Parkinson’s disease management

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Management of Parkinson’s disease (PD) should be tailored to the needs of individual patients and the aim of treatment is to relieve motor and non-motor symptoms (see Box 1, p369, for the management of non-motor symptoms). Available therapies provide symptomatic relief only — currently there is no way to restore function, halt deterioration or cure PD. Management is guided by recommendations from the National Institute for Health and Clinical Excellence and the Scottish Intercollegiate Guidelines Network.1, 9

Motor symptoms

A firm diagnosis of PD is essential before starting treatment (see accompanying article, p361). Most medicines used to manage the motor symptoms of PD enhance the activity of dopamine in the basal ganglia, either through direct replacement, agonism of dopamine receptors, or prevention of the breakdown or reuptake of dopamine. However, there is no recognised, unequivocal first-line treatment and initial choice should take into account: a patient’s clinical symptoms; the relative importance of symptom control versus motor complications; a desire to avoid specific adverse effects; and concomitant medical conditions.

Treatment decisions will also depend on the stage of a patient’s disease: either early disease (those with functional disability requiring symptomatic therapy) or later disease (those who have developed motor symptoms following treatment with levodopa). When to start treatment is discussed in Box 2 (p370).

Early disease

Motor symptoms in early PD are managed with either levodopa, a dopamine agonist or a monoamine-oxidase-B (MAO-B) inhibitor. If a MAO-B inhibitor is used initially, then levodopa would normally be added when further symptom control is required (see Figure 1, p371). The choice of medicine is guided by predominant symptoms, concomitant conditions, age and whether symptomatic relief or avoidance of adverse effects is more important to the patient (see Box 3, p372).

Levodopa

Levodopa has been the gold standard treatment for PD since its introduction in the 1960s. It is still considered the most efficacious medicine for PD, despite the introduction of newer medicines. After starting levodopa treatment, patients experience rapid improvement in their symptoms and quality of life. However, this period is followed by decreased efficacy and levodopa-related motor disturbances, known as dyskinesias. The time this takes to occur can vary from months to years — about half of all patients experience...

There is no definitive first-line treatment for managing the motor symptoms of Parkinson’s disease. Treatment choice should take into account factors such as patient age, adverse effects and comorbidities.

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Patients with Parkinson's disease (PD) can develop non-motor symptoms as the disease progresses. The non-motor features of PD include depression, psychosis, dementia, sleep disturbances and autonomic dysfunction.4

**Depression** Depression has been reported to affect 40–50% of patients with PD. However, this may be an underestimate because diagnosing mild depression in patients with PD is complicated by the fact that many of the clinical features of mild depression are also motor features of PD.1

Managing depression in patients with PD requires a combination of psychotherapy and pharmacotherapy where possible. Although monoamine-oxidase-B (MAO-B) inhibitors and the dopamine agonists pramipexole and ropinirole have some antidepressant effects, PD-related depression is generally managed using selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs). The choice of treatment is dependent on patient characteristics and other medicines that the patient is using (eg, SSRIs can be used for patients receiving rasagiline but TCAs should be avoided).

The role of SSRIs for the management of patients with PD and depression has been debated for many years. Before 2001 there were some reports that these medicines worsened the motor symptoms of PD and increased the incidence of extrapyramidal side effects. However, Dell’Agnello and colleagues demonstrated that SSRIs do not significantly worsen extrapyramidal symptoms.2

Mood swings, anxiety and feelings of dread are possible symptoms of the “off” state of PD. On-off fluctuations should be monitored in these patients and the control of motor symptoms reviewed.

**Psychosis** Around a third of patients with PD develop psychosis secondary to PD and its management presents a challenge.1

Psychosis can be triggered by the introduction of new medicines or by changes in the doses of existing anti-Parkinsonian medicines. Therefore, PD therapy should be reviewed for all patients who develop psychosis and the doses reduced where possible. Many patients are unable to tolerate dose reductions and in such cases the use of medicines to manage patients with moderate-to-severe psychotic symptoms is appropriate. Mild psychotic symptoms in people with PD may not need to be actively treated if they are tolerated by the patient and carer.1

Treatment should be with atypical antipsychotic medicines. Typical antipsychotic drugs (eg, phenothiazines and haloperidol) must not be used because they exacerbate the motor features of PD. Clozapine is the only atypical antipsychotic that is licensed in the UK for the management of psychoses in PD. However, its use is limited due to adverse effects and the monitoring that is required.

