

(14) PARKINSON'S DISEASE

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This article discusses the clinical features, diagnosis, treatment and individual patient care of people with Parkinson's disease

Parkinson's disease (PD) is a progressive neurological disorder, characterised by tremor, rigidity and bradykinesia, which affects at least 120,000 people in the United Kingdom.¹ PD is the result of degeneration of dopaminergic neurones in the substantia nigra of the midbrain and, typically, 70–80 per cent of these neurones have died before the syndrome becomes clinically apparent.

The pharmacological treatment of PD is complicated by controversy surrounding initial choice of agent as well as the progressive nature of the condition, the occurrence of co-morbidities and the long-term effects both of the disease and the drugs used to treat it. Currently treatment is symptomatic only since there is insufficient evidence of the effect of any agent on disease progression.

Pharmaceutical care is directed towards monitoring the effects of therapy and regular medication review to ensure the necessary individualisation of treatment for optimum symptom control.

The cause of PD is unknown, although environmental and genetic factors have been implicated. The lack of a biological marker, and difficulties with clinical diagnosis, make genetic studies difficult. Family history is present in 20–30 per cent of patients and is thought to be most important in those with early-onset disease. Recently, single gene defects have been identified in some families with PD. Mutations of the alpha synuclein gene are an uncommon cause of PD. In contrast, a single gene defect for

the "parkin" gene is a relatively common cause of PD in people aged below 60 years. Genetics might, in the future, have a role in pharmacological treatment, such as in predicting response to treatment or adverse effects.²

Pathological changes in PD occur not only in the substantia nigra but also involve the thalamus, hypothalamus, limbic and neocortex. The pathological hallmark of PD is the presence of Lewy bodies in the neurones. A Lewy body is an intracytoplasmic inclusion body containing alpha synuclein, ubiquitin and proteases. The function of Lewy bodies is unknown but might be related to the disposal of abnormal protein aggregation. Lewy bodies can also be found in the brains of people with other neurological diseases such as Alzheimer's disease and motor neurone disease. It is controversial whether dementia with Lewy bodies represents a specific pathological entity distinct from PD, or whether the two conditions are part of the same spectrum of disease.³

Other neurotransmitters, in addition to dopamine, such as serotonin and noradrenaline are affected in PD and this could explain some of the non-motor abnormalities of the disease, eg, depression.

The existence of different subgroups of PD has been suggested. For example, some elderly patients exhibit more rapidly progressive disease with postural instability and L-dopa-unresponsive features such as cognitive impairment. On the other hand, some younger patients experience a more benign clinical course, with tremor-dominant symptoms and less likeli-

hood of cognitive impairment. The relevance of different subgroups in treatment strategies is unclear.⁴

CLINICAL FEATURES

The three main clinical features of PD are tremor, rigidity and bradykinesia. Other associated symptoms are listed in Panel 1.

EPIDEMIOLOGY AND PUBLIC HEALTH IMPLICATIONS

Parkinson's disease is the second most common neurodegenerative disorder (after Alzheimer's disease). Of the population aged

Panel 1: Clinical features

CARDINAL FEATURES

- **Tremor** Tremor is characteristically present at rest and initially tends to occur unilaterally. Because of the characteristic movements of the fingers, it is described as "pill-rolling" tremor. Postural tremor can also occur
- **Rigidity** Rigidity is resistance to passive movement of a limb. It may occur as "lead-pipe" or "cog-wheel" rigidity
- **Bradykinesia** Bradykinesia is slowness of, and decrease in, automatic movement that affects initiation of voluntary movement. Fatiguing of repetitive movements (where the amplitude of these movements becomes progressively less) also occurs

ASSOCIATED FEATURES

- Hypomimia (mask-like face)
- Micrographia (small writing)
- Impaired blinking
- Monotonous speech
- Reduction in speech volume
- Autonomic abnormalities, including postural hypotension, constipation, urinary problems, sexual dysfunction, impaired thermoregulation, pain and sensory symptoms
- Dysphagia (swallowing difficulty) and sialorrhoea (drooling of saliva)
- Gait abnormalities, postural instability, falls
- Weight loss, sometimes associated with dysphagia
- Neuropsychiatric complications, eg, depression, confusional states, dementia and psychosis
- Sleep dysfunction

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over 65 years, 1 per cent is affected with PD, rising to 2 per cent in people aged over 80 years.¹ The estimated overall prevalence of idiopathic PD is 100–160 per 100,000 of the UK population, with an annual incidence of 12 new cases per 100,000.^{5,6} Prevalence increases considerably with age to 800–900 per 100,000 of those aged 70–79 years and 1,300 per 100,000 of those aged over 80 years.^{5–8} A community pharmacy serving 5,000 patients might be expected to have five to eight patients with PD. Approximately 5 per cent of patients are diagnosed before the age of 40 years. A comparison of prevalence of PD across several European countries has shown no major differences.⁹

Defining the social and economic burden of PD is difficult. Although the prevalence in the general population is not high, the effects of the disease on sufferers, families and carers are considerable.¹⁰ The disease results in decreasing motor function with progressively worsening mobility and impairment in activities of daily living

(ADL). After five years of illness, 25 per cent of patients are unlikely to be able to work, increasing to 80 per cent after nine years.¹¹ The debilitating effect of PD is reflected by increased mortality compared with the general population.^{12,13}

PD patients' quality of life is affected by the fact that they report more pain, less energy, more social isolation and more sleep disorders than healthy elderly people. Depressive symptoms, presence of sleep disorders, and low degree of independence are variables that most strongly predict quality of life scores.¹⁴ Depression, in particular, is common in PD¹⁵ and among carers of people with the disease. Dementia was found in 44 per cent of PD patients over the age of 60 years in a community-based study.¹⁶ Risk factors for dementia include older age at onset of PD, longer duration of disease, severity of initial motor deficit and psychotic reactions to L-dopa.^{17–19}

One study, looking at drug usage in Dutch nursing homes, showed that 6 per

cent of patients had a diagnosis of PD.²⁰ Data from five European studies indicate that patients with PD are about five times more likely to live in an institution than those without PD. The highest risk factors for nursing home admission are old age, ADL score, hallucinations, dementia and disease progression.²¹

CLINICAL MANAGEMENT

Four stages of clinical management have been identified in PD and they might be useful in guiding treatment. They are:²²

- Diagnosis and treatment initiation
- Stable maintenance
- Complex
- Palliative stage

Treatment algorithms have been published²³ and, in the UK, guidelines were produced by the Parkinson's Disease Consensus Working Group in 1998 and updated in 2001.^{24,25} These are guidelines based on the available evidence and clinical expertise of the UK-based working group, although it is accepted that there is a lack of published evidence to support many of the important questions in PD treatment. Figure 1 shows an outline of possible treatment pathways.

L-dopa (levodopa), which is metabolised to dopamine, is the mainstay of treatment of PD. It is almost always combined with a dopa-decarboxylase inhibitor (DCI) which inhibits peripheral breakdown to dopamine. This allows smaller doses of L-dopa to be used and enables more L-dopa to cross the blood brain barrier and produce its therapeutic effect. It also minimises peripheral side effects such as nausea, vomiting and hypotension. The duration of biological effects of L-dopa are more complex and prolonged than can be explained by plasma concentrations and the drug's short plasma half life (approximately 90 minutes). The L-dopa response may comprise a "long duration response" and a "short duration response" where only the latter seems to be linked to plasma L-dopa concentration.²⁶

The development of dopamine agonists (DAs) which bind directly to the postsynaptic receptor has sought to produce a more predictable and sustained biological action than that of L-dopa. There has been interest in the use of agents other than L-dopa early in the disease on the basis that this may delay the long-term adverse effects of L-dopa. In addition DAs do not need to be stored by diseased dopaminergic neurones and they appear to reduce dopamine turnover and resultant free radical production. The implication, theoretically, is that they have a neuroprotective effect, although the clinical relevance is as yet unproven. Table 1 describes the currently available oral dopamine agonists.

