

REVIEWS

Pharmacological treatment of Parkinson's disease

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Parkinson's disease is a neurodegenerative disorder of unknown cause. Age is the most consistent risk factor and incidence in the general population over 75 years of age is 254:100 000.¹ With an aging population the management of Parkinson's disease is likely to prove an increasingly important and challenging aspect of medical practice. Classically Parkinson's disease presents with resting tremor, rigidity, and akinesia often in an asymmetric fashion, but later usually bilateral. However, initial symptoms may be subtle and vague, for example discomfort or mild stiffness in the limbs, and may be misinterpreted. Moreover clinical features are variable with some patients presenting with akinesia and rigidity only and others with a tremor dominant type. About 10%–20% of autopsy cases with a diagnosis of Parkinson's disease were not considered to suffer from it in life.² On the other hand, approximately 25% of patients with a diagnosis of Parkinson's disease in life are shown to have a different diagnosis when postmortem examination is carried out.^{3,4} Diagnosis may thus be difficult particularly as there are no biological markers that unequivocally confirm the diagnosis of Parkinson's disease. The most common differential diagnoses are essential tremor, arteriosclerotic pseudoparkinsonism, drug induced parkinsonism,⁵ and the so-called Parkinson plus syndromes namely multiple system atrophy,^{6,7} progressive supranuclear palsy,^{8,9} and corticobasal degeneration.¹⁰

Drugs used in Parkinson's disease

In the following sections a summary of drugs currently in use in the UK will be provided. The optimum use of antiparkinsonian drugs and the timing of treatment are matters of debate. This will be discussed later. Also, dose recommendations will be given later.

L-DOPA

Degeneration in the basal ganglia in the brains of Parkinson's disease patients primarily affects dopaminergic neurons in the substantia nigra which results in dopamine deficiency. Exogenous L-dopa replaces endogenous deficient neurotransmitter. L-dopa is taken up by remaining dopaminergic neurons where it undergoes decarboxylation in the presynaptic terminal to form dopamine.

Usually L-dopa is combined with benserazide or carbidopa. They do not cross the blood-brain barrier but inhibit the conversion of L-dopa to dopamine peripherally by blocking the enzyme aromatic acid decarboxylase that catalyses this reaction. Dopaminergic adverse effects are thus reduced, central delivery is amplified, and dosage of L-dopa can be

reduced.¹¹ By giving long acting controlled release preparations fluctuations in plasma concentration of L-dopa can be reduced.¹²⁻¹⁴

L-dopa remains the single most effective drug for the treatment of Parkinson's disease.^{11,15} For the first five to 10 years after starting L-dopa treatment all symptoms usually improve, although higher doses may be needed to treat tremor. The drug is tolerated well and side effects, particularly psychiatric symptoms, orthostatic hypotension, and nausea are limited. After several years of a favourable response to L-dopa (the "L-dopa honeymoon") patients often develop disabling motor complications including fluctuations between the "on" and "off" state and dyskinesias.¹⁶ This is mainly related to an increasing loss of dopaminergic nerve terminals. L-dopa can no longer be stored in these terminals and patients' symptoms begin to fluctuate according to the plasma concentration of circulating L-dopa.

In addition to the development of treatment related complications there is theoretical concern that L-dopa is neurotoxic as it has the potential to form free radicals and other toxic metabolites as breakdown products when metabolised.^{17,18} These free radicals might injure surviving dopaminergic neurons and thus speed the progression of Parkinson's disease.¹⁹ However, in vivo toxicity of L-dopa to neurons in the substantia nigra has not been demonstrated^{20,21} and the emphasis on the toxic potential of L-dopa has been criticised.²² Nevertheless, it appears prudent to delay treatment with L-dopa, provided adequate improvement of parkinsonian symptoms is achieved with other drugs.

Alternatives to L-dopa are dopamine agonists, amantadine, anticholinergic drugs, and selegiline.

DOPAMINE AGONISTS

Drugs belonging to this class act directly on dopamine receptors, mimicking the endogenous neurotransmitter. They can be classified into ergot derivatives (bromocriptine, pergolide, lisuride, and cabergoline) and the non-ergolines (apomorphine, pramipexole, and ropinirole).

There are several theoretical advantages of dopamine agonists over L-dopa. Firstly, they usually have a long duration of action that more closely mimics the physiological tonic release of dopamine from normal nigral neurons and may help to prevent or reduce motor fluctuations.²³ However, half life varies between agonists as well as between individual patients.^{24,25} Secondly, they can have a L-dopa sparing effect. Thirdly, due to sparing of

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Submitted 12 February 1999
Accepted 20 January 2000

L-dopa and stimulation of presynaptic autoreceptors resulting in a decrease of dopamine turnover including potentially toxic metabolites, they may also be neuroprotective. Moreover, dopamine agonists are not metabolised by oxidative pathways and do not produce free radical metabolites.²⁶ They may also have direct antioxidative effects.²⁷

In clinical practice dopamine agonists have been shown to be efficacious in Parkinson's disease.²⁸ They are commonly used as adjunctive therapy to L-dopa after motor complications have developed²⁹⁻³⁰ but may also be considered as monotherapy before starting L-dopa, particularly in younger patients.³¹ On dopamine agonist monotherapy patients often do not show motor fluctuations until L-dopa is added to the regimen.³² They usually take longer than L-dopa to reach effective doses and require supplementary L-dopa for relief of symptoms after a varying period of time.¹⁵

A common side effect of dopamine agonists is nausea due to stimulation of the area postrema in the medulla, a region that is outside the blood-brain barrier. The peripherally acting dopamine antagonist domperidone can alleviate this symptom without worsening parkinsonian symptoms.³⁰⁻³³ Psychiatric side effects such as hallucinations are similar to those caused by L-dopa.³⁴

Most long term studies assessing dopamine agonist monotherapy in previously untreated Parkinson patients have investigated bromocriptine. About one third of these patients have shown a good response to this drug and some may not require L-dopa for 2–5 years.¹⁵ A recent study found support for the usefulness of bromocriptine monotherapy at an early stage of Parkinson's disease with adjunctive L-dopa when necessary.³⁵

Pergolide which stimulates both D1 and D2 receptors unlike bromocriptine which only stimulates D2 receptors, has been demonstrated to be beneficial in Parkinson's disease.³⁶⁻³⁷ In a comparative review of pergolide and bromocriptine as adjunctive to L-dopa, pergolide was shown to be more effective than bromocriptine.²⁹

Newer dopamine agonists including pramipexole,³⁸ ropinirole,³⁹ and cabergoline⁴⁰ were demonstrated to have some benefit in previously untreated patients but it is not yet known whether they have better long term efficacy with fewer complications than bromocriptine or pergolide.

An electrophysiological study has shown that pramipexole binds selectively and with high affinity to dopamine D2 and D3 receptors and has a greater efficacy for stimulating dopamine receptors than ergoline dopamine agonist.⁴¹ It appears to be safe, well tolerated, and effective as an add-on therapy in advanced Parkinson's disease with treatment complications such as motor fluctuations.³⁸

Ropinirole is a specific D2 and D3 receptor non-ergoline dopamine agonist that is probably equally effective as L-dopa in mild, early Parkinson's disease.⁴² A report of an ongoing study suggests that monotherapy with ropinirole might be more effective than mono-

therapy with bromocriptine.⁴³ As an adjunct to L-dopa in patients with motor fluctuations it has been shown to improve parkinsonism and to decrease time spent in the "off" state⁴⁴⁻⁴⁵ and permits a reduction in L-dopa dose.⁴⁴

Cabergoline, a long acting predominantly D2 receptor agonist is effective as adjunct therapy in advanced Parkinson's disease and also as monotherapy in de novo patients.⁴⁰⁻⁴⁶ In a trial comparing L-dopa with cabergoline monotherapy for up to one year cabergoline was slightly less effective than L-dopa.⁴⁰

Apomorphine

The use of apomorphine in Parkinson's disease was first reported by Schwab *et al*⁴⁷ who noticed improvement in tremor and rigidity. It was later shown that oral apomorphine reduced "on"/"off" effects but treatment was limited by nausea, vomiting, postural hypotension, and sedation.⁴⁸ However, given subcutaneously by repeated injections or by continuous infusion under domperidone cover it is a well tolerated treatment that effectively reduces daily "off" periods.⁴⁹⁻⁵¹ Due to rapid subcutaneous absorption response to a bolus occurs after 10–15 minutes and the effect lasts for 20–60 minutes. Infusion pumps are generally well tolerated but widespread application is limited by the complexity of the technique. Alternatively, rectal, intranasal, or sublingual preparations have proved effective.⁵²⁻⁵⁴ Side effects are postural hypotension, cognitive impairment, and disabling dyskinesias during "on" phases. When infusion pumps are used, particular attention to the subcutaneous infusion site is needed, as allergic reactions, aseptic necrosis, or infection may occur.

MONOAMINE OXIDASE B INHIBITORS

Selegiline is an example of this class of drug. It selectively and irreversibly inhibits intracellular and extracellular monoamine oxidase B (MAO B) and therefore reduces or delays the breakdown of dopamine to dihydroxyphenylacetic acid (DOPAC) and hydrogen peroxide. The latter has been implicated in oxidative damage in dopaminergic neurons in the substantia nigra. It also inhibits reuptake of dopamine from the synaptic cleft. Adding selegiline to L-dopa may allow a reduction of the L-dopa dose of 10%–15%, occasionally up to 30%.³¹ Mild L-dopa response fluctuations can often be reduced by adding selegiline. Monotherapy in de novo patients delays the need for additional treatment by approximately a year.⁵⁵⁻⁵⁶ Possible neuroprotective effects will be discussed later (see "neuroprotection"). Side effects of L-dopa, including dyskinesias and psychiatric problems, are potentially enhanced by selegiline. Orthostatic hypotension may also occur.⁵⁷

AMANTADINE

This antiviral agent has been used in Parkinson's disease for almost 30 years⁵⁸ and several possible mechanisms of action have been advocated. It may increase dopamine synthesis, it may be a dopamine and noradrenaline presynaptic reuptake blocker, and it also has a mild

anticholinergic action.^{31 59 60} Amantadine influences predominantly akinesia and rigor but has also a mild effect on rest tremor. Two thirds of parkinsonian patients show an improvement on amantadine monotherapy.⁶¹ The beneficial effects of amantadine may be short lived. Recently an NMDA antagonism (NMDA is one of the receptors that binds the excitatory neurotransmitter glutamate) was proposed for amantadine.⁶² This might have implications for the treatment of dyskinesias as functional over-activity of glutaminergic projections to the basal ganglia has been shown to be of importance in the development of dyskinesias.²³ A recent study has indeed confirmed that amantadine can reduce L-dopa induced dyskinesias in patients with Parkinson's disease without altering the antiparkinsonian effects of L-dopa.⁶³

Cautious use of amantadine is recommended in renal failure as it is excreted in the urine. Side effects include hallucinations, insomnia, nightmares, livedo reticularis, and ankle oedema.

ANTICHOLINERGICS

Current drugs available in the UK are biperiden, procyclidine, orphenadrine, benzhexol, and bztropine. Anticholinergic drugs improve tremor and stiffness to a greater degree than akinesia and are overall mildly effective.⁶⁴ Due to a peripheral parasympathomimetic action, side effects such as glaucoma, dryness of the mouth, blurred vision, urinary retention, and constipation can occur. Anticholinergics have a relatively high potential for causing or worsening confusional states and impairing concentration.⁶⁵ They should therefore be used very cautiously in the elderly.

CATECHOL O-METHYL TRANSFERASE INHIBITORS

L-dopa is converted to dopamine by a reaction catalysed by the enzyme aromatic acid decarboxylase which is inhibited by carbidopa and benserazide. Significant peripheral metabolism of L-dopa is also mediated by catechol-o-methyltransferase (COMT) which catalyses the O-methylation of L-dopa to 3-O-methyldopa. As aromatic acid decarboxylase is inhibited by conventional L-dopa preparations the peripheral metabolism is shunted towards the reactions catalysed by COMT. The addition of a COMT inhibitor as adjunctive therapy to L-dopa plus either carbidopa or benserazide reduces peripheral metabolism of L-dopa, prolongs the plasma half life of L-dopa and increases the amount available in the brain.⁶⁶ Peak concentration of L-dopa are not altered by adding COMT inhibitors.⁶⁷ In the brain COMT activity catalyses the metabolism of L-dopa to 3-OMD and of DOPAC to homovanillic acid.

COMT inhibition translates into less fluctuation of L-dopa plasma concentrations so that levels remain within the therapeutic range and benefit from each dose of L-dopa will be prolonged.

Tolcapone inhibits COMT both peripherally and centrally⁶⁸ whereas entacapone acts only peripherally.^{69 70} It could be demonstrated that

tolcapone reduces "off" time by an average of 40% and increases "on" time by about 25% in fluctuating Parkinson patients.⁷¹ Doses of L-dopa could significantly be reduced. In a double blind, multicentre, randomised trial tolcapone reduced the wearing-off time and reduced the requirements for L-dopa in patients with fluctuating disease.⁷²

Oral entacapone generally improves the duration of daily "on" time by 30 to 60 minutes, especially in patients who have a low proportion of "on" time.⁷³⁻⁷⁶ Patients' daily "off" time was found to be reduced by approximately 1.3 hours.⁷⁴ The mean daily L-dopa dosage could be reduced by 12% in two multicentre, double blind randomised placebo controlled studies.^{74 76}

Side effects of COMT inhibitors include potentiation of dyskinesias, nausea, orange discoloration of the urine, and sleep disturbances. Chronic tolcapone use can result in diarrhoea that can be severe. Elevations of liver enzymes have been associated with tolcapone. Because of two cases of fatal toxic hepatitis, tolcapone was recently withdrawn from the market in Europe. Entacapone is currently the only available COMT inhibitor in the UK. No association between the drug and liver toxicity has been shown⁷⁷ and elevations of liver enzymes have not been reported. The dosage should be reduced in patients with hepatic impairment in whom the bioavailability of entacapone is increased. Overall, entacapone appears to be a safe drug. It did not cause significant changes in biochemical or haematological parameters in clinical studies of up to six months' duration or in the report of a 12 month tolerability study.^{74 76 78}

No significant change of autonomic function and no significant haemodynamic effects have been observed in patients with Parkinson's disease.⁷⁷

Treatment strategies

In neurodegenerative disorders like Parkinson's disease any therapeutic intervention that halts or reverses the progression of the disease would be desirable. We shall therefore first consider possible neuroprotective agents and then discuss symptomatic treatment.

NEUROPROTECTION

Until now no drug has been convincingly shown to halt the degenerative process in Parkinson's disease. As the disease progresses an increasing number of dopaminergic neurons in the substantia nigra die. The reduction of the population of these cells in turn stimulates dopaminergic turnover of the remaining neurons with an increase of hydrogen peroxide that is a by-product of dopamine metabolism (MAO-B pathway). Hydroxide peroxide gives rise to the formation to toxic hydroxyl radicals that can cause further cell damage by membrane disruption.⁷⁹

Selegiline inhibits MAO-B and it was therefore postulated that administration of this drug will protect remaining neurons in the substantia nigra.⁸⁰ Moreover in animal experiments selegiline, by inhibiting MAO-B, blocked the

Box 1: Drugs used in Parkinson's disease

- The aim of medical treatment is the restoration of abnormal neurotransmitter function in the basal ganglia.
- L-dopa combined with a peripheral decarboxylase inhibitor remains the single most effective drug to improve parkinsonian symptoms but chronic use is associated with motor fluctuations and dyskinesias. L-dopa can be given as a standard formulation or as a slow release preparation.
- Dopamine agonists offer several advantages over L-dopa and can be tried before introducing L-dopa therapy but they are not as effective as L-dopa and sooner or later supplementary L-dopa is required. They are useful as an adjunct to L-dopa in later stages of the disease.
- Selegiline can delay the introduction of L-dopa. Its neuroprotective properties remain controversial.
- Amantadine can give symptomatic relief and may improve dyskinesias in later stages of the disease.
- Anticholinergics may improve tremor but are otherwise only mildly effective. They should be avoided in the elderly.
- COMT inhibitors increase "on" time, reduce time spent in the "off" state and may allow a reduction of the daily L-dopa dose.

conversion of MPTP to MPP⁺, an exogenous neurotoxin that damages neurons in the substantia nigra,⁸¹ and prevented MPTP induced Parkinsonism in primates. On the basis of these experiments it was hypothesised that MAO-B inhibition might also retard the progression of Parkinson's disease in humans, although this is different from MPTP induced parkinsonism in animals.

Several studies have been undertaken to prove this hypothesis. In the DATATOP study⁸² selegiline very significantly delayed the need for L-dopa by about nine months. However, after three years of follow up, no difference with respect to clinical symptoms was found between the group treated with placebo and L-dopa and the group treated with selegiline and L-dopa. Furthermore methods of the original DATATOP study have been criticised.⁸³ An open label, long term, prospective randomised UK study comparing treatment with either L-dopa alone or in combination with selegiline failed to demonstrate a clinical benefit of the combined treatment.⁸⁴ Compelling evidence to support selegiline as a neuroprotective agent is therefore lacking. Moreover in the UK study⁸⁴ mortality was significantly higher with combination treatment which led to doubts on the chronic use of selegiline in Parkinson's disease. An extension of this study also showed excess mortality in patients treated with combined L-dopa and

selegiline.⁸⁵ Other groups⁵⁶ and a recent meta-analysis⁸⁶ could not confirm this and the issue thus remains a matter of debate.

As outlined above dopamine agonists may have a neuroprotective effect by sparing L-dopa, decreasing dopamine metabolism, and possibly also by a direct antioxidative affect. It has also been suggested that amantadine may have a neuroprotective effect by inhibition of NMDA glutamate receptors.⁸⁷ One study has shown an improved survival of Parkinson's disease patients treated with amantadine⁸⁸ but this requires confirmation.

Apart from preventing oxidative stress and inhibiting excitatory neurotoxicity, future neuroprotective strategies may also focus on anti-apoptotic agents as apoptosis (programmed cell death) appears to play a part in the pathogenesis of Parkinson's disease.⁸⁹ The administration of brain derived neurotrophic factors, antioxidants, or iron chelates to overcome neurodegeneration in the substantia nigra⁹⁰ is still experimental.

SYMPTOMATIC TREATMENT

The optimal management of Parkinson's disease is still controversial and mainly based on empirical experience as properly designed clinical trials are scarce.³⁰ First it has to be decided when treatment is started. This obviously depends on the patient's needs. Although delaying treatment for as long as possible appears prudent since treatment will foster motor complications this is often not feasible, particularly in young patients whose employment may be threatened by the symptoms of Parkinson's disease. On the other hand, delaying treatment in elderly patients may compromise physical independence.

Once treatment has been started the choice of drug becomes the main issue. Ever since the introduction of bromocriptine the controversy emerged whether drug treatment of Parkinson's disease should be started with a dopamine agonist or with L-dopa and this controversy continues.^{91 92} Treatment of early disease generally differs from later stages when various complications occur. It is also influenced by the patients' age. Younger patients usually develop motor complications earlier than older patients and these symptoms can be severe.^{93 94} This has to be taken into account when commencing symptomatic treatment. On the other hand dementia is less common in younger patients who may better be able to tolerate individual but potentially complicated drug regimens that would be inadequate for older patients. We will therefore outline recommendations for young patients (under the age of 50 years) and older patients (above the age of 70 years). For the group of patients between 50 and 70 years a more flexible approach is recommended.

EARLY TREATMENT IN YOUNG PATIENTS (AGE <50 YEARS)

In view of problematic motor complications, L-dopa treatment is best delayed for as long as possible. As selegiline delays the introduction of L-dopa it may be considered as an early

treatment. Selegeline can be administered once a day (10 mg).

Amantadine and anticholinergics can be tried, although they usually give only modest benefit that may not be enough for a young patient who is still employed and depends on a reliable medication to improve motor function. The recommended dose for amantadine is 100 mg daily increased after one week to 100 mg twice daily. The dose of anticholinergics has to be increased very gradually over several weeks to avoid side effects (particularly dry mouth, dizziness, blurred vision, and mental confusion). For instance, benzhexol should be started with 0.5 mg at night and increased by 0.5 mg every five days up to 6 mg daily in two or three divided doses.

Dopamine agonists are possibly the first line treatment as they are most likely to give enough benefit without provoking dyskinesias and often allow delaying L-dopa for at least a year.³¹ Even after a delayed introduction of L-dopa dyskinesias are still less common than if L-dopa had been started earlier.⁹⁵ The same might be true for early combination therapy of L-dopa and a dopamine agonist^{96 97} but this remains controversial.⁹⁸ Dopamine agonists should be introduced with domperidone cover (20 mg three times a day) and should gradually be increased. For most dopamine agonists starter packs are available with detailed but simple instructions how to increase the dose. Dopamine agonists are generally given three times a day, apart from cabergoline that can be taken once a day. Dose equivalents among the different available dopamine agonists is difficult to know with certainty but has been estimated as follows: 30 mg of bromocriptine, 15 mg of ropinorole, 4.5 mg of pramipexole, and 3.0 mg of pergolide.⁹⁹ Recommended daily doses for bromocriptine are 10–40 mg, for ropinorole 3–9 mg, for pergolide 3 mg, for cabergoline 2–6 mg, for lisuride 5 mg, and for pramipexole 4.5 mg.

Eventually symptoms will not be sufficiently controlled and L-dopa has to be added. When introducing L-dopa one can opt for standard formulations (starting with 50–100 mg three times a day) or sustained release preparations (100 mg three times a day). The latter may be more suitable early in the course of the disease as receptor stimulation in the basal ganglia will be continuous and hence more physiological compared with standard formulations that produce rapid excessive plasma peaks followed by troughs and result in the brain being alternately flooded and starved.

EARLY TREATMENT IN OLD PATIENTS (AGE >70 YEARS)

In elderly patients L-dopa remains the treatment of choice even in early stages as it is the drug with the best therapeutic window particularly with regard to psychiatric side effects. In view of their high potential of causing confusion anticholinergics should best be avoided but dopamine agonist and amantadine can be tried. Again, selegeline may be considered but the advantage of delaying L-dopa for several months is less meaningful in this age group.

Box 2: Treatment strategies—early stages

- None of the currently available drugs has a proved neuroprotective effect. Potential neuroprotective agents are under study.
- Treatment should be tailored to the individual patient's needs. The choice of drugs is mainly influenced by age.
- Young patients are more prone to develop motor complications. L-dopa therapy should therefore be delayed for as long as other drugs, particularly dopamine agonist, adequately relief symptoms.
- In elderly patients L-dopa has the best therapeutic index and is the first line treatment.

MANAGEMENT OF LATER STAGES

After the first five years about half the patients develop motor fluctuations or dyskinesias^{100 101} that may be difficult to treat. Commonly the first fluctuations to occur are early morning akinesia and end-of-dose deterioration, also referred to as wearing off. These are predictable periods of immobility or greater severity of other parkinsonian symptoms when the effect of L-dopa wears off. They usually develop gradually over a period of several minutes up to an hour and are related to the timing of antiparkinsonian medication.

To overcome wearing-off, more frequent doses of standard L-dopa are sometimes helpful, for example, five or six instead of three daily doses. Alternatively, changing from a standard L-dopa preparation to a slow release formulation can be tried. The bioavailability of these drugs is usually 70% of that of standard L-dopa. Although they last longer, initial absorption is slower and peak dose concentrations are lower so that patients often need a kick start dose of standard L-dopa first thing in the morning to compensate for that. They may also need occasional top-up doses of L-dopa during the day. Occasionally only very small doses are required. In these situations patients may benefit from dispersible L-dopa to titrate their individual doses.

COMT inhibitors can help to reduce wearing off phenomena, increase the “on” time and allow an overall reduction of the daily dose of L-dopa.^{71–76 78 102} All published studies that have assessed the efficacy of COMT inhibitors in patients with Parkinson's disease have been conducted in patients with an end-of-dose deterioration.^{78 102} It needs to be clarified whether COMT inhibitors also have a role in the treatment of drug naive de novo Parkinson's disease patients. Entacapone, currently the only available COMT inhibitor, is taken with each dose of L-dopa (three up to 10 doses per day). A dose of 200 mg (with each L-dopa dose) is associated with the optimal pharmacokinetic effect on L-dopa.¹⁰³ Another option for the treatment of the wearing off is to partially substitute L-dopa with a long lasting agonist drug.^{29 30}

Box 3: Management of later stages

- Later stages of the disease are complicated mainly by motor fluctuations, dyskinesias, and psychiatric problems.
- Wearing off phenomena can be overcome by more frequent doses of standard L-dopa, switching from standard L-dopa to slow release preparation, COMT inhibitors, or long lasting dopamine agonists.
- Abrupt fluctuations can be caused by delayed gastric emptying or delayed absorption of L-dopa and may be improved by adding cisapride or changing the diet.
- Dyskinesias sometimes improve by partial replacement of L-dopa by a dopamine agonist or adding amantadine.
- "Off" period dystonia may respond to lithium therapy and can be relieved by botulinum toxin injections into dystonic muscles.
- When psychiatric complications occur, drugs with the least therapeutic benefit and highest potential to cause alterations of the mental state should be stopped first before reducing the dose of L-dopa.
- Symptomatic treatment of psychosis and delusions without worsening parkinsonian symptoms is possible with clozapine.

Fluctuations may be abrupt and patients may switch from the "on" to the "off" in a rather unpredictable way within seconds. Also, dose failure might occur. Both indicates a threshold effect of L-dopa which is explained by the fact that in later stages of the disease when exogenous L-dopa can no longer be stored in dopaminergic neurons the effect of L-dopa will solely depend on the plasma level. Small changes in plasma levels may then have dramatic effects.

A delayed "on" or dose failures may be related to delayed gastric emptying¹⁰⁴ and hence inadequate plasma concentrations of L-dopa. This may improve in response to agents that promote gastric motility like cisapride.¹⁰⁵ Amino acids from proteins in the food may interfere with the absorption of L-dopa^{105 106} and confining protein intake may help reducing fluctuations.

The duration of "off" periods may effectively be reduced by subcutaneous administration of apomorphine either as a single rescue dose (2–5 mg, in rare cases up to 10 mg) or as continuous infusion (3–6 mg apomorphine/hour).^{49–51}

Dyskinesias are difficult to manage. Tackling peak dose dyskinesias or "square wave" dyskinesias (that persist throughout the on period) is sometimes possible by reducing the dose of L-dopa or partial replacement of L-dopa by a dopamine agonist. Diphasic dyskinesias that occur at the beginning or the end of a dose can

Questions (answers on next page)

- (1) What are the main differential diagnoses of idiopathic Parkinson's disease?
- (2) Why do motor complications occur?
- (3) What are the theoretical advantages of the use of dopamine agonists?
- (4) