KEY MESSAGES

- Parkinson’s disease (PD) is a progressive neurodegenerative condition with insidious onset, high levels of morbidity and reduced life expectancy
- Pathophysiological changes are widespread and occur in both the central nervous system (CNS) and in peripheral tissues. The progressive spreading pattern of these changes is responsible for appearance of non-motor symptoms (e.g. constipation, anxiety) years before the development of motor symptoms and dementia
- Diagnosis is made clinically and may be supported by radiological investigations
- Patients with higher initial motor impairment scores, with non-motor symptoms, may have a worse prognosis.
- Levodopa (l-dopa) remains the gold-standard treatment, but newer treatments, including non-oral therapies and deep-brain stimulation offer promise in reducing both symptoms and side effects of treatment
- Regardless of treatment, PD remains a progressive disease
- Rasagiline is a selective, irreversible monoamine oxidase (MOA)-B inhibitor indicated for the treatment of PD either as monotherapy or as adjunctive treatment with l-dopa for more advanced disease and for patients with end-of-dose fluctuations
- Some studies suggest that MOA-B inhibitors may have a disease-modifying effect in PD. However, data are conflicting and the search for a treatment regimen that can halt progression of the disease is ongoing.

Introduction

PD is a progressive neurodegenerative condition with insidious onset and reduced life expectancy. Although it is frequently regarded as purely a disorder of movement, this perception is incorrect and in many patients non-motor symptoms are predominant. Furthermore, PD is responsible for considerable morbidity and a high rate of premature mortality, predominantly from aspiration pneumonia.

In the Sydney Multicenter Study of PD, after 20 years follow-up of newly diagnosed patients with PD, 74% had died, with half of those deaths occurring within 10 years of diagnosis.¹ Pneumonia was the most common cause of death and PD was considered to have been a significant contributor to death in 54%. The median time from disease onset to death was 12.4 years. Among the 20-year survivors, 83% had developed dementia. Only one survivor was living independently and half were in nursing homes. Other morbidities evident in survivors are listed in Table 1.
Aetiology and pathogenesis

The aetiology of PD is usually regarded as requiring an interplay between genetic vulnerability and environmental factors. Potential pathogenic risk factors include toxins, pesticides, brain microtrauma, focal cerebrovascular damage and genome effects. The neuropathology in PD is characterised by selective loss of dopaminergic neurons in the substantia nigra pars compacta with formation of Lewy bodies consequent on the accumulation of alpha-synuclein inside of cells. However, research demonstrates that pathology in PD is not limited to merely a local structural change or loss of dopamine. There is also widespread involvement of other (non-dopaminergic) structures in the CNS and peripheral tissues, and PD-related neurodegeneration is likely to occur several decades before the onset of motor symptoms. In the CNS, the formation of Lewy bodies is progressive, spreading from the rostral to upper brainstem and then to other brain areas, including the limbic system and frontal lobes. This progressive spreading pattern, and the presence of Lewy type alpha-synucleinopathy in the brainstem and peripheral tissues, is responsible for appearance of non-motor symptoms (e.g. constipation, anxiety) years before the development of motor symptoms and dementia.

In addition to alpha-synuclein deposition, there are other pathophysiological mechanisms that have been shown to contribute to the pathophysiology of PD and which might represent novel targets for treatment in the future. These include oxidative damage; neuroinflammation and microglial activation; intracellular accumulation of other insoluble proteins; tau and amyloid formation; and growing evidence that alpha-synuclein may behave in a prion-like manner.