Entacapone is useful only as adjunctive treatment to L-dopa. It has no anti-parkinsonian effect of its own and acts by preventing breakdown of L-dopa to dopamine in the periphery through inhibition of catecholamine-O-methyltransferase (COMT). COMT is the secondary pathway

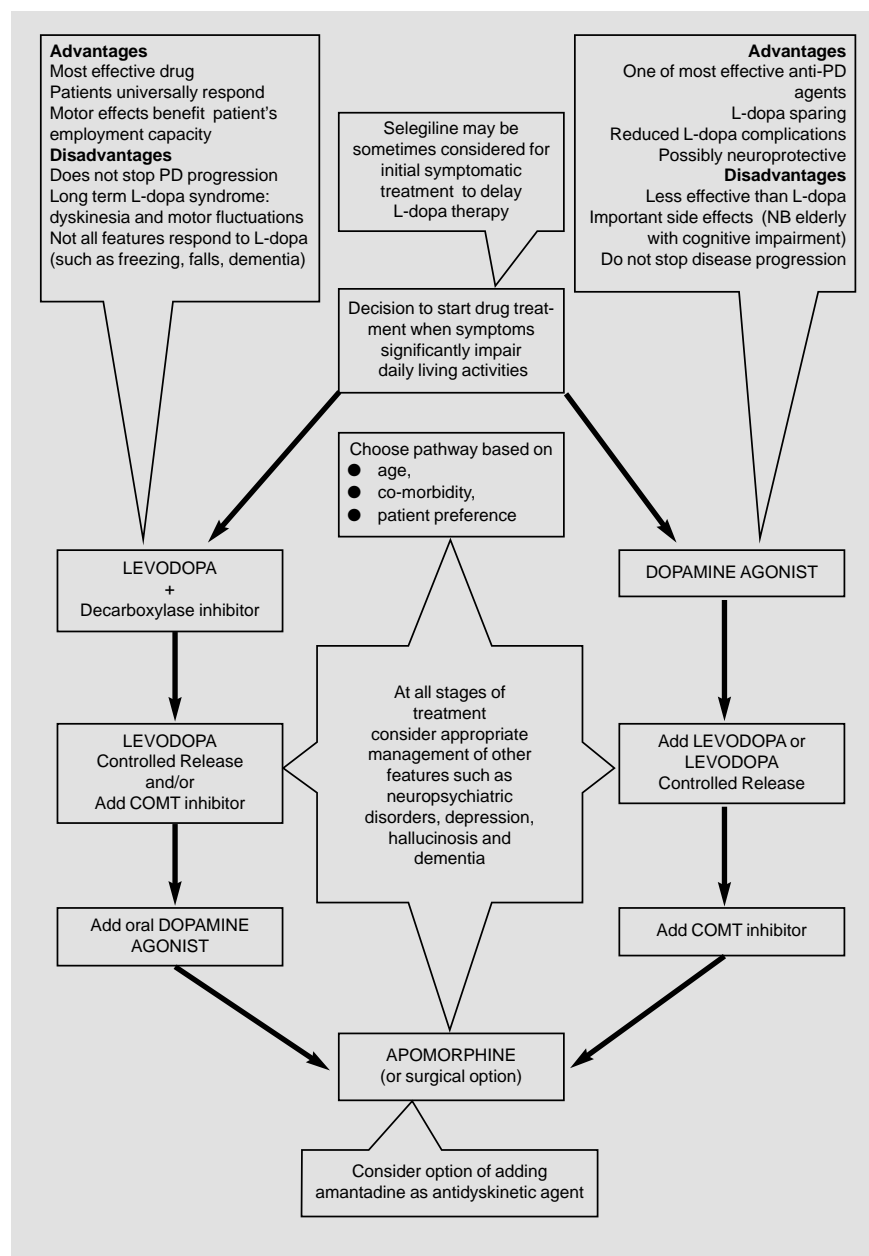


Figure 1: Possible drug treatment pathways in PD (adapted from Bhatia et al²⁴)

for L-dopa metabolism and it becomes more prominent in the presence of dopa-decarboxylase inhibition. The theoretical benefits of COMT inhibition include prolongation of L-dopa duration of action and an increase in L-dopa availability in the brain.

Various surgical techniques have been used in PD. The risk-benefit of surgical treatments requires full assessment of individual characteristics including cognitive assessment and optimal pharmacological management, including apomorphine, which is usually preferred before surgery. There is a lack of evidence for the effectiveness of surgery compared with drug treatment but a major clinical trial is currently under way in the UK.

Diagnosis and treatment initiation Diagnosis and management should be undertaken by a specialist in PD, usually a neurologist or geriatrician, preferably working in a specialist clinic. Diagnosis is made on clinical grounds, and a general practitioner, who is unlikely to have more than three or four PD patients on his list, may find accurate clinical diagnosis difficult. Challenge tests with L-dopa or apomorphine as an aid to diagnosis are no longer routinely recommended.²⁷ GPs are advised not to start L-dopa before referral because of the move towards use of dopamine agonists earlier in disease. Even small amounts of L-dopa theoretically can "prime" the early PD patient for development of long-term complications.²⁴

Early clinical signs can be mistaken for other disorders, such as frozen shoulder. The diagnosis of PD might be incorrectly made in patients who have essential tremor

TABLE 1: DOPAMINE AGONISTS CURRENTLY AVAILABLE FOR ORAL USE IN THE UK

Drug	Type, receptor action	Licensed indications	Usual frequency of dosing
Bromocriptine	Ergot derivative D ₂ receptors	Monotherapy and with L-dopa	Three times a day
Lisuride	Ergot derivative D ₁ and D ₂ receptors	With L-dopa	Three times a day
Pergolide	Ergot derivative D ₁ and D ₂ receptors	Monotherapy and with L-dopa	Two to three times a day
Pramipexole	Non-ergot D ₂ and D ₃ selective	With L-dopa in advanced PD	Three times a day
Cabergoline	Ergot derivative predominantly D ₂ receptors	With L-dopa	Once a day*
Ropinirole	Non-ergot D ₂ and D ₃ selective	Monotherapy and with L-dopa	Three times a day

*Very long acting 7–28 days

or atypical parkinsonian syndromes, such as multiple system atrophy or progressive supranuclear palsy. Symptoms also overlap with other common disorders of ageing, such as Alzheimer's disease and cerebrovascular disease.²⁸ Drug-induced parkinsonism might occur, especially in older persons.¹

Recent drug history should be reviewed at the time of diagnosis. Some drugs precipitate parkinsonism or exacerbate pre-existing PD, particularly in elderly patients in whom dopamine receptor reserve may already be diminished. Although usually reversible, drug-induced parkinsonism persists in approximately 30 per cent of cases and may represent an "unmasking" of subclinical parkinsonism.^{29,30}

Drugs which might precipitate parkinsonism should usually be stopped, and initiation of PD treatment should be delayed for three months, if possible, to see if symptoms resolve. Anticholinergic drugs can be used

to reverse the effect but can increase the risk of irreversible tardive dyskinesia, as well as provoking neuropsychiatric symptoms.³¹ Table 2 shows some drugs associated with parkinsonism. At all stages of treatment it is important to avoid drugs that could exacerbate the condition, wherever possible.

Stable maintenance: Early PD Controversies surround the treatment of early PD, including when to initiate therapy and which drug to use first. There is debate around whether any drugs offer neuroprotective effects, whether delaying initial treatment might minimise the risk of long-term motor complications, and whether early treatment with dopamine agonists offers better long-term outcomes than L-dopa. Treatment should be started when there is significant functional disability affecting ADL, and this should be discussed with the individual patient.¹ Factors influencing initial treatment choice include age-related co-morbidities (particularly cognitive impairment and cardiovascular disease) and severity and type of disease, for instance whether symptoms of tremor or bradykinesia are predominant. Factors such as lifestyle and occupation, as well as patient, carer and prescriber preference, should be considered in deciding which treatment to use.^{23,25} The evidence currently available for treatment choices is summarised in Table 3.

Anticholinergic agents may be effective for treatment of tremor in early disease, but have only mild benefits on rigidity and bradykinesia.²⁴ There is no evidence for benefit in later disease and they may exacerbate cognitive impairment. They should be avoided in elderly patients but psychiatric complications may occur even in younger patients.^{32,33} The UK Parkinson's Consensus Group suggests that anticholinergic drugs should be used sparingly and at the lowest effective dose.²⁵ They should be withdrawn (slowly if appropriate) as the disease progresses and other PD drugs are added. Peripherally acting anticholinergics such as propantheline can sometimes be useful for symptoms of hypersalivation.

