

A review of Parkinson's disease

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Introduction: Parkinson's disease (PD) is one of the most common neurodegenerative disorders.

Sources of data: Literature search using Medline with keywords Parkinson's disease supplemented with previously published papers known to the author.

Areas of agreement: There have been significant recent advances in the understanding of the pathogenesis of the disease. There has also been a greater realization that the disorder may be associated with significant non-motor disturbances in addition to the more commonly recognized motor complications.

Areas of controversy: Although there is growing circumstantial evidence, it remains to be proven whether any of the current treatments for PD have a neuroprotective effect.

Areas timely for developing research: Although there is no cure, there are several management options for the early treatment of PD. As the disease progresses, further treatment options are available; however, the management of late-stage motor complications and non-motor symptoms remains particularly challenging and will benefit from further clinical research.

Keywords: Parkinson's disease/motor complications/non-motor complications

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder—a synucleinopathy—with a prevalence of 160/100 000 in Western Europe rising to ~4% of the population over 80.¹ With an ageing population, the management of PD is likely to prove an increasingly important and challenging aspect of medical practice for neurologists and general physicians. Our understanding of the pathogenesis of the disease has been advanced in the last decade with the identification of several gene mutations which may shed light on the mechanisms of pathogenesis in sporadic cases of PD.

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The diagnosis of PD remains essentially a clinical one, and it is important to recognize the early features together with symptoms and signs suggesting other causes of parkinsonism.

There has also been a rapid expansion in the treatment options both in the early and in the later stages of the illness together with a greater awareness of non-motor complications. Guidelines for the diagnosis and management of patients with PD have been published from the National Institute for Health and Clinical Excellence (NICE) in the UK.²

Pathology, aetiology and pathogenesis

The pathological hallmark of PD is cell loss within the substantia nigra particularly affecting the ventral component of the pars compacta. By the time of death, this region of the brain has lost 50–70% of its neurones compared with the same region in unaffected individuals. The earliest documented pathological changes in PD³ have been observed in the medulla oblongata/pontine tegmentum and olfactory bulb. In these early stages—Braak stages 1 and 2—patients are pre-symptomatic. As the disease advances—Braak stages 3 and 4—the substantia nigra, areas of the midbrain and basal forebrain become involved. Finally, the pathological changes appear in the neocortex.

This pathological staging is based on the distribution of lewy bodies. Lewy bodies are the pathological hallmark of PD. They are α -synuclein-immunoreactive inclusions made up of a number of neurofilament proteins together with proteins responsible for proteolysis. These include ubiquitin, a heat shock protein which plays an important role in targeting other proteins for breakdown. Mutations in the α -synuclein gene are responsible for some familial forms of PD in which lewy bodies are also seen. Mutations in the parkin protein produce a parkinsonian syndrome without lewy bodies in juvenile cases suggesting that the parkin protein plays an important role in the development of the lewy body. It has been shown that parkin facilitates the binding of ubiquitin (ubiquitination) to other proteins such as the α -synuclein interacting protein synphilin-1 leading to the formation of lewy bodies.⁴ Lewy bodies are found in PD and Dementia with lewy bodies (DLB), but are not a pathological hallmark of any other neurodegenerative disease.

The identification of single gene defects in PD has focused interest on the ubiquitin-proteasome system (UPS) as one potential candidate in the development of cell death.⁵ The UPS is important for intracellular proteolysis and a large number of intracellular processes that maintain the viability of cells. It does this by removing unwanted proteins that

are no longer required by the cell. Failure of the UPS leads to the abnormal aggregation of proteins including α -synuclein which are a major component of lewy bodies. One of the first sites for LB deposition in early PD is the olfactory bulb. It is, therefore, of interest that a disturbance in smell and taste is often one of the earliest clinical features in PD raising the possibility that LB formation may be integral for the activation of pathways leading to neuronal dysfunction and death.

The link between UPS and neurodegeneration has been strengthened by the discovery of mutations in genes which code for several ubiquitin-proteasome pathway proteins in PD.

Genetics of PD^{6,7}

Although PD is usually a sporadic disease, there are a growing number of single gene mutations which have been identified. At the time of writing, 11 genes have been mapped by genetic linkage with six genes identified: α -synuclein (SNCA), ubiquitin C-terminal hydrolase like 1 (UCH-L1), parkin (PRKN), LRRK 2, PINK 1 and DJ-1 genes. These single gene defects with the notable exception of LRRK 2 are responsible for only a small number of patients with PD, though more importantly their identification and the proteins that they encode for are providing significant insight into the disease mechanisms that may be responsible for PD and other neurodegenerative diseases. A point mutation of the SNCA gene leads to the early onset of PD in affected members in an autosomal dominant pattern. Of interest, duplication or triplication of the SNCA gene in affected members leads to PD symptoms developing at a later age in the fourth or fifth decades raising the possibility that overexpression of SNCA may be a factor in sporadic disease.

The LRRK 2 gene (PARK8) is the most common cause of familial or the so-called 'sporadic' PD to date.⁸ The frequency of LRRK2 mutations in patients with a family history of PD is 5–7%. The heterozygous mutation, 2877510 g \rightarrow A, produces a glycine to serine amino acid substitution at codon 2019 (Gly2019 ser). This LRRK2 G2019S mutation is the most commonly described, accounting for the majority of familial cases and up to 1.6% of cases of idiopathic PD, though the prevalence seems to be very variable. The LRRK2 gene encodes for a protein named dardarin (derived from the basque word for tremor; the original families described came from Spain and England). Lewy bodies have been identified in some LRRK 2 cases. Many of the LRRK2 patients reported have typical features of PD with onset in middle or late onset. Symptoms at onset may be typical of idiopathic

PD characterized by unilateral bradykinesia and rigidity, with tremor present in some but not all patients.

