agonists **Non-ergoline** Pramipexole Ropinirole Apomorphine Rotigotine **Ergoline** Bromocriptine Cabergoline	Stimulate dopamine receptor sites
Monoamine oxidase B (MAO-B) inhibitors Selegiline Rasagiline	Enhance the synaptic availability of dopamine, by selectively inhibiting MAO-B, one of the enzymes that catabolises dopamine
Mixed MAO-B inhibitor/ glutamate inhibitor Safinamide	Dopaminergic and non-dopaminergic mechanisms of action. Selective and reversible inhibition of MAO-B and state- and use-dependent inhibition of voltage-gated sodium (Na^+) channels, calcium (Ca^{2+}) channel modulation and inhibition of glutamate release
Catechol-o-methyl transferase (COMT) inhibitors Entacapone	Inhibits COMT, which breaks down levodopa
N-methyl-D-aspartate antagonist Amantadine	Not fully understood. Indirect dopamine receptor agonist. May also exert some anticholinergic activity.
Anticholinergics Trihexyphenidyl (benzhexol) Benztropine Biperiden	Reduce acetylcholine effects

Treatment of non-motor symptoms

The management of non-motor symptoms of PD presents a key challenge to the clinician.[9, 21] Non-motor symptoms may include orthostatic hypotension, depression, anxiety, psychosis, bladder dysfunction and dementia (**Table 1**).[2, 10, 32] Non-pharmacological therapies, such as various forms of exercise (yoga, tai chi), cognitive behaviour therapy and transcranial magnetic stimulation have been used to manage depression, anxiety and cognitive problems.[9, 21] Probiotics and prebiotic fibre have been a recent focus for gastrointestinal dysfunctions.[9, 21]

Many of the non-motor symptoms of PD do not respond to dopaminergic medication and other pharmacological treatments may be necessary.[16, 21] However, robust evidence from randomised, controlled trials for pharmacological treatment of non-motor symptoms in PD is limited.[21] Further research in this area is still required,[21] with the broad spectrum of non-motor symptoms in PD highlighting the need for developing non-dopaminergic therapies.[22]

Expert comment

The most widely used staging system for PD is the Hoehn and Yahr scale which defines 5 motor stages of disease in which individuals are characterised according to unilateral (stage 1) or bilateral (stage 2 – 5) disease, the presence of postural instability (stage >2) and ultimately progressing to severe disability (stage 4 and 5).

Increasingly recognised is the role that non-motor symptoms have both in the prodromal or premotor phase of PD and the impact that they have on health related quality of life.[42, 43] While many of the non-motor symptoms represent progression in Lewy body pathology, many non-motor symptoms may be exacerbated by the pharmacotherapies used to treat the motor symptoms. For instance, amantadine is commonly used as an anti-dyskinetic agent in the management of patients with motor response complications, but should be withdrawn in patients with psychosis or troublesome visual hallucinations. Dopamine agonists are more prone to exacerbating orthostatic hypotension in a dose responsive manner and anti-cholinergic agents often worsen cognitive functioning.

In 1997, the World Health Organisation developed the PD charter which stated patients have the right to:

- Be referred to a doctor with a special interest in PD
- Receive an accurate diagnosis
- Have access to support services
- Receive continuous care
- Take part in managing the illness

Delivering individualised and patient-centred care to patients with PD is particularly challenging, given the complex and debilitating nature of this disease. Most PD patients become progressively handicapped by a mixture of cognitive, emotional, non-motor and and motor symptoms. Patients should be given sufficient time and information to understand the disease process and how it may affect them in the future. They need to be looked after by a multidisciplinary team that includes a GP, a neurologist, a geriatrician, pharmacists, specialist nurses, and physiotherapists. There needs to be a balance of the regionalisation of care to specialised centres and teams against the desire of patients to be treated in their own communities so that they can enjoy independent living and a better quality of life. Care providers need to make sure that patients are aware of and make use of community support available to them – including organisations such as Parkinson's Australia and BrainLink. An optimum multidisciplinary team should also include the carers' needs - for example, occupational therapy may help carers cope with people with PD's more complex situations, thereby delaying the need for assisted or residential care. At the appropriate time, patients and their carers will likely need information about and assistance accessing the NDIS or Commonwealth aged care system.

Rural patients represent a particular challenge. PD has a higher prevalence in rural compared to metropolitan regions. People with PD living in rural and regional areas have been found to have lower health-related quality of life than their metropolitan counterparts.[44] While emerging technologies, such as telehealth may help, the lack of consistent access to specialised care, geographical barriers to formal and informal supports, increased isolation in rural communities will continue to disadvantage these patients. Even for metropolitan patients, there continues to be inequality of access. Public funding for deep brain stimulation is limited in many states, so that the therapy is primarily financed by private health insurance.

Conclusions

Although PD is primarily caused by dysfunction of dopaminergic neurons, non-dopaminergic pathways are also involved. The dysfunction of both dopaminergic and non-dopaminergic pathways results in the development of both motor and non-motor symptoms of PD and treatments should involve the targeting of both pathways. Non-motor symptoms of PD are frequently missed or undeclared during routine consultations. Better education of clinicians and caregivers is an essential part of recognising the importance of recognising both motor and non-motor symptoms. Future research into treatments and neuroprotection in PD must involve both dopaminergic and non-dopaminergic strategies.

Expert conclusion

A multidisciplinary team approach – including safety within the home appropriate to the stage of the disease, as well as combining both pharmacological and non-pharmacological treatments – is the optimum approach for such a complex and multifaceted disease. Empowering patients to become actively involved with their treatment and therapy decisions helps improve compliance and leads to improved management of the disease with long-term benefits in outcomes. More research is required to discover treatments that change the way the disease progresses and transform the lives of those who live with PD. Thanks to constant advances in our understanding of PD, new efforts to match the emerging science with innovative therapies are underway around the world.

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