Parkinson’s disease therapy update

Although our understanding has increased since features of Parkinson’s disease were first described almost 200 years ago, a cure remains elusive. Treatments and recommendations for management are outlined by Mohmadshakil Kathawala

Parkinson’s disease (PD) is a disorder resulting from the death of dopaminergic neurons in the substantia nigra, which is located within the basal ganglia. Patients classically present with poverty of movement (hyposkinesia, e.g., a shuffling gait), slowness of movement (bradykinesia), rigidity and resting tremor. Although the disease is predominantly a movement disorder, other problems frequently develop, including psychiatric and autonomic disturbances (see Panel 1, p2) and, later, drug-related effects. The condition progresses to cause significant disability.

PD is the second most common neurodegenerative disease after Alzheimer’s disease, affecting 100–160 per 100,000 of the population. There is a slightly higher prevalence in men. Typically, a community pharmacy with 5,000 patients will serve between five and eight patients with PD. The rising incidence with age raises important public health questions for the future.

Causes

The physical hallmarks of PD are Lewy bodies and death of neurons in the pars compacta of the substantia nigra. Lewy bodies are eosinophilic intraneuronal inclusions containing α-synuclein and ubiquitin proteins and proteases. Clinical signs of PD develop when nigrostriatal cell death reaches 50 per cent and levels of striatal dopamine are reduced by 80 per cent.

The underlying cause of PD remains unclear. A number of environmental factors have been shown to increase risk of the disease. Interest in a toxin as a cause was reduced by 80 per cent.

The paradoxical reduced risk of PD in cigarette smokers and caffeine drinkers has been well established. Recently, istradefylline, an adenosine-A2 antagonist has been reported to improve motor function in PD1 and caffeine is thought to inhibit adenosine-A2 receptors.

Genetic cases of PD are rare but they may provide clues on pathogenesis. Over the past 15 years, 12 PD-causing genes have been found. The first of these to be discovered was α-synuclein (PARK1) gene mutation, causing a form of PD that progresses rapidly. The Parkin (PARK2) gene was next and accounts for half of young-onset (before the age of 40 years) autosomal recessive cases of PD.

A number of abnormalities suggest oxidative stress might play an important role in disease development. For example, reduced glutathione and increased superoxide dismutase levels suggest increased exposure to free radicals. Increased iron levels have been found in the substantia nigra of PD patients and may contribute to neuronal death by catalysing oxidative reactions. A deficiency in mitochondrial complex I activity may also predispose patients to oxidative stress.

Panel 2 (p3) describes some of the significant mechanisms in PD.

Diagnosis

In most cases a diagnosis of PD is made on clinical features (see Panel 1). In the community, 50 per cent of parkinsonian syndromes are misdiagnosed. This is reduced to 6–8 per cent where the diagnosis is made by an expert. Since an accurate diagnosis has implications in terms of treatment and prognosis, National Institute for Health and Clinical Excellence guidelines recommend patients with suspected PD should be referred, untreated, to a specialist.2

Interest in developing diagnostic tests for PD led to partial success with single photon emission computed tomography (SPECT). This scan involves tagging a gamma emitting isotope to a tracer molecule, and giving it by intravenous injection. SPECT demonstrates normal uptake in the striatum in healthy patients and those with essential tremor, antipsychotic-induced parkinsonism or psychogenic parkinsonism. Reduced uptake occurs in dopaminergic deficiency states of PD, multiple-system atrophy and progressive-supranuclear palsy.

A number of clinical rating scales are used to measure disease severity in clinical trials but in practice, physicians will rely on their experience to make assessments. As a simple guide, mild uni- or bilateral limb involvement could be described as mild; bilateral limb involvement with some instability but physical independence as moderate; and bilateral limb involvement, where the patient is only able to stand or is wheelchair or bed bound, as severe.

Medical management

At present, drugs provide only symptomatic relief. There is no single first-line drug of choice and decisions are tailored to the individual after discussing the benefits and drawbacks of the different drug classes. Figure 1 summarises current management approaches based on NICE guidelines.2

Levodopa

Levodopa remains the gold standard treatment. It dramatically improves motor function but causes gastrointestinal side effects.
Figure 1: current management approaches based on NICE guidelines

As the disease progresses, dose increases are necessary to maintain motor function. However, higher doses mean that long-term complications of levodopa develop sooner and current practice uses adjuvant therapy to reduce levodopa dependency. Clinical trials have found the dose of levodopa should be kept at or below 600mg/day to reduce the likelihood of motor complications. NICE guidelines advise that levodopa doses should be kept as low as possible. This can mean aiming for a reasonable quality of life rather than 100 per cent symptom control.