A number of single gene mutations, e.g. parkin and DJ-1 with an autosomal recessive pattern of inheritance, may have a clinical pattern of earlier age of onset, a more benign course with good response to levodopa and the presence of dystonia. However, it is not possible to identify parkin positive young onset PD patients from parkin negative patients on clinical features alone.

There has been a great deal of research into mitochondrial genetics and function in PD. Abnormalities in Complex 1 of the oxidative phosphorylation enzyme pathway is the most consistent finding, having been detected in PD brains, blood platelets and skeletal muscle, although defects in other complexes have also been reported.⁹

It appears that the cells of the pars compacta are particularly susceptible to oxidative damage. Mitochondrial DNA studies have as yet failed to identify a convincing gene mutation to explain the oxidative phosphorylation defects in PD. However, it seems likely that a mitochondrial defect may play a role in the pathways leading to cell dysfunction and death. The PINK1 gene codes for a mitochondrial complex and has been shown to be responsible for an autosomal recessive form of PD, though is not a major risk factor for sporadic disease.

Environmental factors

Identifying environmental factors that predispose to the development of PD has proved elusive. Living in a rural environment appears to confer an increased risk of PD, and perhaps causally linked to this some but not all epidemiological studies have shown a correlation between exposure to pesticide use and wood preservatives.¹⁰ The only consistent environmental factor is a strong negative correlation between cigarette smoking and the development of the disease. It is also possible that mitochondrial dysfunction in PD is triggered by one or more environmental toxins.

Clinical diagnosis of PD

The characteristic features of PD are bradykinesia, rigidity and rest tremor. These may not all be present. Postural instability may be a feature, though early postural instability backwards particularly with a history of falls is more suggestive of progressive supranuclear palsy (PSP). The clinical findings are usually asymmetrical in PD. The clinical diagnosis may often appear straightforward, though it is worth noting

that post-mortem studies have shown an alternative diagnosis in up to a quarter of patients with PD diagnosed by general neurologists.¹¹ Of note, there is substantially less diagnostic error in patients diagnosed in expert movement disorder clinics¹² which strengthens the argument for early referral of patients to specialists expert in movement disorders.

A number of clinical criteria have been established. Table 1 outlines an abbreviated form of the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria.

There are a number of other clinical signs that are worth highlighting. A change of handwriting with micrographia is often an early feature as is reduced facial expression. A loss of arm swing on one side is also an early and useful diagnostic feature. A glabellar tap does not seem to be particularly sensitive or specific.

A reduced sense of smell is, however, worth asking about since this may be one of the first symptoms in early PD.¹³ As the disease becomes more advanced, hypophonia, drooling of saliva (from reduced swallowing) and impairment of postural reflexes may develop.

Table 1 PD–UK PDS Brain Bank diagnostic criteria.

Step 1: Diagnosis of a parkinsonian syndrome

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and at least one of the following: (i) muscular rigidity, (ii) 4–6 Hz rest tremor and (iii) postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Step 2: Exclusion criteria for PD

- (i) History of repeated strokes with stepwise progression of parkinsonian features
- (ii) History of repeated head injury
- (iii) History of definite encephalitis
- (iv) Oculogyric crises
- (v) Neuroleptic treatment at the onset of symptoms
- (vi) More than one affected relative
- (vii) Sustained remission
- (viii) Strictly unilateral features after 3 years
- (ix) Supranuclear gaze palsy
- (x) Cerebellar signs
- (xi) Early severe autonomic involvement
- (xii) Early severe dementia with disturbances of memory, language and praxis
- (xiii) Babinski's sign
- (xiv) Presence of cerebral tumour or communicating hydrocephalus on CT scan
- (xv) Negative response to large doses of levodopa (if malabsorption excluded)

Step 3: Supportive criteria for PD (three or more required for diagnosis of definite PD)

- (i) Unilateral onset
- (ii) Rest tremor present
- (iii) Progressive disorder
- (iv) Persistent asymmetry affecting side of onset most
- (v) Excellent response (70–100%) to levodopa
- (vi) Severe levodopa-induced chorea
- (vii) Levodopa response for 5 years or more
- (viii) Clinical course of 10 years or more

Non-motor complications of the disease often become more troublesome as the disease progresses. It is helpful to enquire about symptoms of depression which occurs in ~40% of PD patients. The commoner conditions that may present with parkinsonian features and are often confused with PD are listed in Table 2. The diagnosis of essential tremor should be considered when a patient presents with a

Table 2 Differentiating commoner causes of parkinsonism.