Quetiapine, olanzapine, risperidone or aripiprazole are often used but are not licensed for this indication.

The place of quetiapine in the management of psychosis in PD has been evaluated in both open-label studies and randomised trials. Eight open-label studies, including 191 patients who received quetiapine, demonstrated an improvement in symptoms of psychosis for 152 patients (80%). Studies comparing quetiapine with clozapine for this indication have had mixed results.2,4 Despite the conflicting evidence, quetiapine remains a first-line treatment for the management of psychosis in PD.4

**Dementia** PD-related dementia (PDD) affects 20–40% of patients with PD and the incidence increases by 13.7% each year for patients aged 70–79 years.

PDD is associated with a reduction in cholinergic functioning within the brain and therefore management can include the use of cholinesterase inhibitors. Rivastigmine is used first line — oral administration appears to improve cognition and activities of daily living for patients with PDD. A clinically meaningful benefit occurs in about 15% of cases. The oral preparation of rivastigmine is the only cholinesterase inhibitor licensed for the management of PDD. Rivastigmine patches are not licensed for this indication but can be used when a patient develops nausea and vomiting as an adverse effect with the oral preparation.

Donepezil and galantamine have demonstrated some limited efficacy for the management of PDD.

The role for memantine in the management of PDD is currently being explored following the positive results of a 24-week randomised controlled trial in 75 patients with PDD or Lewy body dementia. There was a significant difference in “clinical global impression of change” score at week 24 for patients who received memantine compared with placebo.7

**Sleep disturbances** Some 60–90% of patients with PD experience sleep disturbances. These can include daytime sleepiness or an inability to sleep at night due to nocturia, tremor or dyskinesias. Depression can also aggravate existing sleep disturbances.

Treatment requires accurate identification of the cause and interventions to address the underlying issue (eg, adjusting levodopa dose to reduce dyskinesia). Modafinil may provide a therapeutic option for patients with daytime sleepiness.1 Hart and colleagues conducted a double-blind, randomised, placebo-controlled crossover study involving 15 patients and results suggested that sleepiness (measured using the “Epworth sleepiness scale”) was significantly improved with modafinil therapy.4 Although the European Medicines Agency recommends that modafinil should be used only for the treatment of sleepiness associated with narcolepsy, it is prescribed off-label, under the supervision of sleep specialists, for some patients with PD and daytime sleepiness.

**Autonomic dysfunction** Patients who develop autonomic dysfunction, such as postural hypotension, urinary dysfunction or constipation, should receive symptomatic support.
Dopamine agonists are commonly used as initial therapy when levodopa therapy is delayed (especially for younger patients) and as adjuvants to levodopa in later PD. They act on post-synaptic dopamine receptors and have been in use since the 1970s. Ergot-derivative dopamine agonists, such as pergolide and cabergoline, are associated with cardiac valve and pulmonary fibrotic effects and have been largely superseded by the non-ergot-derived dopamine agonists pramipexole, ropinirole and rotigotine. Dopamine agonists are less effective than levodopa at controlling motor symptoms but are considerably less likely to cause dyskinesia.

Modified-release and topical preparations of dopamine agonists offer the convenience of once-daily dosing to patients who are often on complex drug regimens. Adverse effects of dopamine agonists are similar to those of levodopa, but impulse control disorder and somnolence are more common. Impulse control disorders, such as pathological gambling, binge eating and hypersexuality, are thought to be more common in young males and those with a previous history of mood disorders, alcohol abuse and obsessive compulsive disorder. Patients and their carers should be adequately counselled regarding these effects and the causative medicine tapered and discontinued if they occur.

MAO-B inhibitors Rasagiline and selegiline are MAO-B inhibitors. They increase the amount of dopamine at receptors in the striatum by preventing its metabolism. They are used as initial therapy, especially if dopamine agonists should be avoided, or as levodopa-sparing medicines in later disease. Rasagiline is more commonly used because selegiline is associated with hallucinations, insomnia and confusion (caused by amphetamine-like metabolites). Both medicines have the potential to interact with many medicines due to their inhibition of monoamine oxidase, which may not be fully selective for MAO-B.