Motor complications Motor complications include dyskinesias and response fluctuations. Dyskinesias are abnormal involuntary twisting movements of the limbs, trunk or face and are usually caused by peaking of serum levodopa levels. Dystonia (prolonged painful muscle contractions producing unusual postures) is also common. Response fluctuations include a shortening of the response to each dose of levodopa (end-of-dose deterioration), which may be caused by troughs in serum levels, and the unpredictable switching between mobile and immobile phases (known as on/off phenomenon), which can sometimes occur rapidly. This switching is unrelated to the peak-trough effect from dosing.

Factors associated with the development of levodopa-related motor complications include long duration of therapy, high doses, severe disease and age (younger patients are more susceptible). After six years’ treatment motor complications occur in 50 per cent of patients and in all patients under 40 years of age.1

An initial strategy to avoid motor complications is to delay levodopa prescribing by using either a dopamine agonist or monoamine oxidase B inhibitor as monotherapy. Another approach is to fractionate the dose of levodopa (eg, benredopa 62.5mg five times daily instead of 125mg td). This reduces peak dose effects (ie, dyskinesia) while smoothing out troughs that may cause end-of-dose deterioration.

Modified-release preparations of levodopa were originally developed in an effort to overcome motor fluctuations but their bioavailability is variable and reduced to 60–70 per cent of that of standard formulations. In practice, the unpredictability of the response to MR products has largely led to them being abandoned. NICE guidelines recommend these preparations may be used to reduce motor complications in patients with later PD but should not be drugs of first choice.1

In practice their use tends to be restricted to treating nocturnal hypokinesia, where a night-time dose allows patients to turn more freely in bed.

Another strategy is to combine levodopa with a dopamine agonist, catechol-O-methyl

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**PANEL 1: CLINICAL FEATURES**

**Cardinal signs**
- Hypokinesia and bradykinesia
- Rigidity (the clinician may experience this as a resistance to passive movement which may feel smooth [“lead-pipe”] or jerky when tremor is superimposed [“cogwheeling”])
- Resting tremor (in one upper limb, with a frequency of 4–6 Hz [“pill-rolling”])

**Associated features**

**Motor**
- “Freezing” (sudden pause of movement on encountering an external stimulus, such as a door)
- Voice low in volume and monotonous
- Dysphagia (difficulty swallowing, which is a common cause of aspiration pneumonia)
- Dystonia (sustained painful muscle contractions)

**Autonomic dysfunction**
- Urinary frequency, urgency and, rarely, incontinence (due to detrusor hyperreflexia)
- Constipation
- Excessive salivation, drooling (sialorrhoea) and sweating (late disease)
- Erectile dysfunction

**Cardiovascular (postural hypotension)**

**Sleep disorders**
- Vivid dreams and nightmares
- In REM (rapid eye movement) sleep, patients can act out their dreams, sometimes violently
- Daytime hypersomnolence
- Restless leg syndrome

**Mental health**
- Depression affects around 40 per cent of patients, leading to significant reduction in quality of life
- Dementia is prevalent in 40–78 per cent of patients, manifesting as visual hallucinations, and decline in visuospatial abilities and executive function, rather than memory loss
treatment of early PD. It has been formulated pramipexole, ropinirole and rotigotine.

favour of non-ergot derived drugs such as lisuride have brought a decline in their use in agonists (eg, bromocriptine, cabergoline and valvulopathy in ergot-derived dopamine Slow titration can help to minimise them.

effects are similar to those of levodopa but dopamine agonists may help to reduce motor complications, adjuvant therapy with patients on levodopa who have developed monotherapy, especially in younger patients, as levodopa in treating the motor features of motor complications. They are not as effective limited to patients who cannot tolerate apomorphine or who are unfit for surgery.

Dopamine agonists

Dopamine agonists were introduced in the late 1970s as adjuvant therapy in patients with motor complications. They are not as effective as levodopa in treating the motor features of PD but are increasingly being used as initial monotherapy, especially in younger patients, enabling a delayed start to levodopa. In patients on levodopa who have developed motor complications, adjuvant therapy with dopamine agonists may help to reduce motor impairments, off time and levodopa dose.