Condition	History	Clinical features	Investigations	Management
Drug-induced parkinsonism	Previous exposure to drugs mainly neuroleptic treatment and anti-emetics	May be associated with akathisia and oro-mandibular dystonia	Based on history	Discontinue offending drug. Anticholinergic drugs may be helpful for tremor
Multisystem atrophy	Parkinsonism and or gait unsteadiness with or without autonomic dysfunction	Orthostatic hypotension, absence of tremor, symmetrical signs, cerebellar features, erectile dysfunction, poor response to levodopa	MRI brain, sphincter EMG	Levodopa trial, amantidine measures to control postural hypotension, e.g., fludrocortisone
Progressive supranuclear palsy	Early falls backwards, cognitive or behavioural changes	Gaze palsy (down more than up), axial rigidity, frontal and pyramidal signs, poor response to levodopa	MRI brain	Levodopa trial
Normal-pressure hydrocephalus	Urinary incontinence, ataxia, cognitive impairment	Dementia festinating gait	CT or MRI brain, therapeutic lumbar puncture	Evaluate for ventriculoperitoneal shunt
Multiple lacunar strokes	Stepwise neurological impairment	Focal findings, sensory or motor loss	CT or MRI brain	Antiplatelet treatment, control of risk factors (e.g., diabetes, hypertension, increased cholesterol)
Cortico basal degeneration	Associated cognitive impairment	Marked asymmetry of clinical findings, dyspraxia, cortical sensory loss, myoclonus, dystonia, alien limb phenomenon, absence of response to levodopa	EEG, psychometry	
Dementia with lewy bodies	Dementia occurring before or concurrently with parkinsonism	Visual hallucinations	MRI brain, psychometry	Consider cholinesterase inhibitor

symmetrical limb tremor, worse with posture and is suppressed by alcohol. Head or voice tremor may also be present. In this condition, there may be an autosomal dominant inheritance, suppression of the tremor with alcohol and there should be no evidence of rigidity or bradykinesia on examination. Adult onset dystonia may also present with asymmetrical rest tremor and may explain some patients previously labelled as 'benign tremulous PD' who have scans with no evidence of dopaminergic deficit.¹⁴

Although the diagnosis of PD is a clinical one, there are certain situations where investigations can prove useful. Conventional brain imaging with MRI or CT is usually not required unless an alternative diagnosis is suspected such as normal pressure hydrocephalus or vascular parkinsonism.

Single photon emission computerized tomography (SPECT) imaging using a dopamine transporter (DAT) can be helpful in differentiating PD from a number of conditions, including essential tremor and dystonic tremor, neuroleptic-induced parkinsonism and psychogenic parkinsonism all of which demonstrate normal DAT scans. Uptake within the basal ganglia is reduced in PD, the parkinsonian syndromes and DLB.¹⁵

Management of early PD

After establishing a clinical diagnosis, it is vital to take time to explain the condition and its implications to the patient and relatives. It may take for some patients time to come to terms with and accept the diagnosis. Linking patients with PD nurse specialists and PD charitable organizations, if available locally, can be extremely helpful.

The timing when to start drug treatment in PD, particularly in the very early stages of the illness, when there may be little functional deficit can be difficult. The decision which should be made with full involvement of the patient is determined by the degree of physical impairment balanced against the complications that can be related to drug treatment. Of increasing importance is the issue of whether early treatment confers the potential for neuroprotection. This remains unresolved, despite a large number of *in vitro*, *in vivo* and human studies many of the latter using PET or SPECT imaging as surrogate markers of nigrostriatal dopaminergic function.¹⁶

At present, therefore, there are no proven neuroprotective therapies with only symptomatic treatments available.

If the patient and clinician feel treatment is required, what therapy should be commenced? This decision will be based on the age of the patient, the likelihood of proper compliance, the presence of cognitive

impairment, additional medical conditions and the wishes of the patient. Treatment in the initial stage is to alleviate symptoms allowing the individual to be fully independent and to carry out their normal daily activities. It is vital that treatment is well tolerated. For this reason, monotherapy is usually desirable. If patients can remain on treatment with minimal side effects, with a satisfactory reduction of symptoms and a feeling of well-being that allows them to live independently and productively, then the introduction of treatment has clearly been worthwhile.

In patients with minimal or no disability, early treatment may still be initiated. One study has shown that self-reported health status using a Parkinson's Disease Questionnaire (PDQ)-39 at initial consultation and for up to 18 months was worse in untreated PD patients,¹⁷ though the validity of the rating scale in this patient group has been questioned.¹⁸

Should treatment begin with levodopa, a dopa agonist or MAO-B inhibitor?

First line levodopa treatment

For 40 years, levodopa, combined with a peripheral decarboxylase inhibitor, has been regarded as the gold standard for the treatment of PD. It still remains in many respects the most efficacious drug treatment. However, the benefits achieved often come at a price. Long-term levodopa therapy frequently leads to disabling side effects. Levodopa-induced dyskinesias develop at an average rate of 10% per annum after commencing levodopa, although this figure is higher in younger onset patients. Motor fluctuations are most strongly related to disease duration and dose of levodopa exposure, whereas dyskinesias are predominantly due to duration of levodopa treatment.¹⁹ The development of drug-induced dyskinesias in PD seems to be associated with intermittent stimulation of dopamine receptors. Levodopa has a short half-life of 60–90 min, and pulsatile levodopa supply to a denervated striatum seems to be an important aetiological factor. In addition, the more severe the nigral neuronal loss is at the introduction of levodopa, the sooner adverse features are seen. A controversial issue has been whether levodopa could have a neurotoxic effect. The ELLDOPA study^{20,21} tried to address this in a large, randomized placebo-controlled clinical study of patients with early PD who had not previously received symptomatic treatment. The goal of the study was to ascertain whether levodopa treatment affected the rate of disease progression. At the end of a 2-week washout period, the UPDRS scores of patients treated with all three doses of levodopa were better than those

of the placebo group in a dose-responsive pattern. Although this may hint at a neuroprotective effect, it is possible that the 2-week washout period was insufficient. However, the treated groups did show a dose-dependent tendency towards motor complications including dyskinesias. In addition to clinical outcomes, a sub-group of patients underwent β -CIT SPECT imaging which was used as a marker for intact nigrostriatal dopaminergic neurones. This showed a larger decrease in striatal DAT binding in a dose-response pattern. This may infer that levodopa actually hasten the progression of PD, though it is equally conceivable that the changes in uptake reflected a pharmacological effect of levodopa on DAT activity. The issue regarding neuroprotection or neurotoxicity with levodopa remains unclear. However, given the risk of motor complications over time, which are dose dependent, using small doses of levodopa, tailored to the patient's needs are preferable.