Diagnosis

Diagnosis of PD is a clinical one, requiring identification of three cardinal motor manifestations of parkinsonism (bradykinesia plus rest tremor and/or rigidity) and three further categories of diagnostic features (supportive criteria, red flags and exclusion criteria) that establish PD as the cause (Table 2). However, although motor symptoms remain the core clinical feature of parkinsonism, increasing recognition is being given to non-motor symptoms, which occur in almost all people with PD and which often dominate the clinical presentation (Table 3).
In addition to bradykinesia plus rest tremor and/or rigidity:

**Diagnosis of clinically established PD requires:**
1. Absence of absolute exclusion criteria
2. At least two supportive criteria
3. No red flags

**Diagnosis of clinically probable PD requires:**
1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   - If one red flag is present, there must also be at least one supportive criterion
   - If two red flags, at least two supportive criteria are needed
   - No more than two red flags are allowed for this category

### Supportive criteria
1. Clear and dramatic beneficial response to dopaminergic therapy.
3. Rest tremor of a limb.
4. Presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy.

### Absolute exclusion criteria
1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities.
2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades.
3. Diagnosis of probable behavioural variant frontotemporal dementia or primary progressive aphasia.
4. Parkinsonian features restricted to the lower limbs for more than three years.
5. Drug-induced parkinsonism (antidopaminergic drugs).
6. Absence of observable response to high-dose l-dopa.
7. Unequivocal cortical sensory loss (i.e. graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia.
8. Normal functional neuroimaging of the presynaptic dopaminergic system.

### Red flags
1. Rapid progression of gait impairment requiring regular use of wheelchair within five years of onset.
2. A complete absence of progression of motor symptoms or signs over five or more years unless stability is related to treatment.
3. Early bulbar dysfunction: severe dysphonia, dysarthria or dysphagia within the first five years.
4. Inspiratory respiratory dysfunction.
5. Severe autonomic failure in the first five years of disease. This can include:
   - a) Orthostatic hypotension, or
   - b) Severe urinary retention or urinary incontinence (and erectile dysfunction in men).
6. Recurrent (>1/year) falls because of impaired balance within three years of onset.
7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 years.
8. Absence of any of the common non-motor features of disease despite five years disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behaviour disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations).
9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathological hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response).

MDS: Movement Disorder Society; MIBG: iodine-123-meta-iodobenzylguanidin
Non-motor symptoms often precede motor symptoms. As mentioned above, they may be a biomarker of disease progression and are also used as separate criteria to define prodromal PD. They are responsible for high levels of disability and reduced quality of life for both patients and their carers, and timeous identification and management of these symptoms are essential to reduce associated morbidity. In a survey of patients with PD in the UK, patients rated non-motor symptoms, including pain, sleep disorders and anxiety, as more important to impaired quality of life than motor symptoms.

Radiological tests may be useful to support the diagnosis and to exclude other causes of symptoms, but are not reliable enough to make a diagnosis of PD. Classic findings on magnetic resonance imaging (MRI) associated with non-PD conditions with Parkinson’s-like multiple-system atrophy include various interesting pareidolia like the penguin, hockey stick, humming bird, hot cross bun and mickey mouse signs. Functional imaging with radio-isotope marked tracers remains the standard to diagnose parkinsonism and is sensitive to diagnose essential tremor or functional disorders from parkinsonism.

### Prognostic prediction

Currently, because of the heterogeneous nature of the pathophysiology and clinical presentation of PD, there is no clear method by which to predict progression and with which to develop more personalised care approaches in clinical practice.

### Table 3. Non-motor symptom subtypes in PD

<table>
<thead>
<tr>
<th>Braintstem phenotype</th>
<th>Limbic phenotype</th>
<th>Cortical phenotype</th>
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<tbody>
<tr>
<td>1. Sleep dominant</td>
<td>1. Depression</td>
<td>Cognitive dominant</td>
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<tr>
<td>a) Excessive daytime sleepiness</td>
<td>a) Anxiety</td>
<td>a) Dementia</td>
</tr>
<tr>
<td>b) REM sleep behaviour disorder</td>
<td>b) Anxiety/depression</td>
<td>b) Amnestic</td>
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<tr>
<td>2. Autonomic dominant</td>
<td>c) Major depression</td>
<td>c) Mild cognitive impairment</td>
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<tr>
<td>a) Gastrointestinal</td>
<td>2. Fatigue dominant</td>
<td>d) Apathy</td>
</tr>
<tr>
<td>b) Genitourinary</td>
<td>3. Pain dominant</td>
<td></td>
</tr>
<tr>
<td>c) Adrenergic (postural and other hypotension)</td>
<td>4. Weight loss phenotype</td>
<td></td>
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</tbody>
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### Table 4. New approach to PD subtyping based on biomarkers and longitudinal progression

<table>
<thead>
<tr>
<th>Unified PD Rating Scale (UPDRS)</th>
<th>Mild motor predominant</th>
<th>Intermediate</th>
<th>Diffuse malignant</th>
<th>Non-motor symptoms:</th>
</tr>
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<tbody>
<tr>
<td>26.4</td>
<td></td>
<td></td>
<td></td>
<td>Cognitive impairment,</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>REM SBD,</td>
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<td></td>
<td></td>
<td>Dysautonomia</td>
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<td></td>
<td>Low cerebrospinal fluid (CSF) amyloid and amyloid/tau</td>
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<td></td>
<td></td>
<td>++</td>
<td>+++</td>
<td>+++++</td>
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<tr>
<td>Brain atrophy</td>
<td></td>
<td>++</td>
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<td>+++</td>
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<tr>
<td>Clinical progression</td>
<td></td>
<td>++</td>
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<td>+++</td>
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<tr>
<td>Progression</td>
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<td></td>
<td>+++</td>
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**Initial classification:**

- Mild motor predominant: composite motor and all three non-motor scores below the 75th percentile
- Diffuse malignant: composite motor score plus either ≥1/3 non-motor score >75th percentile, or all three non-motor scores >75th percentile
using baseline clinical information. In an attempt to address this, based on longitudinal data including clinical characteristics, neuroimaging, biospecimen and genetic information, a classification system has been developed that identifies three prognostic subtypes of PD, namely mild motor predominant, intermediate and diffuse malignant. During validation of the classification system, patients were initially classified into one of these three groups at baseline according to composite motor score and the presence of three non-motor symptoms (cognitive impairment, REM sleep behaviour disorder [SBD] and dysautonomia) (Table 4).

The patients with diffuse malignant PD had the lowest level of CSF amyloid-β and amyloid-β/total tau ratio and a greater degree of brain atrophy. After an average follow-up of 2.7 years, this group also had the fastest progression of PD (global composite outcome) with a greater decline in motor and cognitive deficits, supported by a faster decline in dopamine functional neuroimaging.

### Treatment of PD

**L-dopa – the mainstay**

L-dopa is the most efficacious and best tolerated pharmacological treatment for PD and remains the gold standard. However, its utility is limited by its lack of 24-hour symptom control (‘on’ and ‘off’ periods), fluctuations in response and the development of motor complications (dyskinesia) when initially used in high doses and with long-term use.

In early disease the incidence of dyskinesia may be limited by delaying treatment with l-dopa and preferentially using a dopamine agonist (e.g. pamiprexole, ropinirole), which may be associated with a lower incidence of motor complications. Nevertheless, these drugs are not as effective as l-dopa and the vast majority of patients will eventually require l-dopa to control their symptoms.

### Symptom fluctuations – influence on therapy

Motor response fluctuations are almost invariably associated with fluctuations in disabling non-motor symptoms. In particular, the early morning ‘off’ state is associated with significant and distressing non-motor symptoms. Although it is recognised that symptom fluctuations are closely related to the dose and pulsatile pharmacokinetics of l-dopa, these are not the only factors that may be important. For example, drug absorption in the small intestine may be impaired by non-motor gastrointestinal problems, such as dysphagia, gastric dysmotility with delayed gastric emptying, alterations in the intestinal microbiota and bacterial overgrowth. Therefore, in addition to end-of-dose wearing off of drug effect, time taken to ‘on’, which is related to drug absorption, is also recognised as an important consideration. Delays to ‘on’ time and dose failures may account for more than 60% of daily ‘off’ time. Nocturnal hypokinesia and early morning ‘off’ is often the longest ‘off’ period in the treatment cycle.

