Parkinson’s disease: diagnosis and current management

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Treatment for Parkinson’s should be tailored to the needs of the patient and adjusted regularly to ensure maximum efficacy and tolerability. Our drug review outlines diagnosis, drug options and advanced therapies, and the management of complications, followed by an analysis of the prescription data.

Parkinson’s disease (PD) is one of the most common neurodegenerative disorders. Part of its core pathology is the loss of the dopaminergic nigrostriatal pathway, which is involved in the control of movements as well as aspects of cognition and possibly motivation. Loss of dopamine neurons in this network classically leads to bradykinesia, rigidity, resting tremor and postural instability. Following the introduction of levodopa in the mid-1960s, management of the motor features of this condition has greatly improved, but at present no therapy has been proven to halt disease progression. Many features of more severe PD, such as falls and dementia, respond poorly to medications, in part because the pathological basis of these aspects of PD lies outside this dopaminergic pathway. This review will address key points in the treatment of PD.

Diagnosis

In the clinic there is currently no definitive test for PD. Diagnosis is based on the UK PD Society Brain Bank Criteria and NICE guidelines. The diagnosis requires inclusion of bradykinesia (slowness of movement) and at least one of the following features: extrapyramidal rigidity, rest tremor, and postural instability (see Table 1) in the absence of exclusion criteria (see Table 2).

The challenge in diagnosing PD is to identify atypical features that could lead to an alternative diagnosis. This can be particularly difficult in the early stages of the disease. Ten per cent of cases diagnosed with PD will later be reclassified as atypical parkinsonism or a Parkinson’s plus syndrome. These forms of parkinsonism can mimic idiopathic PD (IPD); however, they frequently respond poorly to levodopa, are often more symmetrical from onset and may have little or no rest tremor. Although postural instability and falls are part of the criteria for diagnosing PD, they are not usually an early feature of PD. If they occur within the first year or two of diagnosis, this should raise the clinician’s suspicion of atypical Parkinsonism. Other mimics of PD include vascular PD, essential tremor and drug-induced PD. Other mimics of PD include vascular PD, essential tremor and drug-induced PD.
Aetiology
The pathological hallmark of PD is the presence of intracellular protein aggregates called Lewy bodies. The cause of degeneration has been attributed to both environmental and genetic factors. The main genetic contribution to the disease has come from looking at large kindreds with inherited disease, genome-wide association studies in large cohorts of patients with sporadic disease and the recent discovery linking the development of parkinsonism and Gaucher’s disease (GD), a lysosomal storage disorder caused by mutations in glucocerebrosidase (GBA). In the remaining cases of sporadic PD, advancing age remains the major risk factor. Many dopaminergic toxins such as rotenone, a naturally occurring pesticide have been linked by meta-analysis to PD but have not been proven as causative.

Antiparkinsonian medications
Levodopa
Levodopa is the drug of choice to manage the main early functional disability of bradykinesia and rigidity. As oral levodopa is largely metabolised outside the brain, it is administered with a peripheral decarboxylase inhibitor (carbidopa or benserazide) to help reduce peripheral adverse effects such as nausea and hypotension. Levodopa can result in severe motor fluctuations when used chronically as is the case in PD and includes wearing-off effects, drug-induced dyskinesias and neuropsychiatric problems. However, the efficacy of levodopa has been established for over 40 years and has been demonstrated to lower Unified Parkinson’s disease rating scale (UPDRS) scores when compared to placebo.

Recently, the PD MED trial published results of an open trial that enrolled over 1600 patients with early PD who received initial treatment with levodopa or either of the two main alternatives – dopamine agonists or monoamine oxidase type B (MAOB) inhibitors. With up to seven years of follow-up, self-reported scores on scales measuring mobility and quality of life demonstrated small but definite benefits of starting treatment with levodopa rather than the other medications.

Can delaying the introduction of levodopa therapy reduce the occurrence of motor complications?
The timing of the introduction of levodopa treatment is considered important, particularly in younger patients who may have longer to live with the potential side-effects. There is evidence that patients treated with levodopa for four to six years have an approximately 40 per cent risk of developing dyskinesias. However, it has also been shown that patients who were prescribed levodopa as first-line therapy had better functional improvement in early years and better quality-of-life scores compared to patients started on a dopamine agonist.

Another argument for administering levodopa early is that later stage management of the advanced side-effects such as dyskinesias can be controlled with deep brain stimulation (DBS) surgery and infusional therapies. Levodopa has a superior efficacy and tolerability compared to dopamine agonists but the treatment strategy should be based on shared decision making between the clinician and patient. The goal is to optimise control of current motor symptoms while trying to minimise the risk of developing motor complications in the future.

Dopamine agonists
Dopamine agonists have a proven antiparkinsonian effect and are often used as monotherapy in de novo patients, as well as being a useful adjuvant therapy to levodopa in more advanced disease. Ergot derived dopamine agonists such as bromocriptine, cabergoline and pergolide are no longer recommended due to the risk of cardiac valvulopathy and fibrotic reactions. The most commonly prescribed dopamine agonists in the UK currently are the non-ergot derived rotigotine (Neupro), ropinirole and pramipexole. Rotigotine is available as a transdermal once-daily patch, while ropinirole and pramipexole (Mirapexin Prolonged Release) are oral tablets available in both short-acting and prolonged-release formulations.

Common side-effects of the dopamine agonists include hallucinations, nausea, orthostasis, leg oedema and drowsiness. It is important that patients who are still driving are aware of the possible risk of daytime somnolence associated with these medications. Patients need also to be informed about the risk of developing impulse control disorders (ICDs) while on dopamine agonist therapy including gambling, hypersexuality, binge eating and compulsive shopping, which can affect up to one in six patients, and in some cases can have devastating consequences to the patient and their family. If side-effects prevent the agonist being titrated to a clinically efficacious dose, then an alternative dopamine agonist, or a different class of drug should be tried.

Table 1. Clinical features of PD

<table>
<thead>
<tr>
<th>Cardinal motor symptoms</th>
<th>Non-motor symptoms</th>
<th>Autonomic symptoms</th>
<th>Sleep disturbance</th>
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<tbody>
<tr>
<td>tremor at rest</td>
<td>dementia</td>
<td>neurogenic bladder</td>
<td></td>
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<tr>
<td>rigidity</td>
<td>depression</td>
<td>erectile dysfunction</td>
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<tr>
<td>bradykinesia</td>
<td>anxiety</td>
<td>constipation</td>
<td></td>
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<tr>
<td>postural instability</td>
<td>apathy</td>
<td>sleep fragmentation</td>
<td></td>
</tr>
<tr>
<td>freezing of gait</td>
<td>anosmia</td>
<td>REM sleep disturbance</td>
<td></td>
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Table 1. Clinical features of PD

of current motor symptoms while trying to minimise the risk of developing motor complications in the future.
Some clinicians may prescribe a dopamine agonist along with a low dose of levodopa as initial therapy, but the efficacy of such an approach has been poorly studied.

**MAOB inhibitors**
Selegiline and rasagiline inhibit the action of MAOB. MAOB inhibition prevents the breakdown of dopamine, producing greater dopamine availability. Their beneficial effect on motor features are more modest than levodopa but they are generally well-tolerated (particularly rasagiline), and their once daily dosing regimen is convenient for patients. One delayed-start clinical trial (ADAGIO) demonstrated slower disease progression at 18 months in people who received early treatment with rasagiline, as measured on the UPDRS, than those who were diagnosed at the same time but who started the same treatment nine months later. The result raised the question of a neuroprotective effect of rasagiline, however the findings with the 1mg dose of rasagiline were not replicated with the 2mg dose, and the possibility of disease modification remains unproven.12

**Glutamate antagonists**
Amantadine is not usually recommended as a drug of first choice for patients with early PD as its efficacy has not been proven in trials, and it is more commonly recommended as adjuvant therapy in PD, particularly in patients with dyskinesias for which two RCTs have demonstrated that it can have a modest effect.13,14

**Anticholinergics**
These are the oldest class of medications used to treat PD. They are thought to work by targeting the relative overactivity of central cholinergic activity that results from the progressive reduction in dopaminergic activity. There is insufficient evidence to suggest that anticholinergics have a positive effect on the motor features of PD, and they are usually avoided in the elderly as they can cause adverse cognitive and neuropsychiatric problems. However they may still have a role in improving tremor or ‘off’ dystonia in some young-onset patients.15

**Managing motor complications**
Most of the medications described above work most effectively in early disease when the nigrostriatal pathway is relatively intact, but with disease progression the uptake and efficacy of the dopaminergic therapies becomes less predictable. Eventually almost all patients treated with levodopa for PD will develop motor complications. Dyskinesias may be reduced by minimising dopaminergic medications or fractionating the doses used, and the addition of amantadine can be very useful. Several different approaches can be used to tackle wearing-off symptoms including:
- Addition of a MAOB inhibitor or dopamine agonist. To date no one dopamine agonist has proven more efficacious than another, however switching from one dopamine agonist to another may sometimes be beneficial.
- Increasing levodopa dose and/or frequency (four to six times daily may be required).
- Addition of a catechol-O-methyltransferase (COMT) inhibitor such as entacapone or tolcapone (Tasmar) to levodopa. These can only be used with levodopa to increase ‘on’ time as they have no antiparkinsonian effect when administered by themselves. Entacapone is usually preferred to tolcapone due to the risk of hepatotoxicity with the latter. For ease of administration it is can be offered to patients in a triple combination preparation of levodopa, carbidopa and entacapone (Stalevo).
- Changing to a controlled-release preparation of levodopa has improved ‘on’ times in some studies.

**Advanced therapies**
These are treatments usually reserved for patients with more advanced PD, where a patient’s clinical features are no longer responding well to manipulation of their oral medications. The three main therapies currently approved by NICE are apomorphine (APO-go), jejunal levodopa gel infusions (Duodopa) and DBS therapy. In order for patients to benefit from any of these treatments, it is critical that they demonstrate levodopa responsiveness. There are no head-to-head trials comparing each of these therapies. Choice of treatment is therefore usually pragmatic and tailored to the individual patient, based on factors such as patient preference, treatment availability and costs.16

**Apomorphine**
This is a potent dopamine agonist that can either be administered as intermittent bolus injections to rescue patients from severe ‘off’ periods, or alternatively may be given as a continuous infusion through a subcutaneous pump. Total daily dose of levodopa can usually be halved. It frequently precipitates nausea and vomiting, and therefore is usually administered with the antiemetic domperidone, which is a peripheral dopamine antagonist. Other potential side-effects include injection-site reactions and psychiatric symptoms. In patients with a tendency to hallucinations or

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**Table 2. Exclusion criteria for PD**

<table>
<thead>
<tr>
<th>Exclusion criteria for PD</th>
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<tr>
<td>• History of repeated strokes with stepwise progression of parkinsonian feature</td>
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<tr>
<td>• History of repeated head injury</td>
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<tr>
<td>• History of definite encephalitis</td>
</tr>
<tr>
<td>• Oculogyric crises</td>
</tr>
<tr>
<td>• Neuroleptic treatment at onset of symptoms</td>
</tr>
<tr>
<td>• More than one affected relative</td>
</tr>
<tr>
<td>• Sustained remission</td>
</tr>
<tr>
<td>• Strictly unilateral features after three years</td>
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<tr>
<td>• Supranuclear gaze palsy</td>
</tr>
<tr>
<td>• Cerebellar signs</td>
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<tr>
<td>• Early severe autonomic involvement</td>
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<tr>
<td>• Early severe dementia with disturbances of memory, language and praxis</td>
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<tr>
<td>• Babinski sign</td>
</tr>
<tr>
<td>• Presence of cerebral tumor or communication hydrocephalus on imaging study</td>
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<tr>
<td>• Negative response to large doses of levodopa in absence of malabsorption</td>
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<td>• MPTP exposure</td>
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dopaminergic psychosis, DBS or duodopa treatment may be preferable to apomorphine.

**DBS**
This is a neurosurgical procedure that may be suitable for patients who develop motor complications that prove refractory to medical therapy, such as disabling dyskinesias and difficult motor fluctuations. It does not offer superior control of the cardinal symptoms of IPD compared to levodopa. Stimulation of the subthalamic nucleus reduces ‘off’ time, so dopaminergic medication can be reduced, hence reducing dyskinesias. Elderly patients with significant co-morbidities are generally considered unsuitable for this type of therapy, as are patients with dementia or significant psychiatric co-morbidities. Risks of surgery include infection, haemorrhage and wire breakage. More recently there has been a move to employ this therapy earlier in the disease course especially in younger patients.

**Duodopa**
This is a system whereby levodopa gel is delivered via continuous infusion into the jejunum, to ensure more smooth and predictable levels of plasma levodopa which is then delivered to the brain. Patients can be treated over 16 hours, or continuously over 24 hours if nocturnal symptoms are a problem. The main complications are related to surgical issues (infection, inflammation) and malfunctioning devices (tubes kinking and becoming displaced). Its use is restricted in the UK by its cost (£30,000 per annum).

The NHS stipulates that the options of apomorphine infusion or DBS surgery must be explored before a funding application for Duodopa will be considered.

**Managing cognitive and psychiatric aspects**
Although Parkinson’s disease is primarily thought of as a movement disorder, it has been increasingly recognised over the last two decades that it is also associated with a wide range of non-motor symptoms, many of which can be very debilitating for patients, leading to a significant reduction in their quality of life (see Table 1). Dementia is now known to occur in up to 50 per cent of patients 10 years after diagnosis, and is a major risk factor for nursing home placement and mortality. Cholinesterase inhibitors such as rivastigmine and donepezil can have a positive effect on cognitive function in PD, but may have a deleterious effect on motor function, particularly tremor. Hallucinations can also respond to cholinesterase inhibitors. Quetiapine and clozapine are sometimes used to treat psychosis in PD; however, there is a lack of good evidence from controlled trials to support the use of quetiapine, and while there is better evidence to support the use of clozapine, physicians are often reluctant to use it as it is associated with haematological adverse events.

Anxiety and depression are both common in PD and may even predate the onset of motor symptoms. There is a paucity of clinical trial data but it is probable that all the major classes of antidepressants can be helpful in PD. There is a theoretical
risk of serotonin syndrome when using an SSRI in combination with an MAO-B inhibitor, but this does not seem to be relevant to the doses used in clinical practice. The dopamine agonists, such as pramipexole and ropinirole, have also demonstrated beneficial effects in depression associated with PD. Some patients with anxiety may benefit from short-acting benzodiazepines like lorazepam or alprazolam. Anxiety that occurs in ‘off’ time may be managed by minimising motor fluctuations, using the strategies discussed above.

Conclusion
Evidence-based guidelines are available to support clinicians to select appropriate therapies for individual patients with PD. However, there remains a degree of uncertainty regarding the effectiveness of certain pharmacological treatments for individual patients. Even with levodopa, which has been the mainstay of treatment for years, there is ongoing debate regarding the perceived advantages and disadvantages of starting it as first-line therapy in newly diagnosed patients. Heterogeneity in both PD motor and non-motor symptoms, the presence of co-morbidity, other medications and psychosocial factors all influence the potency of the treatment and the potential risk of adverse reactions. PD therapy should, therefore, be tailored to the needs of the individual patient, and adjusted at regular intervals to ensure maximum efficacy and tolerability.

The availability of infusional dopaminergic treatments and DBS to manage motor fluctuations has helped many PD patients to maintain their quality of life and functional ability. Clinical trials have not yet unequivocally demonstrated any treatment that can halt or slow down the progression of the disease, and there is still an unmet need for therapies that can improve some of the most disabling aspects of PD such as freezing during ‘on’ states, postural instability and dementia.

References

Declaration of interests
None to declare.

Lucy Collins is a PhD student, Dr Gemma Cummins is clinical research fellow and Roger Barker is a professor of clinical neuroscience and honorary consultant neurologist at the John Van Geest Centre for Brain Repair, Cambridge

Prescription analysis
In 2013, GPs in England wrote 3.2 million prescriptions for drugs to treat PD at a total cost of £94.6 million (excluding bromocriptine, which the HSCIC categorises under endocrine drugs). This was a small increase on 2012 but still less than preceding years due to lower prices for pramipexole and ropinirole. There were about one million prescriptions for antimuscarinic drugs (orphenadrine, procyclidine, trihexyphenidyl), costing £5.8 million.

Of the levodopa formulations, which account for just over half of prescription volume, the most expensive – other than specials – are co-careldopa 25/100mg (£24.22 per script) and co-careldopa 25/250mg (£24.52). Sinemet, the branded equivalent, is about half the price. Branded pramipexole (Mirapexin) is the most expensive oral dopamine agonist, with m/r 2.62mg and 3.15mg averaging £313 and £357 respectively for around one month’s supply.

The apomorphine pen and injection are the most expensive items and prescribing has changed little for several years. By contrast, that of levodopa/carbidopa/entacapone (Stalevo) has been rising slowly and the use of other dopamine agonists (pramipexole, ropinirole, rasagiline and the rotigotine patch) has grown steadily. Prescribing of selegiline, which was never high, has been declining.