First line dopamine agonist treatment

There are six orally acting dopamine agonists available in the UK. Four are ergot derivatives: bromocriptine, pergolide, cabergoline and lisuride; and two non-ergot drugs: ropinirole and pramipexole. Rotigotine is a non-ergot agonist available by transdermal patch. These drugs all work by stimulation of the post-synaptic dopamine receptors. The dopamine agonists were initially licensed for use in conjunction with levodopa in patients with advanced PD. Their introduction as first-line agents came about as a result of their efficacy in improving motor symptoms in addition to their ability to delay the introduction of levodopa and the subsequent development of levodopa complications. Monotherapy trials have been undertaken comparing dopamine agonists with levodopa. The first such trial using bromocriptine in the 1980s showed a delay in the onset of dyskinesias with bromocriptine monotherapy compared with levodopa therapy, but no effect with regards to the onset of motor fluctuations.²² Trials of the more recently introduced dopamine agonists showed a significant reduction in the development of motor complications in patients initiated on agonist monotherapy compared with levodopa.^{23–25} However, in the published trials of ropinirole and pramipexole monotherapy, patients treated with levodopa showed improved UPDRS scores (parts II and III) compared with those on dopamine agonists, although during the trials, patient and physician assessments for the two arms were comparable. Quality of life (QoL) outcome measures over the 4 years of the CALM-PD study²⁴ were the same for the levodopa and pramipexole groups. The side effect profile of the dopamine agonists is similar to levodopa, but

confusion and hallucinations are more frequent than with levodopa therapy alone.

The dilemma of first line treatment in PD is therefore this: dopamine agonists produce fewer motor complications and the same QoL scores, but the price for this is a higher incidence of side effects and reduced efficacy as determined by the UPDRS. There has been a general belief that the potential for side effects with dopa agonist monotherapy is much greater in elderly patients, but studies with the newer agonists do not bear this out and these drugs can be well tolerated in patients over 75 years. However, as suggested above, additional caution is required in using agonists in the elderly.

The decision on which dopamine agonist to initiate is often an empirical one. There have been few head-to-head comparative studies between the agonists. Cabergoline is an ergot derivative with a high affinity for the D2 and D3 receptors. However, there have been increasing reports of non-inflammatory fibrotic degeneration of cardiac valves with the ergot agonists,^{26,27} specifically cabergoline and pergolide, and for this reason, they are no longer recommended as first-line treatments. Regular monitoring including ESR, chest X-ray and 6-monthly echocardiography are recommended for those continuing on ergot-derived agonists.

Commonly used non-ergot-derived dopamine agonists include ropinirole, pramipexole and rotigotine. An uncommon, but important, side effect most frequently reported to date with pramipexole is an increased risk of pathological gambling.^{28,29}

First-line MAO-B inhibitors

MAO-B inhibitors were widely used following the DATATOP study³⁰ for their proven efficacy in symptom improvement and presumed 'neuroprotective' effect. However, a subsequent study by The United Kingdom Parkinson's Disease Research Trial Group³¹ following over 700 patients with mild early PD appeared to show a significant increase in mortality in patients treated with selegiline and levodopa compared with levodopa alone or bromocriptine alone. This finding was not replicated in further studies which indeed suggested the opposite, a possible reduction in mortality.³² A more recent meta-analysis of 17 randomized trials involving a total of 3525 patients came to the conclusion that MAO-B inhibitors reduce disability, the need for levodopa and the incidence of motor fluctuations, without substantial side effects or increased mortality.³³ Many of these studies have been of short duration and have not compared selegiline with initial treatment with a dopamine agonist. However, MAO-B inhibitors do have

a potential role as first-line monotherapy in PD patients. Studies using rasagiline, a novel MAO-B inhibitor, have demonstrated efficacy in early and advanced disease. The TEMPO wash-in trial³⁴ gave results compatible with a disease modifying effect, although like the dopamine agonist studies cited above, additional work needs to be done to confirm a neuroprotective effect.

The treatment of late motor complications of PD

After some years of stable, sustained response to levodopa therapy, most patients with PD experience fluctuations in motor performance, the effect of a single levodopa dose becoming progressively shorter (wearing-off phenomenon). Also, periods of immobility unrelated to times of levodopa supply occur in most advanced cases (on-off phenomenon). Levodopa-induced dyskinesias occur with increasing duration of therapy, and more than 50% of patients will begin to develop motor fluctuations and dyskinesias between 5 and 10 years after commencing levodopa with 20–30% developing dyskinesias after <2 years. In younger patients, the situation is worse, with almost all patients under the age of 40 developing motor complications after 6 years from the introduction of levodopa. Treatment of levodopa-induced dyskinesias remains unsatisfactory. Simply reducing the daily dose frequently renders patients rigid and immobile.