Nonadherence to therapy is also an important cause of sub-therapeutic l-dopa levels, breaks in symptom control and treatment-associated motor complications. Poor adherence is significantly associated with younger age, lower quality of life, higher depression scores and with taking more tablets per day.

### Novel treatments

A number of novel treatments have been developed to address some of these obstacles to continuous symptom management (Table 5). They include longer-acting drug preparations and non-oral therapies such as injections or infusions that do not rely on gastrointestinal absorption, and which hold the most promise when oral treatments do not provide sufficient control. Rasagiline increases ‘on’ time with fewer side effects than l-dopa and is helpful, especially in early PD. It may also be useful in combination with l-dopa in patients with more advanced disease...
and symptom fluctuations, especially in respect of freezing and gait disturbances, motor symptoms, mood symptoms and impaired bladder control. Apomorphine injection is quick acting and very effective. It works immediately and may be very useful as a rescue therapy for sudden and unexpected episodes of ‘off’. L-dopa subcutaneous infusions controlled by a pump that is worn by the patient provide true 24-hour symptom control.

Additional considerations for patient management include attention to improving gastrointestinal function, which may improve drug absorption, speed up time to ‘on’ and extend symptom control.

Importantly, patients should be asked about non-motor symptoms. Without identification and management of these symptoms, quality of life is unlikely to improve and is likely to deteriorate.

Cannabis in various forms is frequently used by patients with PD and may help with sleep disturbance. There is no current evidence of efficacy for other symptoms of the illness. Physiotherapy and physical activity that requires anticipation of movement, such as non-combative boxing or Tai Chi, can improve mind-muscle coordination and may help to reduce the incidence of falls.

**Deep brain stimulation**

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus pars interna (GPi) is an important treatment tool for patients with PD and especially those with significant symptoms. It significantly improves off-treatment time and quality of life. DBS reduces dyskinesia through both a direct therapeutic response and because it allows for reduced doses of concomitant anti-PD medication. Nevertheless, even with DBS, PD remains a progressive disease with gradual worsening of axial signs, including postural instability, freezing of gait, posture abnormalities, dysarthria and non-motor symptoms that do not respond to l-dopa, with development of falls and dementia. Studies are ongoing using novel targets for DBS (e.g. the pedunculopontine nucleus, caudal zona incerta, thalamic centromedian-parafascicular complex, substantia nigra) and multi-target strategies. In addition, new options in software programming for STN stimulation hold promise for improvement in sustained symptom control.

**Focus on rasagiline for the treatment of PD**

Rasagiline is a selective, irreversible MOA-B inhibitor. In South Africa it is indicated for the treatment of PD either as monotherapy or as adjunctive treatment with l-dopa for more advanced disease and for patients with end-of-dose fluctuations.

MAO-B is the predominant MAO
isoenzyme in the basal ganglia. It is responsible for breakdown of dopamine and of phenethylamine, which stimulates the release of dopamine from neurons and inhibits its uptake. Unlike selegiline, rasagiline is not metabolised to amphetamines and therefore it does not share the sympathomimetic and neurological effects that may occur with the former drug.\textsuperscript{14}

The therapeutic efficacy of rasagiline, either as monotherapy in early disease or as add-on therapy to l-dopa has been demonstrated in five large randomised, double-blind, placebo-controlled studies, which showed that rasagiline is helpful in early and late disease with few side effects.\textsuperscript{14}

In the TEMPO\textsuperscript{15} and ADAGIO\textsuperscript{16} studies, monotherapy with rasagiline 1mg significantly slowed worsening of UPDRS score. The ADAGIO study investigated the possible disease-modifying effect of rasagiline, in terms of the slope of the change in UPDRS score. Patients were randomised to receive rasagiline 1mg or 2mg/day for 72 weeks (early start group), or placebo for 36 weeks followed by rasagiline (1mg or 2mg/day) for a further 36 weeks (delayed start group). Early start rasagiline 1mg differed from placebo, suggesting a disease-modifying effect, but 2mg/day did not. Because of this difference in outcomes with the two doses, the investigators were unable to definitively conclude that rasagiline 1mg/day does modify the course of the disease.\textsuperscript{16}

In the PRESTO\textsuperscript{17} and LARGO\textsuperscript{18} studies of adjunctive therapy to l-dopa in patients with motor fluctuations (≥2.5 hours ≥1 hour of ‘off’ time on optimal doses of l-dopa, respectively), rasagiline 0.5mg or 1mg/day significantly reduced total daily ‘off’ time and improved Clinical Global Impression (CGI) score, UPDRS activities of daily living subscale during off time and the UPDRS motor subscale during ‘on’ time. In both the monotherapy and adjunctive therapy studies, rasagiline was well tolerated with a low incidence of cognitive and behavioural adverse effects and, in three of the studies, no significant difference in incidence of adverse effects between the placebo and rasagiline groups.

The potential of rasagiline as a disease-modifying agent in PD is intriguing, but, at present, uncertain. It has demonstrated neuroprotective effects in a variety of \textit{in vitro} and \textit{in vivo} models of neurodegenerative disease (Table 6). A few small studies in patients treated with l-dopa have suggested that MOA-B inhibitors may provide increasing benefit with longer duration of exposure, potentially consistent with slowing of disease progression, but, due to relatively small sample sizes, high withdrawal rates and different primary endpoints, they are difficult to interpret. In a recent study of 1616 patients with PD published this year, over a mean follow-up period of four years, a significant association was demonstrated between duration of MOA-B exposure and less progression of impairment in activities of daily living, ambulatory capacity and the modified Rankin Scale.\textsuperscript{19}

However, as mentioned above, in the ADAGIO study early treatment with rasagiline 1mg provided benefits consistent with a disease-modifying effect, but 2mg did not.\textsuperscript{16} Furthermore, a follow-up study of patients in ADAGIO was unable

\begin{table}[h]
\centering
\caption{Potential neuroprotective effects of rasagiline\textsuperscript{14,20}}
\begin{tabular}{|l|
\hline
• Reduces oxidative stress \\
• Stabilises the mitochondrial membrane \\
• Prevents apoptosis: increases activity of anti-apoptotic factors, such as B-cell lymphoma (BCl)2 and antioxidant enzymes \\
• Neurorestorative activity \\
  – increased the proportion of tyrosine hydroxylase-immunopositive neurons in animal studies; \\
  – induces protein kinase (PK)C\textalpha, brain-derived neurotrophic factor (BDNF) and \epsilon, glial cell-derived neurotrophic factor (GDNF) \\
• Has been shown to activate nuclear transcription factor, elevating transcription of pro-survival genes \\
• Accelerates recovery of motor function and spatial memory after closed head injury in mice \\
• Reduces the incidence of stroke and increases survival in stroke-prone spontaneously hypertensive rats \\
\hline
\end{tabular}
\end{table}
to demonstrate sustained benefits in the early start group five years after completion of the original trial and clinically important milestones had occurred in a substantial proportion of patients where overall, 43.6% of patients had onset of unsteady gait/balance impairment, 35.7% had fallen, 26.2% had freezing of gait, and 33.1% had cognitive decline.21

Conclusions
In the absence of a cure for PD, the next best treatment would be one that stops, or at least slows disease progression while providing symptomatic relief. Emerging insights into the pathogenesis and natural history of PD are enabling new approaches to individualised management based on predominant symptomatology. However, at the moment, even with available treatments, PD remains a progressive disease. It is hoped that novel treatment approaches and a better understanding of the potential neuroprotective and neurorestorative effects of pharmacotherapy will lead to future strategies with significant improvements in long-term quality of life for patients with PD.

References