Parkinson's disease

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Tremor, often combined with slowness and stiffness in an arm, presents frequently in general practice. It may be caused by essential tremor, which affects 2-3% of the population.¹ Parkinson's disease is less common (prevalence 0.2%), although its prevalence increases with age (4% of those aged over 80 years).² Differentiating essential tremor from Parkinson's disease can be difficult, even for experienced physicians.

Recently published guidelines from the National Institute for Health and Clinical Excellence (NICE) advise that all patients with suspected Parkinson's disease should be referred to an expert in secondary care for an accurate diagnosis and management of the condition.³ However, non-experts need to be aware of the features of Parkinson's disease to ensure rapid referral and should have a basic understanding of how the condition is treated to facilitate shared care between primary and secondary care.

How does Parkinson's disease present?

The cardinal symptoms of Parkinson's disease are shaking, stiffness, and slowness and poverty of movement. The condition leads to physical signs including tremor at rest, rigidity on passive movement, slowness of movement (bradykinesia), and poverty of movement (hypokinesia). These features are unilateral at onset, but become bilateral as the condition progresses. Later, postural instability and falls, orthostatic hypotension, and dementia can develop.

What conditions can it be confused with?

Differentiating types of tremor (box 1) is done by examining the patient with the hands resting in the lap (to look for rest tremor), with the arms outstretched (postural tremor), then in a "finger-nose" test (intention tremor). Another way to identify rest tremor is when patients are walking with their arms by their sides. Essential tremor usually produces a symmetrical postural tremor of the outstretched hands which interferes with actions such as holding tea cups and writing. Parkinson's disease usually produces an asymmetrical rest tremor, which disappears when a posture is maintained.

A parkinsonian or akinetic-rigid syndrome consists of rigidity, bradykinesia, and hypokinesia. Some patients may have tremor—around 80% in Parkinson's disease. A parkinsonian syndrome is not diagnostic of Parkinson's disease (box 2); many older patients have

one or two features of parkinsonism as a result of ageing, making differential diagnosis difficult.⁴

How is it diagnosed?

The diagnosis of Parkinson's disease remains clinical in most cases. Most experts use the UK Parkinson's Disease Society's Brain Bank diagnostic criteria.⁵ The NICE guidelines recommend that people with suspected Parkinson's disease should be referred quickly and untreated to a specialist with expertise in differential diagnosis. They recommend that all patients with suspected Parkinson's disease should be reviewed regularly and the diagnosis reviewed if atypical features develop.³ This guidance is based on the circumstantial evidence that the diagnostic error rate in a community sample was 47%⁶ and that in a UK brain bank series representing standard neurological and geriatric practice the error rate was 26%,⁷ whereas in expert movement disorders clinics the error rate was 2% to 8%.⁸⁻¹⁰

It is difficult for experts to differentiate essential tremor from Parkinson's disease when asymmetric postural and action tremor of the upper limbs appears at rest. In this situation, single photon emission computed tomography (SPECT) is useful and is supported by NICE.³ A gamma ray emitting isotope is tagged to a cocaine derivative (ioflupane; ¹²³I-FP-CIT), which is administered intravenously. This binds to the pre-synaptic dopamine reuptake site in the striatum (caudate and putamen), which is visualised using a gamma camera (fig 1). Uptake is normal in controls and in patients with essential tremor, neuroleptic induced parkinsonism, and psychogenic parkinsonism but is

SOURCES AND SELECTION CRITERIA

This review is based on the guidelines from the National Institute for Health and Clinical Excellence (NICE) published in June 2006.³ The guidelines were based on literature searches by information scientists with a final search date of February 2006. These are consistent with the guidelines of the American Academy of Neurology, which were developed in a similar manner and published in a series of papers in 2006.²⁶⁻³⁰ As co-author of the Clinical Evidence chapter on Parkinson's disease and editor of the National Electronic Library for Health's Parkinson's disease website, I have also included the trials and systematic reviews that were identified in literature searches up to February 2007.

Fig 1 | ^{123}I -FP-CIT SPECT scans. A: Essential tremor with normal uptake. B: Early Parkinson's disease with asymmetric loss of uptake in the putamen seen as loss of the "comma" from the left hemisphere. C: Late Parkinson's disease with severe loss of putamen uptake bilaterally seen as loss of both tails resulting in two "full stops." Courtesy of Dr A Notgi. Reproduced with permission from Clarke CE. *Parkinson's Disease in Practice*. 2nd ed. London: RSM Press, 2007

reduced in those with Parkinson's disease, Parkinson's disease dementias, and parkinsonian syndromes.

How should the early stages of the disease be treated?

Neuroprotective or disease modifying treatment to slow or halt progression does not yet exist; many agents have been investigated for neuroprotective properties in vitro and in vivo but without success.³

Most clinicians delay the introduction of symptomatic treatment until symptoms interfere with functional disability, on the basis that symptomatic treatment is unlikely to be effective for mild symptoms that are not interfering with life. However, this view may change if it is found that early symptomatic treatment slows progression, as has recently been suggested.¹¹

The NICE guidelines recommend that once motor symptoms interfere with everyday life, a drug should be started from one of three firstline drug classes: levodopa, dopamine agonists, or monoamine-oxidase-B inhibitors (table 1). Evidence from randomised controlled trials and systematic reviews supports the efficacy of each of these drug classes.³ What is not clear is which class to choose in any given clinical situation. For example, many specialists have adopted the policy of using a dopamine agonist in younger patients to delay the onset of motor complications (abnormal involuntary movements, end of dose wearing off, and unpredictable switching between decreased mobility (off-periods) and

Box 1 | Common causes of tremor

Rest tremor

- Parkinson's disease

Postural and action tremor

- Essential tremor
- Exaggerated physiological tremor
- Hyperthyroidism
- Drug induced (such as β agonists)
- Dystonic tremor

Intention tremor

- Cerebellar disorders

times when the medication is working and symptoms are controlled (on-periods)); these complications are more frequent if levodopa is the initial treatment.³ However, levodopa treats motor symptoms better than dopamine agonists, and many young patients may still require fine motor skills for work. In an attempt to resolve this uncertainty, the Health Technology Assessment Programme has funded the ongoing UK PD MED trial (www.pdmed.bham.ac.uk).

How should the motor complications of the disease be treated?

Most patients will eventually require levodopa, so motor complications are inevitable. At this stage, the NICE guidelines recommend adjuvant therapy to levodopa with a dopamine agonist, a monoamine-oxidase-B inhibitor, or a catechol-*O*-methyltransferase inhibitor (table 2).³ There is good evidence from randomised controlled trials and systematic reviews to show that these drugs reduce off-periods and levodopa dose, but at the expense of frequent side effects.³ However, it is not clear whether one class of adjuvant agent is superior to any other. This is the subject of the second part of the PD MED trial.

How should more advanced disease be treated?

Three randomised controlled trials were included in a Cochrane review of amantadine used to treat dyskinesias in later Parkinson's disease.¹² Even though the number of patients included was small ($n=53$) and the trials were short, the NICE guidelines recommend that amantadine should be used as an anti-dyskinesia agent.³

Table 1 | Options for initial symptomatic therapy for Parkinson's disease

	First choice option	Degree of symptom control	Risk of side effects	
			Motor complications*	Other adverse events*
Levodopa	Yes	Good	Increased	Increased
Dopamine agonists	Yes	Moderate	Reduced	Increased
Monoamine-oxidase-B inhibitors	Yes	Limited	Reduced	Increased
Anticholinergics	No	Lack of evidence	Lack of evidence	Lack of evidence
β blockers	No	Lack of evidence	Lack of evidence	Lack of evidence
Amantadine	No	Lack of evidence	Lack of evidence	Lack of evidence

Adapted with permission from NICE.³

*Evidence of increased or reduced risk of motor complications or other adverse events.

Box 2 | Common causes of a parkinsonian syndrome

- Parkinson's disease
- Alzheimer's disease
- Multiple cerebral infarction
- Drug induced parkinsonism (such as by phenothiazines)
- Wilson's disease
- Other degenerative parkinsonian syndromes: progressive supranuclear palsy, multiple system atrophy

The dopamine agonist apomorphine is not effective orally owing to extensive first pass metabolism in the liver. It was developed in the form of intermittent bolus injections to rescue patients from severe off-periods or as a subcutaneous infusion for patients with frequent off-periods. Both uses require continuous treatment with the antiemetic domperidone to prevent nausea and vomiting. Three small trials (n=56) documented the efficacy and safety of intermittent injections of apomorphine, but only observational studies are available for the subcutaneous infusion.³ Nevertheless, the NICE guidelines approved both for use in treating motor complications that are intractable to changes in oral therapy.

The NICE guidelines were prepared before the continuous infusion of a levodopa gel (Duodopa) directly into the jejunum was licensed for the management of severe motor complications. Small trials showed that these infusions reduce off-periods and improve motor function, activities of daily living, and quality of life.^{13 14} However, use of this gel infusion will be restricted by cost—£30 000 (€45 000; \$61 000) a year—and by the need for a gastrostomy in potentially ill patients.

When should surgery be considered in advanced disease?

Improved understanding of the neural mechanism of Parkinson's disease showed that the subthalamic nucleus is overactive.¹⁵ This led to the development of bilateral subthalamic stimulation surgery to switch off this nucleus. There have been many uncontrolled case series of such surgery but few randomised controlled trials.^{3 16} These showed that subthalamic stimulation reduces off-periods (and the associated disability), so medication can be reduced, thereby reducing dyskinesia. The NICE guidelines recommend subthalamic stimulation for those patients with motor complications refractory to best medical treatment who are biologically fit, have no clinically significant active comorbidity, are responsive to levodopa, and have no clinically significant active mental health problems (depression or dementia).³ Questions still remain about the long term safety of subthalamic stimulation as depression and suicide may be more common; also, more information on cost effectiveness of this expensive procedure is required. The ongoing UK PD SURG trial (www.pdsurg.bham.ac.uk/) should be able to answer these questions.

Table 2 Options for adjuvant therapy in later Parkinson's disease

	First choice option	Degree of symptom control	Risk of side effects	
			Motor complications*	Other adverse events*
Dopamine agonists	Yes	Moderate	Reduced	Increased
Catechol-O-methyltransferase inhibitors	Yes	Moderate	Reduced	Increased
Monoamine-oxidase-B inhibitors	Yes	Moderate	Reduced	Increased
Amantadine	No	Not significant	Reduced	Increased
Apomorphine	No	Limited	Reduced	Increased

Adapted with permission from NICE.³

*Evidence of increased or reduced risk of motor complications or other adverse events.

Fig 2 Management of psychosis in Parkinson's disease. Adapted with permission from NICE³

What are the non-motor features of the disease?

The motor features of Parkinson's disease can be controlled reasonably well in most patients with the measures outlined above. It is the non-motor features of the disorder which now present the greatest management challenge. Box 3 lists these non-motor features, many of which may present in primary care.

The NICE guidelines found a paucity of treatment trials for non-motor features.³ What evidence there was related to mental health conditions, particularly dementia. The trial evidence to support the efficacy and safety of cholinesterase inhibitors for Parkinson's disease dementia was inadequate, and further trials are required.³ The NICE guideline provides useful

Box 3 | Common non-motor features of Parkinson's disease

- **Mental health problems**—Dementia, depression, psychosis, anxiety, apathy
- **Falls and potential fractures**
- **Sleep disturbance**—Hypersomnolence, rapid eye movement sleep behaviour disorder, restless legs syndrome, inverted sleep-wake cycle, nocturnal akinesia
- **Autonomic disturbance**—Bowel dysfunction (including constipation), dysphagia, weight loss, dribbling of saliva, bladder dysfunction, sexual dysfunction, postural hypotension, excessive sweating
- **Pain**—Disease related (dystonia), comorbid joint disorders

Box 4 | Roles of allied health professional interventions in Parkinson's disease³**Physiotherapy**

- Gait re-education, improvement of balance and flexibility
- Enhancement of aerobic capacity
- Improvement of movement initiation
- Improvement of functional independence, including mobility and activities of daily living
- Provision of advice on safety in the home

Occupational therapy

- Maintenance of work and family roles, home care, and leisure activities
- Improvement and maintenance of transfers and mobility
- Improvement of personal self care activities, such as eating, drinking, washing, and dressing
- Education on environmental issues to improve safety and motor function
- Cognitive assessment and appropriate intervention

Speech and language therapy

- Improvement of vocal loudness and pitch range, including speech therapy programmes such as Lee Silverman Voice Treatment
- Teaching strategies to optimise speech intelligibility
- Ensuring an effective means of communication is maintained throughout the course of the disease, including use of assistive technologies
- Review and management to support the safety and efficiency of swallowing to minimise the risk of aspiration

practical advice for experts on the management of psychosis in Parkinson's disease (fig 2).

What nursing and allied health professional interventions are effective in the disease?

Three randomised controlled trials assessed the efficacy of Parkinson's disease nurse specialists versus standard care.³ The benefits of nurse specialists related to the overall patient care and the delivery of services rather than to outcome measures such as quality of life or health economics. Therefore, the NICE guidelines recommend nurse specialists for clinical monitoring and medication adjustment, a continuing point of contact for support, and a reliable source of information about clinical and social matters for patients and carers.³

SUMMARY POINTS

- Parkinson's disease should be suspected in someone with tremor, stiffness, slowness, balance problems, or gait disorders
- All patients with suspected Parkinson's disease should be referred untreated to a specialist in differential diagnosis and be reviewed regularly by the specialist for accurate diagnosis and treatment
- Much debate surrounds which drug class should be used as initial treatment for Parkinson's disease and which adjuvant therapy should be added when patients taking levodopa develop motor complications
- Patients should have access to a Parkinson's disease nurse specialist and allied health professionals throughout the course of the disease

The evidence for use of physiotherapy, occupational therapy, and speech and language therapy in Parkinson's disease is based on a small number of trials with few participants, but clinical experience suggests that they are valuable.^{3,17} The NICE guidelines conclude that all three interventions should be available to patients throughout the disease (box 4).

What treatments can we expect in the near future?

It is crucial that neuroprotective agents are found to slow or halt the progression of Parkinson's disease. However, fundamental questions remain about the design of neuroprotection trials, particularly "delayed start" trials and futility studies.^{18,19}

Continuous dopaminergic stimulation throughout 24 hours may reduce motor complications by avoiding pulsatile stimulation of dopamine receptors. The new dopamine agonist rotigotine has been formulated in a transdermal delivery system that provides 24 hour stimulation.²⁰ Once daily, prolonged release versions of the non-ergot agonists pramipexole and ropinirole are undergoing clinical trials and should be available in the next few years.²¹

Much effort has gone into developing non-dopaminergic agents for parkinsonian symptoms and/or dyskinesias (such as the adenosine A2A receptor antagonist istradefylline). However, many such agents have proved disappointing in clinical trials, perhaps because animal models do not truly reflect Parkinson's disease.²²

The prospect of restoring function to the damaged nervous system (neurorestoration) with stem cell grafts continues to generate considerable attention. However, two trials of fetal mid-brain grafts found that, although beneficial effects occur, severe off-period involuntary movements developed that necessitated pallidotomy in some cases.^{23,24} It will be many years before stem cell implants are shown in large clinical trials to be free of tumour formation and capable of controlled dopamine release. In the meantime, various nerve growth factors may be shown to stimulate the development of remaining dopaminergic neurones.²⁵

Contributors: CEC is the sole contributor.

ADDITIONAL EDUCATIONAL RESOURCES**Resources for healthcare professionals**

- National Institute for Health and Clinical Excellence. *Parkinson's disease: diagnosis and management in primary and secondary care*. London: NICE, 2006. (<http://guidance.nice.org.uk/CG35>)
- Clarke CE. *Parkinson's disease in practice*. 2nd ed. London: RSM Press, 2007.

Resources for patients

- Parkinson's Disease Society (www.parkinsons.org.uk/)
- European Parkinson's Disease Association (www.epda.eu.com/)
- American Parkinson's Disease Association (www.apdaparkinson.org/user/index.asp)
- National Parkinson Foundation (www.parkinson.org/NETCOMMUNITY/Page.aspx?&pid=201&srcid=-2)
- National Institute of Neurological Disorders and Stroke (www.ninds.nih.gov/disorders/parkinsons_disease/parkinsons_disease.htm)
- National Institute for Health and Clinical Excellence. *Parkinson's disease: information for the public*. (<http://guidance.nice.org.uk/CG35/publicinfo/pdf/English>)

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A depressed gorilla

My secretary said: "There is a very unusual patient..." (being a psychiatrist, however, I don't find "unusual patients" really come as a surprise to me) "a gorilla, an agitated gorilla."

"Is it in A&E?" I blurted out.

"No, no, it's in the zoo. The vet wants your advice."

The whole unit soon knew the story: the consultant in whose catchment area the zoo fell claimed it should be his patient, one colleague asked in an irritated manner if we were now supposed to cover the zoo as well, and many, including my room-mates, wanted to join me at the initial assessment.

So far so good, but when I got there the story was not funny at all. The gorilla, who had been the alpha male for years and was a very easy going guy, had suddenly lost interest in the leadership position and become withdrawn, which had led to fights between the other males for the leadership. The worst part was that he was constantly chewing his feet. He had already lost the proximal phalanx of one of his big toes and had a few big holes in his soles.

The vet couldn't find any medical reason for the gorilla's condition and so had resorted to a psychiatrist.

After two hours of discussion with the zookeeper and the vet and observing the dynamics of the gorillas, I came to the conclusion that my patient was depressed and decided to give him a gradually increasing dose of escitalopram. We increased this up to 50 mg as his weight was around 200 kg. At first, this seemed to have a good effect: he became less irritable and let the zookeepers care for his wounds. Everyone was enthusiastic about his progress apart from me, as I knew that the course of psychiatric illness is unpredictable and that I should not get too excited if a patient gets better or too disappointed if he gets worse.

I was right, as his improvement was not maintained. I suggested antipsychotics, as indicated in humans for automutilation, but his carers declined. Their backup plan was to send him to a zoo in Spain, and, as far as I know, he is still waiting to go to a sunnier place.

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