Furthermore, choreic-dystonic involuntary movements appear as a concomitant of motor response to levodopa in most patients suffering from motor fluctuations. Dyskinesias are usually present during periods of maximum motor response (peak-dose dyskinesias) or during the entire ON phase (square wave dyskinesia), but a diphasic pattern, with dyskinesias present at the beginning and end of motor response, also exists. Peak-dose dyskinesias are related to high-plasma concentrations of levodopa and can be managed by fractionating levodopa doses. Amantidine has also been shown to reduce peak-dose dyskinesias. Long-acting dopamine agonists such as rotigotine may also be helpful by providing continuous dopaminergic stimulation. Biphasic dyskinesias occur when plasma levodopa levels are rising or falling. They often affect the lower extremities to a greater extent. They may be difficult to control, but may respond to higher levodopa doses or a fast-acting agonist such as subcutaneous apomorphine injection. Off-period dystonia also affects the lower limbs preferentially and is associated with periods of inadequate mobility. This may respond to a dispersible levodopa preparation or subcutaneous apomorphine injection. The pathophysiology of motor complications during chronic levodopa therapy (levodopa long-term syndrome) is only partially

understood. Currently, the consensus is that they reflect both progression of the underlying disease and the effects of intermittent, pulsatile levodopa supply to a denervated striatum.

A number of treatments have been used to reduce the severity and frequency of motor complications. The dopamine agonists have shown beneficial effects in the reduction of 'off' time and a concomitant reduction in levodopa dose in the later stages of the disease. However, this has to be balanced against a possible increase in dyskinesias. Other side effects which are commoner include somnolence and hallucinations. It does seem that the more recent agonists such as pramipexole and ropinirole have benefit over bromocriptine by reducing 'off' time.^{35,36}

Amantadine, an NMDA receptor antagonist, was originally developed as an anti-viral agent. By chance it was discovered to have additional properties including efficacy in PD. There is evidence that amantadine can reduce the frequency of motor complications including freezing, 'off' periods and dyskinesias,^{37,38} although the evidence for efficacy was felt to be insufficient in a Cochrane review.³⁹ There is, particularly in the elderly, a relatively high incidence of side effects which include confusion, hallucinations, ankle swelling and livedo reticularis.

Parenteral administration of a dopamine agonist in the form of subcutaneous apomorphine⁴⁰ may be a useful adjunct to treatment by reducing 'off' time without increasing the tendency towards dyskinesias or confusion. Similarly, duodenal levodopa infusion therapy has been shown to reduce 'off' time, to improve motor function and improve QoL with no increase in dyskinesias in patients with advanced PD.⁴¹

COMT inhibitors

Entacapone is a peripheral catechol-O-methyltransferase COMT inhibitor that complements the action of amino acid de-carboxylase (AADC) inhibitors. Assuming that the volume of distribution remains unchanged, the addition of entacapone increases the plasma half-life of levodopa by ~45% after each dose. Similarly, tolcapone produces a dose-dependent increase in levodopa half-life, even though it is given independently of the levodopa dose regime. When entacapone or tolcapone are added to levodopa/AADC-inhibitor therapy, they inhibit COMT—one of the enzymes responsible for the metabolism of dopamine—resulting in greater and more sustained plasma and central nervous system levels of dopamine than with levodopa/carbidopa alone, producing a prolonged duration of antiparkinsonian action and subsequent improvements in motor function. COMT inhibition,

therefore, translates into less fluctuation of levodopa plasma concentrations, so that levels remain within the therapeutic range and benefit from each dose of levodopa will be prolonged. Tolcapone was originally withdrawn because of reports of hepato-toxicity, but has recently been re-introduced for restricted use under strict monitoring guidelines. This is not the case with entacapone which is also available as a combined triple medication (with levodopa and an AADC inhibitor) to improve compliance.

The introduction of a COMT inhibitor can be a safe and effective way of smoothing out fluctuations in motor response. COMT inhibitors reduce 'off' periods, prolong the 'on' time and allow a reduction of the levodopa dose.⁴² They do not, however, have a levodopa sparing effect.

Entacapone and tolcapone are potent, specific and reversible COMT inhibitors that offer significant benefits, particularly in managing motor fluctuations in patients with late-stage Parkinson's disease, when wearing off is an important factor. They are also likely to have an increasing role in the earlier stages of the illness. A study is currently underway to determine whether the introduction of levodopa and entacapone together reduces the development of dyskinesias compared with levodopa alone.

The role of surgery in PD^{43–45}

The use of surgery in PD dates back over 50 years. In the early 1950s, patients particularly those with severe tremor would on occasion be referred for ablative surgery usually to the contralateral thalamus. With the introduction of levodopa, surgical treatment fell from vogue. It is somewhat ironic that the widespread recognition of levodopa-induced complications prompted surgeons and clinicians to revisit the area of surgical intervention. Initially, this concentrated on lesion surgery usually in the form of pallidotomy which was shown to be successful particularly for levodopa-induced dyskinesias.