There is now evidence to support the possible benefits of using DAs instead of L-dopa as first line treatment^{23,25} although the issue is controversial.^{34,35} DAs may be selected, even though they offer slightly reduced motor benefit compared with

TABLE 2: SOME DRUGS WHICH CAN INDUCE OR EXACERBATE PARKINSONISM^{29,30,37}

Drug/drug class	Evidence for effects and comments on management
Antiemetics ● Metoclopramide ● Prochlorperazine	Well documented evidence, particularly in elderly patients. Drug of choice for treating nausea in PD is domperidone, which is a peripheral dopamine antagonist
Antipsychotics	Antipsychotics such as haloperidol are a well-documented cause of drug-induced parkinsonism. This is a dose-dependent effect and seems to be related to the extent of dopamine D ₂ -receptor blockade. It may be less common with the newer atypical antipsychotics. The choice of antipsychotics in patients with PD is discussed further in Table 5
Calcium channel blockers ● Flunarizine ● Cinnarizine	Some reports of exacerbation/precipitation of PD, particularly with flunarizine and cinnarizine. Research is ongoing into the potential benefits of calcium channel blockers in PD but no conclusive evidence is available at this stage
Other drugs ● Naproxen/other NSAIDs ● Captopril ● Amiodarone ● Phenytoin ● Valproate ● Lithium ● Oral contraceptives ● Selective serotonin reuptake inhibitors (SSRIs): fluoxetine, paroxetine, fluvoxamine and sertraline	These drugs have all been implicated in case reports in causing or exacerbating parkinsonism but these cases are mainly anecdotal and causality has not been established. Tremor with valproate is well documented. The evidence of a problem with SSRIs is limited to case reports and is insufficient to preclude their use where required

TABLE 3: SUMMARY OF CLINICAL EVIDENCE FOR USE OF ANTIPARKINSON'S DRUGS

Evidence based findings	Recommendations ²⁵
<p><i>L-dopa (combined with decarboxylase inhibitors)</i> L-dopa provides effective symptomatic treatment in 80 per cent of patients²⁵ but ultimately limited by motor fluctuations (especially in young-onset patients), dyskinesias and neuropsychiatric problems.²⁵ Comparison with dopamine agonists in early PD found early L-dopa use associated with development of dyskinesia. Although accelerating disease progression occurring as a consequence of potentially neurotoxic radicals derived from L-dopa metabolism has been postulated this has never been confirmed in human studies.¹ Detrimental effects on disease progression (perhaps attributed to neurotoxic radicals²³) await confirmation.³⁸ Modified release preparations may improve motor control early in disease but there is insufficient evidence of long-term reduction of complications.³⁹⁻⁴¹</p>	<p>L-dopa remains the gold standard in PD treatment and is particularly useful for bradykinesia and rigidity. Strategies to avoid long-term complications include use of other drugs such as dopamine agonists for symptomatic relief, especially in biologically younger patients. All patients will eventually need L-dopa whether as adjunctive or initial treatment. The L-dopa dose inevitably needs to be increased as symptoms progress. Slow improvement in patient response during the first six to 18 months is generally maintained for about two years before slow decline occurs. Conversion to modified release L-dopa may be useful to help manage motor fluctuations in which case altered bioavailability may necessitate slightly larger doses.</p>
<p><i>Selegiline</i> Selegiline delays the need for L-dopa therapy in PD by approximately one year.⁴²⁻⁴⁴ Although a neuroprotective effect has been suggested, benefit is not sustained over time^{45,46} and it is likely to be a symptomatic effect. An association between selegiline and excess mortality in one study has not been confirmed by a meta-analysis of five studies.^{45,47}</p>	<p>Selegiline can be considered as a possible neuroprotective agent early in disease but evidence is from <i>in vitro</i> studies. Its main use is as an option in patients with "wearing off" fluctuations with L-dopa in later disease where it can increase the duration of dopaminergic response.⁴⁸ Alternative options such as sustained release L-dopa, COMT inhibitors, and dopamine agonists should also be considered. Despite a decline in selegiline use, there is no need to withdraw patients already established on the drug if it is well tolerated. Selegiline should not be used in patients with postural hypotension or dementia because of a risk of falls.</p>
<p><i>Amantadine</i> The only evidence for amantadine is from small trials. It can improve akinesia (freezing) and rigidity, but has only mild effects on tremor. It can also improve dyskinesias for six to 12 months.⁴⁹⁻⁵¹ The mean dose of 350mg used for dyskinesia in clinical studies was higher than usually prescribed. Lower doses can also be effective since benefits have been reported in some patients during dose titration.</p>	<p>Amantadine can be used in early disease to delay use of L-dopa but there is less evidence for this compared with other agents. Tolerance can develop, although there is insufficient evidence to substantiate this. A trial of oral amantadine may be reasonable before progressing to more complex treatments such as apomorphine or surgical procedures.</p>
<p><i>Entacapone</i> A combination of entacapone and L-dopa maintains consistent L-dopa delivery to the brain.⁵² However, there is a lack of comparative data with other first-line treatments. For patients already established on L-dopa, entacapone increased "on" time by 30-60 minutes, especially in patients who had a low proportion of "on" time, and reduced "off" time by approximately three hours, with a 12 per cent reduction in L-dopa dosage in clinical trials (NOME/COMT, SEESAW trials).^{53,54} In one study comparing the addition of a COMT inhibitor (tolcapone, no longer available) with dopamine agonist (bromocriptine) as adjunctive treatment to L-dopa, similar effects on motor function were identified although tolcapone had benefits in terms of side effects and dose titration.⁵⁵</p>	<p>Use as adjunctive treatment to L-dopa. It has theoretical benefits at any stage of the disease.</p>
<p><i>Oral dopamine agonists</i> <i>As monotherapy early in disease</i> Oral dopamine agonists are effective in early PD for study periods of up to 12 months.⁵⁶⁻⁵⁸ Studies over two to five years comparing L-dopa with a dopamine agonist, in early PD, found a lower incidence of dyskinesias and hallucinations with pramipexole, cabergoline or ropinirole.⁵⁹⁻⁶² Although there are concerns about the adverse effects of dopamine agonists in the elderly⁶³ (eg, cognitive impairment and postural hypotension), a recent retrospective study of 69 patients aged over 80 years indicated that they were well tolerated in 46 per cent of patients, indicating the potential benefit of these agents in carefully selected patients in this age group.⁶⁴ <i>As adjunctive therapy</i> Various studies have shown the benefits of dopamine agonists as adjunctive therapy to L-dopa.⁶⁵⁻⁶⁷</p>	<p>Dopamine agonists have theoretical advantages over L-dopa, including a longer half-life resulting in more prolonged dopaminergic stimulation. The results of the clinical trials comparing L-dopa with dopamine agonists in early disease may also be more applicable to younger patients who may more closely match the patients included in the trial and be less likely to have co-existing dementia or other co-morbidities.⁶⁸ Dopamine agonists are increasingly being used as monotherapy, early in disease, in suitable patients for the prevention of dyskinesias.</p>
<p><i>Apomorphine</i> Apomorphine is a useful treatment for motor fluctuations. It can reduce daily "off" time by more than 50 per cent in patients with on-off motor fluctuations, with extended benefits seen in up to eight years of follow-up.⁶⁹ Continuous infusion results in reduction in dyskinesias.^{70,71}</p>	<p>Apomorphine given as intermittent injections is useful as "rescue" therapy for "off" periods, particularly for patients who have two or three "off" periods a day, and can relieve associated dystonia (sustained muscle contractions causing twisting and repetitive movements or abnormal posture) and pain. In those requiring multiple injections, or who are unable to anticipate "off" periods and inject in time, continuous infusion is preferred. Continuous infusion (usually only during waking hours) is useful for troublesome dyskinesias. It can allow reduction in oral dopaminergic medication and reduction in dyskinesia.</p>

L-dopa, because this reduced motor benefit may be less disabling than severe dyskinesias later in disease, and so may be offset by a reduction in these effects. Such considerations may be particularly relevant in younger pa-

tients. Consideration also needs to be given to patient acceptability of an increased risk of hallucinations with dopamine agonists.³⁶ Other considerations in treatment choice include the use of non-ergot derivatives,

which can have an improved safety profile (in terms of ergot-related side effects), or use of longer acting agents such as cabergoline to allow less frequent dosing.

In practice, L-dopa plus a DCI remains

the therapy of choice in older patients because of its greater effectiveness in improving functional ability. Very elderly patients with limited life expectancy are likely to receive L-dopa for a shorter time, thus lowering the likelihood of L-dopa-related motor complications emerging. In patients with cardiac disease or cognitive impairment L-dopa may also be a better first choice than DAs because of a lower risk of cardiovascular or central side effects.^{23,25} Future decisions about drug choice will depend on the outcome of further research into whether DAs are neuroprotective. Theoretically, L-dopa can increase oxidative stress with resultant neurotoxicity, although this is not proven *in vivo*.

Treatment initiation is usually followed by a "honeymoon" period of stable maintenance where symptoms are well-controlled.

Complex stage and progressive disease As PD progresses, adjustment of medication by addition of adjunctive agents, increased doses and/or increased frequency of doses is usually required. Disease management also becomes complicated by the development of motor fluctuations requiring an increasing resort to polypharmacy. Almost 50 per cent of patients on L-dopa develop motor fluctuations after five years of therapy and almost all patients experience this effect after 10 years. Fluctuations can be unpredictable and difficult to manage, particularly in late-stage disease. Associated neuropsychiatric and autonomic symptoms can become troublesome and the management of the patient becomes a balancing of the cost of unwanted effects against the motor benefits of L-dopa. Current strategies being researched in early disease aim to reduce or delay these long-term complications. Tables 4 and 5 describe motor fluctuations and neuropsychiatric symptoms and possible management strategies.

Advanced/late stage disease (palliative phase) In the late stages of PD, treatment is complicated by lack of effectiveness and increasingly severe side effects. Therefore, reducing the burden of unnecessary drug treatment is important. A palliative approach to patient symptoms is required. Features of disease progression that do not readily respond to L-dopa include freezing episodes, autonomic dysfunction (including postural instability and falls), communication problems, mood disturbances and dementia. Management of disease progression requires co-ordinated multidisciplinary care.

INDIVIDUAL PATIENT CARE

The care of patients with PD is shared between primary and secondary care teams. Specialist clinics have become prominent. It is preferable for the clinics to be responsible for medication changes and dose adjustments, since most GPs will have limited experience of the disease. There is increasing interest in the development of multidisciplinary teams and PD specialist nurses.⁹²⁻⁹⁴ The UK Parkinson's Disease Society has

TABLE 4: MOTOR COMPLICATIONS IN THE TREATMENT OF PD^{1,23}

Features	Management options
<p><i>End of dose/wearing-off effects</i> Usually predictable deterioration of motor symptoms before the next dose of drug is due. Akinesia (freezing) can be troublesome at night.</p>	<ul style="list-style-type: none"> ● Sustained release L-dopa preparations (especially for night-time akinesia) ● COMT inhibitor added to prolong the effects of L-dopa ● Long-acting oral dopamine agonist or apomorphine ● Fractionation of dose. However, use of >5 doses a day is not recommended and can result in worsening control (the "no 'on' effect") because of inadequate individual doses
<p><i>Morning "off"</i> Including difficulty "getting going" and painful "off" period dystonia</p>	<ul style="list-style-type: none"> ● Dispersible L-dopa as a small dose immediately on waking ● Modified-release L-dopa preparation or long-acting dopamine agonist at night ● Subcutaneous injection of apomorphine may occasionally be required
<p><i>"On-off" phenomenon</i> Unpredictable motor fluctuations. Periods of mobility ("on") may be accompanied by severe L-dopa-induced involuntary movements (dyskinesias) fluctuating with disabling parkinsonism, unresponsive to medication ("off"). Painful dystonia, panic attacks and depression can accompany the "off" periods. Akinesia can occur in either "on" or "off" periods.</p>	<ul style="list-style-type: none"> ● Consider patient preference. Many patients prefer to have decreased periods of "off" time even at the expense of increased periods of dyskinesias
<p><i>Dyskinesias</i> Severe L-dopa-induced involuntary movements initially associated with high plasma L-dopa concentrations (peak-dose dyskinesia). Later, a diphasic pattern can follow at lower plasma L-dopa concentrations as the patient is switching "on" and "off". This may necessitate using larger and less frequent doses of L-dopa. Motor fluctuations can also result from erratic absorption and accumulation of L-dopa during the day leading to dyskinesia in the evening ("time-bomb effect"). Various movements can occur, including dystonia, which can also be a feature of "off" periods, making necessary the careful assessment of symptoms in relation to dose. With advancing disease, dyskinesias can become severe and disabling with a narrow therapeutic window between "on" periods and dyskinesia with L-dopa.</p>	<ul style="list-style-type: none"> ● Reduction of L-dopa dose ● Switch to ordinary release preparations from sustained release preparations ● Add COMT inhibitor or a dopamine agonist with a reduction in L-dopa dose ● Add amantadine ● Add apomorphine infusion with reduced oral dopaminergics

been instrumental in developing a network of PD specialist nurses in the UK who are able to co-ordinate multidisciplinary care. Good communication between specialists and primary team members and carers is important and regular contact between patients/carers and their pharmacist plays an important part in chronic disease management. A guide for primary care teams dealing with PD has recently been published by the Parkinson's Disease Society⁹⁵ and this group, among others, supports the pharmacist's role in teams managing patients with PD.^{96,97} Examples of UK pharmacists' initiatives include plans for a medicines management project⁹⁶ and a pharmacy service providing a "PD medication helpline" in Wales.⁹⁷ Support for carers is also important to address the stress and social isolation they sometimes experience.^{98,99} Adverse mental health effects are widely reported among carers, and can be worse if the patient for whom they are caring is cognitively impaired.¹⁰⁰ A patient education programme can improve both the patient's and carer's quality of life.^{101,102}

Community pharmacists can easily identify the PD patients served by their pharmacy, although they sometimes have more personal contact with the carers than with the patients themselves. Patient medication records offer an important check when changes in dose and formulation of medicines are made. Swallowing difficulties may necessitate changes in formulation of medicines.

Patients' diaries of timing of medication doses in relation to symptoms can be useful. Over-use or under-use of medication can severely affect the assessment and management of motor fluctuations. Confusion can contribute to compliance problems and simplification of dosage regimens is not usually possible in PD. Complex dosage regimens can also limit the use of compliance aids.

Table 6 summarises the range of pharmaceutical care issues arising from the management of PD. The major challenge in pharmaceutical care is to optimise the use of agents available to manage the symptoms of disease. Individualisation should take into account all the patient's associated clinical

problems. Although the focus of drug therapy discussion may be the control of motor symptoms, neuropsychiatric symptoms can be troublesome for many patients. Problems such as depression, dementia, psychosis, sleep disturbances and fatigue, coupled with impaired functional activities, highlight the need for patients to be assessed individually.¹⁰³

Patient education about drug therapy is important at all stages of treatment of PD, especially when treatment is introduced, when changes to treatment are made, when patients request information and when problems are identified. There is evidence that patients often lack knowledge about their disease and its management.¹⁰⁴ Difficulties with communication can occur when talking to patients with PD, and this can be addressed by timing discussions around the best time for the patient.

Minimising side effects is important in the management of PD and requires strategies such as timing adjustment, addition of adjunctive therapy, starting at low doses and only increasing doses gradually. In the case of dopamine agonists, confusion and postural hypotension can be minimised by gradually increasing the dose at the start of treatment. Tolerance to side effects develops over days or weeks. When dopamine agonists are used as an adjunct to L-dopa, a corresponding reduction in the L-dopa dose may be possible. Dose titration can be facilitated by use of "starter packs" which are available for some of the newer agents. These packs include tablets for the first few weeks of treatment which are taken at increasing doses. Patients require careful education on the correct use of these packs, and the changeover to maintenance dose, to avoid the confusion that can arise when increasing tablet strengths are used.

Occasionally it is useful to change from one dopamine agonist to another, for example if a side effect has occurred or where additional benefit may be expected. Two strategies for changeover have been suggested: either by starting the new agent at a low dose and increasing gradually while tailing off the original agent, or by switching overnight, usually under medical supervision, to an equivalent dose of the new agent. The latter approach may be more successful and cause less disability during modification.¹⁰⁵

Selegiline can cause sleep disorders, including vivid dreams and hallucinations, due to its metabolism to amphetamine and amphetamine derivatives. To minimise effects on sleep it should not normally be given after 2pm. The lyophilisate formulation of selegiline (Zelapar) is absorbed buccally and, theoretically, metabolite generation should be reduced with potential clinical advantages, although results of trials to confirm this are awaited. Selegiline can contribute to postural hypotension, which is a symptom that can be troublesome in PD patients. Selegiline should be avoided/withdrawn from use in susceptible patients because of the risk of falls. Postural hypotension may also be a limiting factor in the use of dopamine agonists.

TABLE 5: NEUROPSYCHIATRIC COMPLICATIONS IN THE TREATMENT OF PD

Features	Management options
<p><i>Depression</i> Depression occurs in about 40 per cent of clinic patients and is under-diagnosed and under-treated.⁷² Symptoms include apathy, fatigue and sleep disturbances. Most PD patients will develop depression at some time. No clear association between depression and motor disability has been found.⁷³ There may be an association with cognitive dysfunction, with an increased risk of developing dementia.⁷⁴</p>	<ul style="list-style-type: none"> ● Although depression is linked to a reduction in brain catecholamines, serotonin or dopamine, it is not always alleviated by L-dopa or dopamine agonists. However, strategies to reduce motor fluctuations can help some patients where mood changes correspond to "off" periods ● There are few controlled studies of antidepressants in PD, and none with SSRIs.⁷⁵ Tricyclic antidepressants started at low doses have demonstrated adequate efficacy and tolerability⁷⁶ but may worsen cognitive impairment or postural hypotension. Although SSRIs have anecdotally been associated with extra pyramidal side effects, this is insufficient to preclude use and there is some evidence that paroxetine is tolerated.⁷⁷ SSRIs should not usually be used in patients taking selegiline because of a risk of serotonin syndrome.⁷⁸ In practice, selegiline would normally be discontinued if an SSRI was required ● The use of non-pharmacological treatments, eg, psychotherapy, should also be considered
<p><i>Psychosis</i> Psychosis occurs in 20 per cent of PD patients and is the commonest cause of nursing home placement.^{79,80} Antipsychotic drugs can exacerbate parkinsonism and can cause severe reactions (eg, neuroleptic malignant syndrome⁸¹).</p>	<p>Psychosis requires careful step-wise adjustment of drug treatment⁸² and a trade-off between control of psychosis and reduced control of motor function:</p> <ul style="list-style-type: none"> ● Reduce or stop anti-PD medication, starting with those agents with the least favourable risk ratio, eg, anticholinergics first, followed by selegiline, amantadine, dopamine agonists and COMT inhibitors. If neurotoxicity is precipitated by a recent addition, it is sensible to withdraw that agent first ● Reduce L-dopa dose ● Add an antipsychotic at a low dose (see below) <p>The most substantial evidence of benefit in treating psychosis without exacerbating parkinsonism relates to clozapine.^{83,84} However, its adverse effect profile, including blood dyscrasias, haematological monitoring requirements and cost, precludes its use as first line treatment in the UK. Quetiapine has shown promising results in small studies but further controlled trials are awaited.⁸⁵⁻⁸⁷ Olanzapine may be useful but is associated with deterioration in motor function.^{82,88} Early interest in risperidone has declined due to associated exacerbation of parkinsonism</p> <p>Antipsychotics, including atypical agents, are not routinely recommended for use in patients who have dementia with Lewy bodies or PD since they may be sensitive to their effects.⁸¹ Use of antipsychotics therefore requires specialist guidance. Cholinesterase inhibitors are an alternative option and are discussed in more detail below</p>
<p><i>Dementia</i> Some PD patients exhibit cognitive impairment. Severe dementia occurs in at least 10-30 per cent of patients with advanced disease and many others have some degree of cognitive impairment.⁸⁹</p>	<ul style="list-style-type: none"> ● Drugs that cause cognitive impairment, such as anticholinergics, should be avoided if possible.⁹⁰ Drug withdrawal should be slow to avoid worsening of confusion ● See above for adjustments of PD drug treatment ● Cholinesterase inhibition, in particular the use of rivastigmine (an unlicensed indication), has been tried⁹¹

Care should be taken to ensure the drugs are started at low doses, especially in the elderly, and individualised accordingly. For example, selegiline should be started at 2.5mg daily in the elderly to avoid confusion and agitation. L-dopa therapy should be started at a low dose, especially in the elderly (50mg L-dopa, eg, as 62.5mg co-careldopa, three times a day), and increased gradually to a dose that provides symptomatic control with minimal side effects. Ideally, an L-dopa preparation which provides a sufficient daily dose of DCI is used. A DCI dose of 75mg of benserazide in co-beneldopa (Madopar) or carbidopa in co-careldopa (Sinemet) is recommended, although this is not achievable at the lowest starting doses.

There is no evidence for either co-careldopa or co-beneldopa being more effective,

but some centres use only one product to minimise confusion. Both products can be given to patients with swallowing difficulties (Madopar is a dispersible formulation and Sinemet tablets can be crushed and dissolved) although dispersion of the tablet before administration will shorten the onset and duration of action. The faster onset of action can be utilised clinically by administration of a small dose dissolved in water as the patient wakes to provide morning mobility. Pharmacists and prescribers should be vigilant to ensure that the patient receives the L-dopa formulation that is intended. A chart outlining the preparations available with a photograph of each individual tablet is available from the Parkinson's Disease Society and is useful for clarifying individual preparations being taken by the patient.

L-dopa should be taken with food, at

TABLE 6: PHARMACEUTICAL CARE IN PARKINSON'S DISEASE

Stage of treatment	Actions	Points to consider at each stage
<p><i>Treatment plan</i></p> <ul style="list-style-type: none"> ● Patient comprehension/active participation ● Patient's characteristics ● Indication (the need for each drug) ● Drug history ● Choice of medication ● Contraindication/interaction ● Conformity to guidelines ● Continuity of care 	<p><i>Verify the plan in respect of</i></p> <ul style="list-style-type: none"> ● Patient's characteristics ● Medication suitability ● Patient's needs for education ● Concordance and agreed expectations <p><i>Modify the plan to address</i></p> <ul style="list-style-type: none"> ● Specific educational needs ● Need for individualisation of treatment plan 	<ul style="list-style-type: none"> ● Stage of treatment, ie, initiation/stable maintenance/complex/palliative stages ● Specialist confirmation of diagnosis and treatment plan ● Conformity of drug choice with current guidelines or specialist recommendations ● Shared care arrangements and hospital/clinic attendance ● Presence of co-morbid states that complicate diagnosis and management ● Concomitant therapy that may influence treatment/evaluation. Consider drugs that can exacerbate or precipitate associated conditions, eg, anticholinergics can exacerbate dementia. Identification of medication that can cause or aggravate parkinsonism, or interact with medication, eg, antipsychotics, anti-emetics ● Accuracy of drug history for all prescribed and non-prescribed medicines ● Whether the patient is receiving hypotensive medication because dopaminergic drugs may reduce blood pressure ● Health beliefs of the patient, understanding of disease, expectations with regard to treatment goal, complications and impact on quality of life, social circumstances, family environment, family understanding of condition and support ● Patient comprehension of the continuous nature of therapy and the likely changes in responses necessitating medication adjustment ● Self-management plan and patient's records of symptoms in relation to dosing. Knowledge of patient's daily routine may help decisions about medication timing ● Responding to patient's information needs. Access to patient support groups, eg, the Parkinson's Disease Society. Explain expected adverse effects and ensure treatment plan addresses them, eg, nausea and hypotension caused by dopamine agonists might require domperidone
<p><i>Implementation</i></p> <ul style="list-style-type: none"> ● Dose ● Frequency ● Timing ● Compliance ● Clinical signs ● Laboratory markers 	<p><i>Monitor the patient for</i></p> <ul style="list-style-type: none"> ● Continuing suitability of drug/dose regimen ● Signs/symptoms of effectiveness and toxicity <p><i>Adjust the process by</i></p> <ul style="list-style-type: none"> ● Further individualisation in response to monitoring 	<ul style="list-style-type: none"> ● Compliance with current therapy, including ability to handle and swallow formulations prescribed. Blister packs may be problematic ● Patient involvement in self-monitoring and documentation of symptoms. Patient diaries recording dose times/symptoms can be useful ● Initiation of treatment at low doses with dose titration to avoid adverse effects ● Individualisation of medication dose and timing to suit patient preferences and lifestyle to obtain optimal effect while maximising compliance and minimising side effects. Systems of regular drug administration rounds in hospitals and residential/nursing homes may cause difficulty ● Securing support and information from relatives/carers and health care professionals, eg, district nurses, where appropriate to help with complicated treatment regimens, eg, apomorphine ● Asking and advising patient about use of self-medication/ complementary medicines ● Considering effects of changes in mental and physical function on ability to self-medicate ● Over-use of medication may be a specific problem requiring education of patients on the disadvantages (eg, limiting future therapeutic options, increasing risk of immediate and long-term adverse effects) ● Specific tests required for drugs used, eg, Coomb's test for apomorphine, blood pressure monitoring with dopamine agonists ● Checks for drug interactions including purchased and complementary products ● Transfer of information between primary and secondary care ● Changes in doses of current medication when new medication introduced, eg, entacapone might necessitate reduced L-dopa dose
<p><i>Clinical outcome</i></p> <ul style="list-style-type: none"> ● Therapeutic benefit ● Safety ● Unwanted symptoms ● Recorded adverse drug reaction 	<p><i>Confirm evidence of treatment success</i></p> <ul style="list-style-type: none"> ● Reassure patient in relation to agreed expectations <p><i>Prompt a review from</i></p> <ul style="list-style-type: none"> ● Identification of treatment failure ● Patient's newly identified needs ● Sharing information and discussion of implications with the prescriber and other team members 	<ul style="list-style-type: none"> ● Acknowledgement of degenerative nature of condition and patient expectations of treatment ● Attainment of therapeutic goals, eg, reduction in "off" periods or dyskinesias, improvement in functional ability and quality of life ● Indications for treatment plan revisions, such as persistent symptoms, disease progression, complicating features (such as adverse effects, co-morbidity and polypharmacy), changes in compliance, referral for clinical review ● Reporting adverse effects to the Committee on Safety of Medicines where appropriate ● Need for adjunctive medication. Control of symptoms, eg, hypersalivation can be helped by peripherally acting anticholinergic drugs such as propantheline, constipation can be helped by fibre supplements, sympathomimetic agents can help with postural hypotension ● Signs of specific drug-induced symptoms, eg, breathlessness with ergot alkaloids should be investigated for possible pleural fibrosis, selegiline should be avoided in patients with postural hypotension because of the risk of falls ● Clinical evidence of toxicity or undertreatment ● Management of side effects not controlled with usual prophylactic measures

least in the early stages of treatment, to minimise gastrointestinal (GI) disturbance. If nausea and vomiting are a problem, domperidone is the anti-emetic of choice and may only be required for a short time. Domperidone also helps to offset postural hypotension if troublesome and might have to be continued long-term in some patients. These patients may need to be reassured if the specialist chooses to exceed the 12-week maximum length of treatment stated in the manufacturer's literature. In

later stages, there might be benefits in giving L-dopa before food. The standard British National Formulary warning label on L-dopa preparations which advises that it should be taken with or after food is not always appropriate. L-dopa is absorbed from the GI tract, and transported across the blood-brain barrier by a competitive active transport system for large neutral amino acids. Large protein meals might reduce L-dopa absorption and, therefore, L-dopa may be better absorbed on an empty

stomach, which might be a useful strategy in later stages of the disease. In some cases, redistribution of protein in the diet, under dietetic advice, is useful.

Practical issues with COMT inhibitors include the possible need to reduce L-dopa dose, the need to administer them with each dose of L-dopa and the need to warn patients about urine discoloration, which is harmless but may cause alarm.¹⁰⁶ Two approaches can be used for treatment initiation. A dose of COMT inhibitor can be

added to each L-dopa dose, maintaining the current L-dopa dose initially and then reducing it if required, eg, if dyskinesias occur. Alternatively, the L-dopa dose is reduced at the time of initiating the COMT inhibitor, initially by approximately 25 per cent, with further titrating of the L-dopa dose after a few days if necessary. The approach taken should depend on whether dyskinesias or "off" periods are more troublesome. It is recommended that when dopaminergic effects such as dyskinesia occur with combined treatment, the L-dopa dose, rather than the COMT inhibitor dose, is reduced.

In all patients, transfer of information on changes in drug therapy from specialist care to the community pharmacist can assist continuity of care and patient compliance, by ensuring treatment continues to be individualised to patients' assessed needs. Issues in the continuity of care in the elderly PD patient are illustrated in Case 1.

The importance of pharmaceutical care in complex treatment in advanced disease is illustrated in Case 2, which outlines care issues in the initiation of apomorphine. Although apomorphine is used in relatively few patients at present, it has been suggested that this treatment option is under-utilised and its use is likely to become more widespread.¹⁰⁷ Case 2 illustrates use of apomorphine for disabling dyskinesia, but it may also be used for patients with "on-off" syndrome as intermittent injections. The expected onset (five to 10 minutes) and duration (40–90 minutes) of intermittent injections should be discussed with the patient, and the patient and/or carer should be shown how to operate a pre-filled apomorphine pen. There are numerous practical issues in the management of patients on apomorphine, necessitating a multidisciplinary team approach.¹⁰⁸ Education of the patient, carer and relevant community health care professionals, such as district nurses, with continued back-up from the hospital team is of paramount importance to the success of treatment.

Pharmaceutical care requires health care providers to be vigilant for symptoms indicating changes in patients' needs, eg, constipation requiring laxative use, dry eyes needing artificial tears and the need for osteoporosis prophylaxis in at-risk patients because of the risk of falls.¹⁰⁹ Certain purchased medicines should be avoided, such as sympathomimetic agents in cough remedies and antimuscarinic agents in motion sickness products. Appropriateness of analgesic use should be considered because pain associated with PD is often unresponsive to analgesics and they may contribute to problems such as constipation. Drugs that contribute to falls should be avoided where possible.¹¹⁰

Sometimes it is necessary to use a drug that might exacerbate symptoms. For example, SSRIs should be monitored carefully, particularly in the first month of therapy, for worsening of symptoms. Antipsychotics, which are sometimes necessary for hallucinations, should be started at the lowest dose and the dose titrated gradually. Dosing of

Panel 2: Parkinson's Disease Society of the UK

The Parkinson's Disease Society (PDS) works with people who have PD, their families and carers, and health and social care professionals. The mission of the PDS is the conquest of PD and the alleviation of the suffering and distress it causes through research, education, welfare and communication.

The work of the PDS includes:

- Research into the cause, cure and prevention of PD, and improvements in treatments
- A helpline staffed by nurses offering medical information, support and a listening ear
- Information and advice on all aspects of PD including drug treatments, surgery, therapies, social and health care rights, benefits, driving, insurance, and employment
- Publications, audio tapes and video tapes for people with PD, their families and carers, and professionals
- Comprehensive education and training programme for professionals
- A national network of field staff and branches, offering local information, support, advice and social activities across the country

For further information please contact:

Parkinson's Disease Society National Office, 215 Vauxhall Bridge Road, London SW1V 1EJ, tel 020 7931 8080, e-mail enquiries@parkinsons.org.uk, website www.parkinsons.org.uk. Freephone helpline tel 0808 800 0303, available on Monday to Friday (except Bank Holidays) from 9.30am until 5.30pm.

antipsychotics may require splitting available tablet strengths because required doses are lower than those currently available in licensed formulations. For example, quetiapine should be started at 12.5mg (quarter of a tablet) at bedtime and titrated at three to five day intervals, as tolerated, until symptoms are controlled or a maximum of 50mg is reached.

A recent survey highlighted the fact that withdrawal of regular medication is associated with an increased risk of postoperative complications in patients with PD.¹¹¹ Management of medication should be fully addressed in patients admitted to hospital for surgery or other reasons. This means that advice might need to be given on readjusting dose schedules or the use of alternative agents such as subcutaneous apomorphine in patients who are unable to swallow.

Many patients seek information on complementary therapies. There are few data available on the extent of their use in PD patients but one survey found that approximately one-third of patients had tried complementary therapies.¹¹² Various alternative medicines have been proposed, including melatonin, octacosanol, and nicotinamide adenine dinucleotide (NADH) but there is currently no evidence that these treatments are of any benefit. There has also been much interest in the possible benefits of vitamins, minerals and other nutrients, eg, vitamin C, vitamin E and selenium, in slowing the progression of PD but there is insufficient evidence of benefit. Vitamin E at a dose of 2,000 units daily was tested as a neuroprotective treatment for PD as part of the DATATOP study but no delay in disease progression was detected. Concerns over a potential increased risk of falls with the use of vitamin E in other neurodegenerative conditions have been highlighted.¹¹³

Sleep disorders can be particularly problematic in PD patients. Dopaminergic

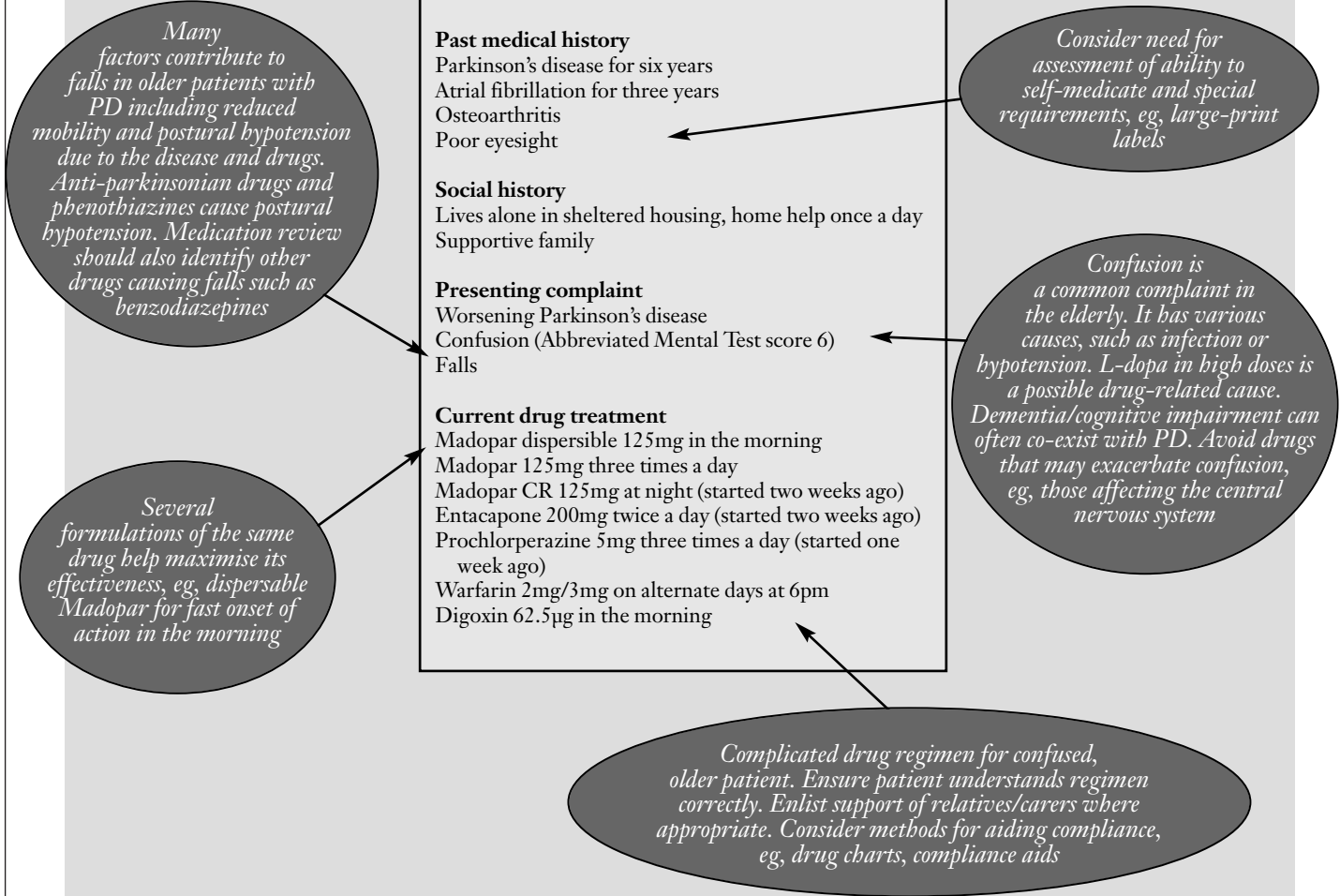
therapy is associated with sudden onset of sleep which has been reported mainly, but not exclusively, with non-ergot oral dopamine agonists. Because of reports of "sleep attacks" while driving, it has been suggested that patients taking ropinirole and pramipexole be advised not to drive¹¹⁴ and this is emphasised in the manufacturers' product information. However, all dopaminergic therapy can be associated with sudden excess daytime somnolence and it is unclear whether there is an additional risk with these agents.¹¹⁵ Some 80–90 per cent of patients with PD have sleep disturbances for various reasons. This problem should be anticipated and fully discussed, especially with patients who drive. Sleep disturbances might have important implications for the use of dopamine agonists early in disease. Concomitant sedative drugs should be avoided.¹¹⁶ The Driver and Vehicle Licensing Agency (DVLA) may allow patients to continue to drive after individual assessment, and patients should advise their insurance companies if they are taking these agents. The Parkinson's Disease Society offers further advice to patients on this issue.

The importance of optimum medication has been shown through measurable improvements in health-related quality of life.¹¹⁷ It is therefore important for pharmacists to develop their contribution to the pharmaceutical care of PD patients.

Information and support for patients, their carers and health care providers on all aspects of PD is available from the Parkinson's Disease Society (see Panel 2). Another group, YAPPERS (Young Alert Parkinsonian Patients and Partners) is also available to help patients with young-onset PD and their carers.

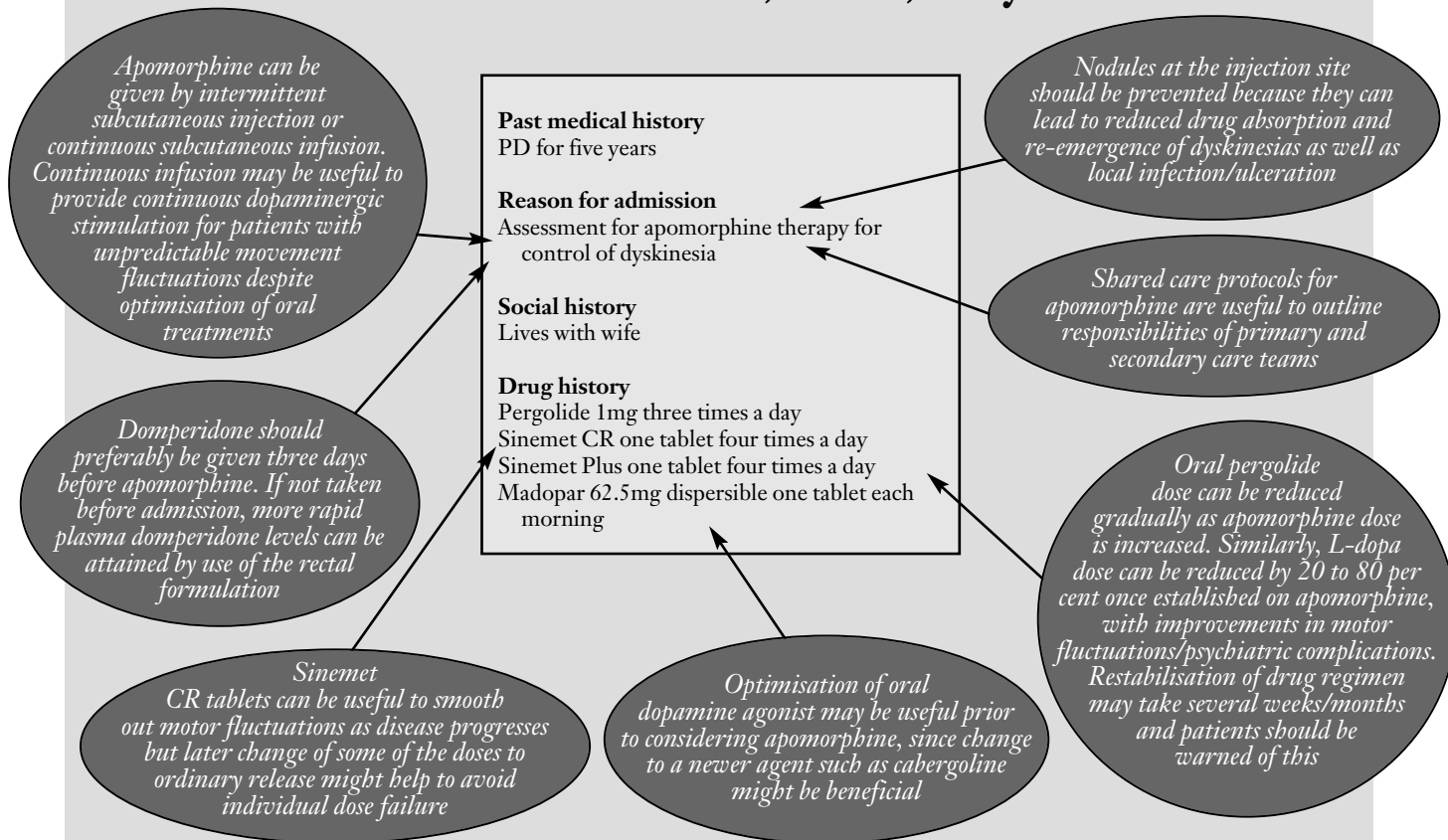
The Parkinson's Disease Society website (www.parkinsons.org.uk) and the WeMove website (www.wemove.org) also provide useful information.

Case 1: Patient HT, female, 79 years, weight 55kg



PHARMACEUTICAL CARE PLAN	
CARE ISSUES	ACTION TAKEN AND FUTURE PLANS
1 Verify medication history from patient for PD treatment	Consider potential under-use or over-use of medication in view of complicated PD regimen. Discussion with the patient established that she had been taking an extra Madopar 125 daily because of a misunderstanding following a previous change to her treatment plan.
2 Prompt review of treatment plan	For next stage in managing PD, use of entacapone must be reviewed. Recommendations are to use it with every dose of L-dopa rather than twice a day. L-dopa doses might need to be reduced accordingly. Future treatment options could include readjustment of L-dopa dose/timing and/or introduction of dopamine agonist (with caution because of the risk of confusion/postural hypotension).
3 Adjust dose of L-dopa	Nausea and vomiting could be due to increased effect of dopamine following introduction of entacapone and the effect of the extra Madopar. Consider option of reducing the L-dopa dose.
4 Prompt a review of anti-nausea medication	Prochlorperazine started for symptoms of nausea and vomiting caused by PD drugs is likely to be exacerbating PD. Prochlorperazine can also cause postural hypotension which should be considered as a possible risk factor for falls in PD patients. Advise change to more suitable alternative, such as domperidone, if required.
5 Monitor warfarin dose	Monitor INR, especially in view of falls and confusion over medication. Warfarin continuation may not be appropriate. Consider replacement with aspirin or other antiplatelet therapy.
6 Monitor patient compliance	Consider the patient's ability to self-medicate from social circumstances and mental state. Patient appears confused and non-compliance is suspected. Consider simplification of medication regimen, if possible, and use of compliance aids. Use PMR to track compliance.
7 Verify communication between primary and secondary care	Ensure information about compliance and changes in treatment plan are communicated between primary and secondary care, including reasons for changes, and share records of adverse effects.
8 Modify patient comprehension	Ensure patient has a written treatment plan and that it is amended when changes are made. Provide patient information leaflets and make the patient aware of available support for patients/carers from Parkinson's Disease Society and local PD nurse specialist.

Case 2: Patient HS, male, 59 years



PHARMACEUTICAL CARE PLAN	
CARE ISSUES	ACTION TAKEN AND FUTURE PLANS
1 Verify drug history with the patient	Eliminate possibility of use of medicines, prescribed and purchased, known to exacerbate PD, including complementary medicines.
2 Verify indication for apomorphine (local guidelines)	Drug history confirms that alternative options (addition of COMT inhibitors or amantadine) have already been tried. Tolcapone already tried with lack of additional benefit (and it is now withdrawn from market).
3 Verify patient comprehension of apomorphine treatment option	Apomorphine treatment pros and cons discussed with patient and carer before decision to initiate treatment. Patients should be reminded that apomorphine has no opiate or addictive properties. Video material from manufacturers and/or PDS supports patient's decision-making. Ideally patient and/or carer, taught by pharmacist or PD nurse, to be responsible for preparation and administration. Liaison with district nurse to make arrangements for follow up and/or training. Patient keen to pursue therapeutic apomorphine trial.
4 Verify patient education on use of apomorphine	Patient and/or carer should be educated on all aspects including subcutaneous injection technique, preparation of syringe (including information on quantities of apomorphine and diluent), aseptic technique, syringe rate setting and troubleshooting. Ensure economic efficiency from minimal wastage of apomorphine by addressing dilutions and daily amount required for administration time.
5 Verify prophylaxis of side effects of apomorphine	Patient given domperidone 20mg orally three times a day for three days before admission as prophylaxis against peripheral side effects of apomorphine, eg, nausea and vomiting, and postural hypotension.
6 Monitor administration technique	Nodule formation to be prevented since it causes pain and irritation at injection site, treatment failure due to reduced absorption, and it risks apomorphine discontinuation. Advise adequate dilution of injection with normal saline, rotation of injection sites and aseptic technique. Massage or ultrasound therapy can be used as a treatment for nodules but may be of limited efficacy.
7 Monitor for other unwanted effects	Other possible side effects discussed with patient including neuropsychiatric effects, yawning, postural instability and dyskinesias.
8 Monitor dose of apomorphine at appropriate dose (local guidelines)	Local treatment protocols for initiation vary. For dyskinesias, one option is to start at a low dose, eg, 1mg/hour for 16 hours daily, and increase gradually while reducing oral dopaminergics.
9 Monitor use of syringe driver	Advise on selection of suitable syringe drivers and the local arrangements for maintenance and servicing required.
10 Verify continuity of care after discharge	District nurse, community pharmacist and general practitioner informed of current drug regimen. Training provided for pump use and injection preparation. Arrangements for follow-up, contacts, advice and for supplies of diluent, administration sets, syringes and needles made. Written information given to primary health care team and patient/carer.

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INTERNATIONAL PHARMACEUTICAL STUDENTS FEDERATION

The International Pharmaceutical Students Federation was established in 1949, following an initiative by the British Pharmaceutical Students Association. It is a non-political, non-religious organisation represented in more than 45 countries. It has 33 national pharmacy student associations as full members, plus a number of local student organisations as associate members. Individual membership is available to students, new pharmacy graduates and pharmacists who have been registered for less than five years.

The focal point of IPSF activities is its 10-day annual congress. This includes general assemblies, at which policy issues and future projects are discussed, plus symposia, workshops, a poster exhibition and social activities. Jointly with the International Pharmaceutical Federation, the IPSF also

presents a students' day during the annual FIP congress. IPSF projects include work on national and international educational and health issues and "village concept" schemes, in which pharmacy students work with others to improve the standard of living and health conditions in remote areas of developing countries. A student exchange scheme gives IPSF members the opportunity to work in a branch of pharmacy in another country for a short period. The federation's publishing activities include project reports and a thrice-yearly news. Those wishing to support IPSF through individual membership should apply to the IPSF Secretariat, International Pharmaceutical Federation, Andries Bickerweg 5, 2517 JP Den Haag, The Netherlands (tel +31 70 3 63 1925; fax +31 70 3 65 9047; e-mail ipsf@fip.nl; website www.ipsf.org).

RETURN OF CANCELLED CERTIFICATES

A certificate of registration as a pharmaceutical chemist is by law the property of the Royal Pharmaceutical Society and must be returned to the Society when a member dies. If the pharmacist's next of kin or other close family wish to preserve the certificate as recognition of the deceased's achievement of registration, the Society's registration section is able to cancel it discreetly and send it back. However, it is only possible to do so if a request is received at the same time as the return of the certificate, since a lack of storage space means that certificates are normally destroyed as soon as they have been returned.

This procedure also applies if a replacement certificate is requested by a woman pharmacist who has changed her name on marriage.