Later-stage disease Over time a patient’s response to initial treatments will decline. When this occurs, patients experience “switching off”, also referred to as “wearing off” or “off time”, as plasma drug concentrations reach a trough (this manifests as akinesia and rigidity). In addition, motor complications, such as dyskinesia and dystonia, occur at peak serum levels. Patients can fluctuate rapidly or erratically between these two states — this is known as the “on-off” phenomenon.

Wearing off can be countered by increasing the dose of a patient’s medicines or shortening the interval between doses. However, increasing the dose can induce or worsen motor complications, especially with levodopa. If amendments to dosing regimens fail to correct the problems, combinations of drugs will be necessary (see Figure 1, p371).

Catechol-O-methyltransferase inhibitors. The catechol-O-methyltransferase (COMT) inhibitors, entacapone and tolcapone, increase the amount of levodopa that can cross the blood brain barrier by preventing its metabolism to 3-O-methyldopa. They mainly act peripherally, although tolcapone might also have some central action.

COMT inhibitors increase the half-life of levodopa and are useful in reducing off time for patients with fluctuating motor symptoms, especially when these occur at the end of a dose interval. The dose of levodopa may need to be reduced when a COMT inhibitor is added because increased levodopa levels can worsen dyskinesia. COMT inhibitors are rarely used with levodopa as initial therapy because the combination has been shown to
shorten the time to onset of dyskinesia. COMT inhibitors can worsen dyskinesia, cause abdominal discomfort and colour the urine.

Tolcapone is a more potent COMT inhibitor than entacapone but, due to hepatotoxicity, is reserved for patients with an inadequate response to entacapone.

Entacapone is available in a combination product with levodopa and carbidopa (Stalevo). The use of this product may improve adherence and the range of strengths available enables small adjustments of levodopa dose.

Antimuscarinics

Antimuscarinics were the first available medicines for PD, but their use has been superseded by drugs that are more efficacious and better tolerated (troublesome adverse effects include urinary retention, constipation and confusion).

Generally, the use of these drugs is now limited to younger patients with severe tremor and dystonia in their feet, and patients with later-stage disease and dyskinesia (for these patients it is useful because the mode of action does not involve dopaminergic stimulation).
Low doses of tricyclic antidepressants are also occasionally used for nocturnal akinesia, impaired sleep, and for patients with early morning symptoms (due to their long half-life).

**Amantadine** Amantadine has been used for the management of PD since 1968 and works by preventing the reuptake of dopamine at synapses. It is now used only for the management of levodopa-induced dyskinesias. However, increasing doses are often required to overcome tachyphylaxis and eventually for many patients the drug will need to be stopped.

**Apomorphine** Apomorphine is a potent dopamine receptor agonist. It is administered subcutaneously to avoid extensive first-pass metabolism. Apomorphine has a rapid onset of action and a short duration of action (up to 100 minutes). Intermittent bolus doses are used for rapid termination of off periods and continuous subcutaneous infusions are used for patients with advanced motor symptoms.

Treatment with apomorphine is started by specialists after a trial (using bolus administration of escalating doses) to assess response and tolerability. The medicine can be highly emetic so patients are given domperidone, 20mg three times a day, for two to three days before starting treatment. Apomorphine is associated with fewer psychiatric effects than other dopamine agonists.

**Levodopa intestinal gel** Duodopa is a soluble gel form of levodopa plus carbidopa that is administered directly into the duodenum via a percutaneous gastrostomy tube. Because of its expense and the invasive route of administration, the use of Duodopa is limited to those with severe motor fluctuations that are not managed by other drug therapies.

**Non-pharmacological options** Patients with idiopathic PD associated with severe motor complications that are unresponsive to oral, topical and invasive pharmacological treatments may be considered for deep brain stimulation (DBS). DBS is a neurosurgical procedure that involves implanting electrodes into either the ventro-intermediate nucleus of the thalamus, the globus pallidus internum or the subthalamic nucleus. The electrodes are connected to a pulse generator, which is implanted subcutaneously on the anterior chest wall. Once the electrode is activated the electrical stimulation causes a depolarising block within the pathway between the specific nucleus and the substantia nigra and aims to interfere with the abnormal electrical impulses that cause PD symptoms.

DBS is associated with psychiatric adverse effects, dysphagia and gait problems. DBS has been recommended by NICE since 2003 but, before this, ablative surgical procedures were used as last-line options for the symptoms of PD. The ablative surgeries (subthalamotomy, pallidotomy or thalamotomy) used electrical current to destroy tissue within areas of the brain where inappropriate activity can cause the symptoms of PD. These procedures are associated with seizures and facial weakness.

**Interrupting therapy** “Drug holidays” were previously used to decrease or delay the onset of dyskinesias for patients with later-stage disease. This strategy is no longer recommended due to the risk of inducing neuroleptic malignant syndrome through the rapid withdrawal of dopamine stimulation. In addition, patients experience worsening of their motor

### Box 3: Medicines used for the treatment of Parkinson’s disease

<table>
<thead>
<tr>
<th>MEDICINE</th>
<th>PLACE IN THERAPY</th>
<th>DEGREE OF SYMPTOM CONTROL</th>
<th>MOTOR COMPLICATIONS</th>
<th>UK PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>First-line or adjuvant therapy</td>
<td>+++</td>
<td>Yes</td>
<td>Co-beneldopa, co-careldopa</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>First-line or adjuvant therapy</td>
<td>++</td>
<td>No</td>
<td>Bromocriptine, cabergoline, pergolide, pramipexole, ropinirole, rotigotine</td>
</tr>
<tr>
<td>MAO-B inhibitors</td>
<td>First-line or adjuvant therapy</td>
<td>++</td>
<td>No</td>
<td>Rasagiline, selegiline</td>
</tr>
<tr>
<td>COMT inhibitors</td>
<td>Adjuvant to levodopa</td>
<td>++</td>
<td>No</td>
<td>Entacapone, tolcapone</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Reduction of dyskinesia</td>
<td>Lack of evidence</td>
<td>No</td>
<td>Amantadine</td>
</tr>
<tr>
<td>Antimuscarinics</td>
<td>Young patients with early PD and severe tremor, adjuvant in dyskinesia</td>
<td>Lack of evidence</td>
<td>No</td>
<td>Orphenadrine, procyclidine, trihexyphenidyl</td>
</tr>
<tr>
<td>Modified-release levodopa</td>
<td>Used to improve adherence and to provide symptom control overnight and on waking</td>
<td>+++ (initial therapy)</td>
<td>Yes</td>
<td>Co-beneldopa MR, co-careldopa MR</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Severe motor complications and “off-time” with other therapy</td>
<td>+</td>
<td>No</td>
<td>Apomorphine</td>
</tr>
<tr>
<td>Levodopa intestinal gel</td>
<td>Severe motor complications and “off-time” with other therapy</td>
<td>+++</td>
<td>Yes</td>
<td>Co-careldopa (Duodopa)</td>
</tr>
</tbody>
</table>
symptoms, which is often more troublesome than the dyskinesia itself.

Therapy interruptions are sometimes unavoidable (eg, for patients undergoing surgery, especially gastrointestinal surgery) and can occur if patients become unable to take their usual oral treatments. The consequences of missing doses varies from minor loss of control to neuroleptic malignant syndrome. Patients with PD undergoing surgery are more likely to experience post-operative complications and this may, in part, be due to omitted doses. If enteral administration is not possible then alternative methods of drug administration should be used, such as topical rotigotine or subcutaneous apomorphine. 

**Future treatments**

Neuroprotection (therapeutic strategies intended to slow or halt the progression of loss of dopaminergic neurones) and neurorestoration (replacing the missing or damaged dopaminergic cells) are believed to be the future of PD management.

**Neuroprotection**

Although it has been proposed that antioxidants, such as ubiquinone (co-enzyme Q10) or vitamin E, could offer neuroprotection by scavenging harmful free radicals, there is little evidence to support their use in PD.

A small study conducted in 2002 reported that ubiquinone at doses of 1,200mg per day provided a significant change in total “unified Parkinson’s disease rating scale” from baseline compared with placebo after 16 months. There have been no other large-scale studies that support or refute the use of ubiquinone.

Other products could offer neuroprotection and require further investigation, including those with anti-apoptotic or pro-mitochondrial properties. It is believed that rasagiline may be anti-apoptotic and research into this is under way.

**Neurorestoration**

The role of neurorestoration for the management of patients with PD is being explored. Studies investigating the place of gene therapy (eg, the growth factor neurturin) and tissue transplantation (human and animal) are under way currently, and it is hoped that new therapeutic options will be made available in the future.

References


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