Dopamine agonists bind to post-synaptic dopamine receptors in the striatum. Side effects are similar to those of levodopa but occur more frequently and with greater severity (especially neuropsychiatric effects). Slow titration can help to minimise them. Concerns about serosal reactions and cardiac valvulopathy in ergot-derived dopamine agonists (eg, bromocriptine, cabergoline and lisuride) have brought a decline in their use in favour of non-ergot derived drugs such as pramipexole, ropinirole and rotigotine.

Rotigotine was recently launched for the treatment of early PD. It has been formulated as a once-daily transdermal patch (Neupro), producing fairly constant plasma drug levels over 24 hours. Long-term trials are needed to assess whether this results in fewer motor complications than levodopa.

MAOB inhibitors

Selegiline is an irreversible inhibitor of MAOB that improves the availability of dopamine at the stratal synaptic cleft. Studies involving selegiline use in early PD showed that it improves motor symptoms and delays the need for levodopa. It is licensed for use as initial monotherapy but dopamine agonists are more effective and preferred in practice. Selegiline is also used as an adjunct to levodopa therapy to reduce response fluctuations in people with motor complications. It can cause typical dopaminergic side effects but, because of its amphetamine metabolites, it can also trigger insomnia, vivid dreams and nightmares.

The more recently launched rasagiline is licensed for use as monotherapy or adjuvant therapy. Unlike selegiline, it is not metabolised to amphetamine derivatives so it is potentially free of any alerting side effects. Trials have established the efficacy of rasagiline, but no evidence comparing rasagiline with selegiline, dopamine agonists or levodopa is available.

Other drugs

Once motor complications develop, adjunctive therapies should be considered.

COMT inhibitors Despite the co-administration of peripheral dopa-decarboxylase inhibitors, only 5–10 per cent of levodopa crosses the blood-brain barrier, the rest is metabolised by COMT. In the early 1990s, the COMT inhibitors were launched. They work by prolonging the effect of each dose of levodopa, thereby reducing end-of-dose effects and allowing a reduction in levodopa dose. Tolcapone, the first COMT inhibitor to be licensed, works centrally and peripherally. It was withdrawn following several cases of fatal hepatitis, but later reintroduced (Tasmar) for use under specialist supervision. It is recommended as second-line therapy after trial with the peripherally acting entacapone has failed. COMT inhibitors cause dopaminergic side effects along with yellow discoulouration of urine and diarrhoea. A combination product of levodopa, carbidopa and entacapone (Stalevo) is aimed at improving compliance.

Amanadine In the 1970s, amantadine was investigated as an antiviral agent and, by chance, found to be effective in PD. Recently, it was found to work as a glutamate antagonist. In the past, amantadine was used to delay levodopa therapy; now it is mainly used to reduce dyskinesia in later disease, caused by an overactive glutamatergic subthalamicopallidal pathway.

Apomorphine Apomorphine is a highly potent D1 and D2 dopamine agonist. In the late 1980s, it was found that subcutaneous bolus doses and continuous infusions of apomorphine were effective at reversing off periods in patients with advanced PD. More recently, infusions in patients with severe dyskinesia were shown to reduce dyskinesia by 65 per cent in severity and 85 per cent in frequency and duration; suggesting apomorphine may be an alternative to surgery. Its use enables many to withdraw oral dopamine agonist therapy and to reduce levodopa dose substantially. Common side effects include injection site reactions, and nausea and vomiting (domperidone should be started two days before apomorphine).

Anticholinergics Generations of students were taught that anticholinergics exert their effect by restoring the cholinergic overactivity and dopaminergic underactivity balance in PD but this concept is too simplistic to explain developments over the past decade. With the introduction of levodopa, the use of anticholinergics declined. In current practice, anticholinergics (eg, selective centrally active muscarinic receptor antagonists, trihexyphenidyl and orphenadrine) may be used in young PD patients with severe tremor. They should not be drugs of first choice, especially in the elderly, due to limited efficacy and the tendency to cause cognitive impairment, psychotic symptoms, urinary retention and glaucoma.

Prescribing for non motor features

It has been realised that the non-motor disorders in PD cause the most deterioration in quality of life. One such disorder is PD dementias. These present after motor symptoms, with decline in visuospatial abilities, category learning, verbal fluency and executive function, and visual hallucinations, rather than the memory loss commonly seen in Alzheimer’s or vascular dementia.

Cholinesterase inhibitors are effective in treating not only the cognitive decline but the psychotic features of the condition. Initial reluctance to prescribe cholinesterase inhibitors was because of the belief that cholinergic excess in the striatum contributes to motor dysfunction (the principles of

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anticholinergic therapy for PD). However, evidence from randomised, placebo-controlled trials of cholinesterase inhibitors show that they are effective and safe. At present, only rivastigmine has a product license in the UK.

Parkinson’s disease in early PD is often caused by dopaminergic medication but, in later disease, it is also the harbinger of dementia. Current practice in the management of psychosis in PD is to withdraw antiparkinsonian medicines one at a time and monitor deterioration mobility. An alternative approach is to add the atypical antipsychotic clozapine. This can reduce psychotic symptoms without deterioration in motor function caused by typical antipsychotics (eg, haloperidol) and, to lesser extent, other atypical antipsychotics through blocking dopaminergic transmission in motor pathways. However, neutropenia occurs in 1–2 per cent of patients and blood monitoring is required.

Depression is a major problem in around 40 per cent of patients with PD. Clinical trials and a Cochrane review failed to find any significant benefit of tricyclic antidepressants or selective serotonin reuptake inhibitors over placebo. Consequently no guidance has been given for clinical practice.

Constipation is also common in PD. It should initially be treated with increased fluids, fruit and fibre before resorting to laxatives individually then in combination depending on response. A significant proportion of PD patients develop bladder dysfunction due to central abnormalities in the pontine micturition centre in the brain. It responds well to the peripheral antimuscarinics oxybutynin and tolterodine. Clonazepam 0.25–1mg at night can help to reduce symptoms of sleep behaviour disorder.

Surgery

Bilateral subthalamic nucleus deep-brain stimulation (STN-DBS) is indicated for patients with severe motor complications unresponsive to drugs. It reduces off time so is unresponsive to slow symptom progression in early PD but further evidence is required before it can be recommended routinely.

Results of studies of dopamine agonists versus levodopa, have suggested a slower rate of nigrostriatal loss in patients on dopamine agonists. However, there were numerous methodological problems. Consequently, NICE guidelines suggest the delay of motor complications by dopamine agonists may be due to a pharmacokinetic or pharmacodynamic effect rather than neuroprotection.

The attention of current research now turns to neurorestoration. One approach involves implanting fetal grafts into the striatum to form new dopamine producing neurones. Trials showed a small improvement in motor function but patients suffered from unregulated transmitter release and thus severely off period dyskinesia and dystonia.

An alternative way to restore dopaminergic innervations to the striatum is to stimulate the remaining neurones to produce further connections (and thus more dopamine) by administering nerve growth factor. A recent small trial produced dramatic improvements in motor function but this was not replicated in larger studies and the trial was stopped.

A role for pharmacists

Despite optimal medical and surgical therapy, patients with PD suffer increasing disability due to disease progression. Alternative interventions provided by a multidisciplinary team including Parkinson’s disease nurse specialists (PDNS), physiotherapists, occupational therapists and speech and language therapists can be beneficial. PDNS act as key workers to co-ordinate the patient’s care package, advise on medication issues, and educate patients, carers and medical staff. NICE guidelines are supportive of them but current low referral rates reflect issues such as services being overstretched and the perceived lack of efficacy.

Pharmacists are ideally placed to support patients with PD, whether from a community pharmacy or in a specialist clinic working alongside a neurologist. They can:

- Provide advice on medication and side effects to patients and carers
- Monitor for side effects of therapy
- Ask if medicines are working (If not, are tablets being taken at the correct time?)
- Address compliance issues (Can monitored dosage schemes help?)
- Suggest alternative formulations once dysphagia becomes problematic
- Make emergency supplies (sudden withdrawal of treatment can cause acute akinesia or neuroleptic malignant syndrome)
- Advise on complementary and over-the-counter remedies (eg, laxatives)

Signposting and resources

- The Parkinson’s Disease Society provides information and support for patients, their carers and health professionals (including training) on all aspects of PD (www.parkinsons.org.uk)

References


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