A further development came with the introduction of stimulators. This involved high-frequency deep brain stimulation (DBS) of discrete brain areas producing functional and reversible inhibition of the target site. A number of areas within the basal ganglia can be targeted. The procedure most commonly carried to reduce bradykinesia, tremor and rigidity and which also reduces drug-related motor complications is bilateral subthalamic stimulation. This can produce very dramatic benefit. The operation is technically difficult, but in experienced hands the risk of adverse events is low. However, the infrastructure and support team required to assess, carry out and monitor patients limits

the availability of this form of treatment. Furthermore, there is concern about the increased incidence of psychiatric side effects, particularly depression following DBS. Patients with cognitive impairment or significant depression are, therefore, not suitable for this form of treatment. In terms of patients most suitable for treatment,⁴⁶ STN DBS tends to be performed in patients under the age of 75 without significant systemic co-morbidity and in the absence of obvious structural abnormality on MR imaging. Patients should be levodopa-responsive who are disabled while 'off' and independent while 'on' with medication. Most patients will have had disease duration of at least 5 years to allow for other causes of atypical parkinsonism to become evident.

Age seems to be less critical in Vim DBS performed for disabling tremor. Recent studies have suggested that DBS of the pedunculopontine nucleus may be beneficial in improving axial stability. Assessment of a patient for DBS requires assessment by an experienced multidisciplinary team.⁴⁶

Non-motor complications

With the progression of the disease, there are a number of non-motor complications in PD that are often seen. In many cases, these are not directly related to involvement of dopaminergic pathways and may therefore develop even in patients where motor symptoms are well controlled.

Sleep and PD

Sleep disorders are frequent in PD. This includes both disturbed nocturnal sleep and excessive daytime somnolence. Nocturnal sleep disturbance occurs in 60–98% of patients and correlates with disease severity and levodopa intake. Although the underlying pathology of PD may be in part responsible, it is important to also exclude associated disorders such as medication-related sleep disturbance including off-dystonia, depression, obstructive sleep apnoea, REM sleep behavioural disturbance (RBD), periodic limb movements of sleep and restless leg syndrome (RLS). RBD is a parasomnia characterized by the loss of normal skeletal muscle atonia during REM sleep with prominent motor activity accompanying dreaming and is increasingly recognized in patients with neurodegenerative disease, particularly the synucleinopathies. There is evidence that its development can predict cognitive impairment in PD patients without dementia.⁴⁷ If troublesome, it may respond to a small amount of clonazepam at night.

Daytime sleep events are also more common in PD. In the most extreme form, this can constitute sudden irresistible attacks of sleep attacks without warning.^{48,49} These episodes have been reported in patients on levodopa monotherapy alone, but are more frequent with the use of dopamine agonists, particularly ropinirole and pramipexole. Patients need to be counselled to stop driving and to avoid operating machinery if these develop. These settle spontaneously as the offending drug is withdrawn.

Cognition in PD

Cognitive involvement in PD seems to be common. Many patients with PD develop dementia, typically 10 years or more after the onset of motor symptoms. The frequency of overt dementia varies from study to study depending on definition, methods of cognitive assessment and population differences, but is of the order of 40% for all PD patients. More subtle cognitive disturbance particularly of executive function is extremely common even in early PD.

Dementia in PD may be related to a number of pathologies. However, it seems to be the development of cortical lewy bodies and/or Alzheimer pathology which are most relevant. The cholinesterase inhibitors rivastigmine, donepezil and galantamine have been shown in open studies to have a modest benefit in cognitive function and in the amelioration of hallucinations and psychosis in patients with PD-related dementia, although robust evidence-based data are strongest at this time for rivastigmine⁵⁰ and to a lesser extent donepezil.⁵¹

Dementia with lewy bodies or Parkinson's disease with dementia?

There has been controversy over the differentiation of Parkinson's disease with dementia (PDD) and DLB. DLB is diagnosed when dementia occurs before or concurrently with parkinsonism. An arbitrary cutoff is often used—the 1 year rule—where a diagnosis of PDD is made if extrapyramidal motor symptoms are present for 12 months or more before the onset of dementia and DLB if the onset of dementia precedes or occurs within 1 year of parkinsonism. Revised criteria for the clinical diagnosis of DLB have been published.⁵² These rely on the presence of a dementing process with additional core features of fluctuating cognition and variation in attention and alertness, recurrent visual hallucinations and parkinsonian features. Parkinsonian signs have been correlated with the severity of dementia in DLB. There are several features that may help distinguish DLB from PD: myoclonus, absence of rest tremor and poor

response to levodopa and severe neuroleptic sensitivity. Both DLB and PDD are characterized pathologically by the presence of lewy bodies, though in PDD patients there is greater neuronal loss within the substantia nigra whereas in DLB patients there is greater cortical beta-amyloid deposition. In DLB, the dementia produces marked deficit in visuo-spatial and executive function with prominent visual hallucinations and fluctuating attention. DLB patients are often less levodopa-responsive. It is important to remember in both patient groups that dopaminergic drugs can substantially exacerbate confusion and visual hallucinations in both conditions. Both conditions respond to cholinesterase inhibitors. For a recent update on the distinction between PDD and DLB, please refer to the review by McKeith.⁵³

Mood disturbance and PD

Depression is the most common mood disturbance in PD occurring with a prevalence of up to 50%⁵⁴ and occurring at any stage of the illness. Patients should be screened for underlying metabolic disturbances such as hypothyroidism which can be easily confused with a depressive illness. Mood fluctuations are commoner in more advanced disease and have a stronger correlation with motor fluctuations.⁵⁵

Depression, when diagnosed, can be treated with cognitive behavioural therapy and antidepressants including tricyclics and short acting serotonin uptake inhibitors (SSRIs). There is evidence that pramipexole has a significant antidepressant action.⁵⁶

Psychosis and confusion in PD

Psychosis can occur in up to 30% of PD patients.⁵⁷ It often presents with hallucinations which are usually visual together with delusions and agitation or sometimes aggression. Patients may become paranoid particularly towards partners or other family members. Psychosis is possibly mediated by loss of dopaminergic neurones particularly in the nigro-mesolimbic projections. It is often a feature in the development of PDD or DLB.

Most of the older antipsychotic agents tend to substantially worsen motor symptoms and should be avoided. The newer 'atypical' antipsychotic agents such as quetiapine and clozapine are better tolerated and often effective. Clozapine requires close monitoring of the white cell count because of a 1% incidence of agranulocytosis. Acetylcholinesterase inhibitors may also be beneficial in reducing hallucinations and delusions in PD patients.

Conclusion

PD is a common neurodegenerative illness. A combination of genetic and environmental factors is likely to be important in producing abnormal protein aggregation within select groups of neurones, leading to cell dysfunction and then death. The diagnosis remains a clinical one, and there should be a high index of suspicion to exclude other causes of parkinsonism. A large number of agents together with surgical interventions are now available to treat early and late complications of PD. Increasing attention is being given to the diagnosis and treatment of non-motor complications in PD. Future developments in PD are likely to focus on the concept of disease modifying drugs which offer neuroprotection.

References

- 1 Mutch WJ, Dingwall-Fordyce I, Downie AW *et al.* (1986) Parkinson's disease in a Scottish City. *BMJ*, **292**, 534–536.
- 2 National Institute for Health and Clinical Excellence (2006) *Parkinson's Disease: Diagnosis and Management in Primary and Secondary Care*. London: NICE (<http://guidance.nice.org.uk/CG35>).
- 3 Braak H, Bohl JR, Müller CM *et al.* (2006) Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. *Mov Disord*, **21**, 2042–2051.
- 4 Chung KK, Zhang Y, Lim KL *et al.* (2001) Parkin ubiquitinates the alpha-synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease. *Nat Med*, **7**, 1144–1150.
- 5 Betarbet R, Sherer TB, Greenamyre JT (2005) Ubiquitin-proteasome system and Parkinson's diseases. *Exp Neurol*, **191** (Suppl 1), 17–27. Review.
- 6 Warner TT, Schapira AH (2003) Genetic and environmental factors in the cause of Parkinson's disease. *Ann Neurol*, **53** (Suppl 3), S16–S23; discussion S23–S25. Review.
- 7 Cookson MR, Xiromerisiou G, Singleton A (2005) How genetics research in Parkinson's disease is enhancing understanding of the common idiopathic forms of the disease. *Curr Opin Neurol*, **18**, 706–711.
- 8 Gilks WP, Abou-Sleiman PM, Gandhi S *et al.* (2005) A common LRRK2 mutation in idiopathic Parkinson's disease. *Lancet*, **365**, 415–416.
- 9 Schapira AH (2008) Mitochondria in the aetiology and pathogenesis of Parkinson's disease. *Lancet Neurol*, **7**, 97–109.
- 10 Dick FD (2006) Parkinson's disease and pesticide exposures. *Br Med Bull*, **79–80**, 219–231.
- 11 Hughes AJ, Daniel SE, Kilford L *et al.* (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*, **55**, 181–184.
- 12 Hughes AJ, Daniel SE, Ben-Shlomo Y *et al.* (2002) The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain*, **125**, 861–870.
- 13 Hawkes CM (1995) Diagnosis and treatment of Parkinson's disease. Anosmia is a common finding. *BMJ*, **310**, 1668. No abstract available. Erratum in: *BMJ* (1995) **311**, 129.
- 14 Schneider SA, Edwards MJ, Mir P *et al.* (2007) Patients with adult-onset dystonic tremor resembling parkinsonian tremor have scans without evidence of dopaminergic deficit (SWEDDs). *Mov Disord*, **22**, 2210–2215.
- 15 Poewe W, Scherfler C (2003) Role of dopamine transporter imaging in investigation of parkinsonian syndromes in routine clinical practice. *Mov Disorders*, **S7**, 16–21.

- 16 Schapira AH, Olanow CW (2004) Neuroprotection in Parkinson's disease. *JAMA*, **291**, 358–364.
- 17 Grosset D, Taurah L, Burn DJ *et al.* (2007) A multicentre longitudinal observational study of changes in self reported health status in people with Parkinson's disease left untreated at diagnosis. *J Neurol Neurosurg Psychiatry*, **78**, 465–469.
- 18 Hagell P (2007) Self-reported health in people with Parkinson's disease left untreated at diagnosis. *J Neurol Neurosurg Psychiatry*, **78**, 442.
- 19 Schrag A, Quinn N (2000) Dyskinesias and motor fluctuations in Parkinson's disease: a community-based study. *Brain*, **123**, 2297–2305.
- 20 Fahn S (1999) Parkinson disease, the effect of levodopa and the ELLDOPA trial (earlier vs later L-dopa). *Arch Neurol*, **56**, 529–535.
- 21 Parkinson Study Group (2004) Levodopa and the progression of Parkinson disease: the ELLDOPA study. *N Engl Med J*, **351**, 2498–2508.
- 22 Lees AJ, Stern GM (1981) Sustained bromocriptine therapy in previously untreated patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*, **44**, 1020–1023.
- 23 Rascol O, Brooks DJ, Korczyn AD *et al.* (2000) A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. *N Engl J Med*, **342**, 1484–1491.
- 24 Parkinson Study Group (2000) Pramipexole vs Levodopa as initial treatment for Parkinson Disease: a randomized controlled trial. *JAMA*, **284**, 1931–1938.
- 25 Parkinson Study Group (2004) Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. *Arch Neurol*, **61**, 1044–1053.
- 26 Muller T, Fritze J (2003) Fibrosis associated with dopamine agonist therapy in Parkinson's disease. *J Clin Neuropharmacol*, **26**, 109–111.
- 27 Zanettini R, Antonini A, Gatto G *et al.* (2007) Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med*, **356**, 39–46.
- 28 Voon V, Hassan K, Zurowski M *et al.* (2006) Prospective prevalence of pathologic gambling and medication association in Parkinson disease. *Neurology*, **66**, 1750–1752.
- 29 Imamura A, Uitti RJ, Wszolek ZK (2006) Dopamine agonist therapy for Parkinson disease and pathological gambling. *Parkinsonism Relat Disord*, **12**, 506–508.
- 30 Parkinson's study group (1989) Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*, **321**, 1364–1371.
- 31 The Parkinson's Disease Research Group of the United Kingdom (1995) Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ*, **311**, 1602–1607.
- 32 Parkinson Study Group (1996) Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. *Ann Neurol*, **39**, 37–45.
- 33 Ives NJ, Stowe RL, Marro J *et al.* (2004) Monoamine oxidase type B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525 patients. *BMJ*, **329**, 593. Epub August 13, 2004.
- 34 Parkinson Study Group (2002) A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. *Arch Neurol*, **59**, 1937–1943.
- 35 Mizuno Y, Yanagisawa N, Kuno S *et al.* (2003) Japanese Pramipexole Study Group: randomized, double-blind study of pramipexole with placebo and bromocriptine in advanced Parkinson's disease. *Mov Disord*, **18**, 1149–1156.
- 36 Brunt ER, Brooks DJ, Korczyn AD *et al.* (2002) A six-month multicentre, double-blind, bromocriptine-controlled study of the safety and efficacy of ropinirole in the treatment of patients with Parkinson's disease not optimally controlled by L-dopa. *J Neural Transm*, **109**, 489–502.
- 37 Verhagen ML, Del DP, van den Munckhof P *et al.* (1998) Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology*, **50**, 1323–1326.
- 38 Lugging E, Wenning GK, Bosch S *et al.* Beneficial effects of amantadine on L-dopa-induced dyskinesias in Parkinson's disease. *Mov Disord*, **15**, 873–878.
- 39 Crosby N, Deane KHO, Clarke CE (2005) Amantadine in Parkinson's disease (Cochrane Review). *The Cochrane Library*, Issue 2.
- 40 Poewe W, Wenning GK (2000) Apomorphine: an underutilized therapy for Parkinson's disease. *Mov Disord*, **15**, 789–794.

- 41 Nyholm D, Nilsson Remahl AI, Dizdar N *et al.* (2005) Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology*, **64**, 216–223.
- 42 Rinne UK, Larsen JP, Siden A *et al.* (1998) Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. *Neurology*, **51**, 1309–1314.
- 43 Gross RE, Lozano AM (2000) Advances in neurostimulation for movement disorders. *Neurol Res*, **22**, 247–258.
- 44 Limousin P, Krack P, Pollack P *et al.* (1998) Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med*, **339**, 1105–1111.
- 45 Volkmann J, Allert N, Voges J *et al.* (2001) Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. *Neurology*, **56**, 548–551.
- 46 Moro E, Lang AE (2006) Criteria for deep-brain stimulation in Parkinson's disease: review and analysis. *Expert Rev Neurother*, **6**, 1695–1705.
- 47 Vendette M, Gagnon JF, Decary A *et al.* (2007) REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. *Neurology*, **69**, 1843–1849.
- 48 Frucht S, Rogers JD, Greene PE (1999) Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology*, **52**, 1908–1910.
- 49 Brown RG, Marsden CD (1984) How common is dementia in Parkinson's disease. *Lancet*, **2**, 1262–1265.
- 50 Emre M, Aarsland D, Albanese A *et al.* (2004) Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med*, **351**, 2509–2518.
- 51 Ravina B, Putt M, Siderowf A *et al.* (2005) Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study. *J. Neurol Neurosurg Psychiatry*, **76**, 934–939.
- 52 McKeith I, Dickson D, Emre M *et al.* (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*, **65**, 1863–1872. Epub October 19, 2005. Review. Erratum in: *Neurology*, (2005) **65**, 1992.
- 53 McKeith I (2007) Dementia with Lewy bodies and parkinson's disease with dementia: where two worlds collide. *Pract Neurol*, **7**, 374–382.
- 54 Dooneief G, Mirabello E, Bell K *et al.* (1992) An estimate of the incidence of depression in idiopathic Parkinson's disease. *Arch Neurol*, **49**, 305–307.
- 55 Richard IH, Frank S, McDermott MP *et al.* (2004) The ups and downs of Parkinson disease: a prospective study of mood and anxiety fluctuations. *Cogn Behav Neurol*, **17**, 201–207.
- 56 Rektorova I, Rektor I, Bares M *et al.* (2003) Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. *Eur J Neurol*, **10**, 399–406.
- 57 Naimark D, Jackson E, Rockwell E *et al.* (1996) Psychotic symptoms in Parkinson's disease patients with dementia. *J Am Geriatr Soc*, **44**, 296–299.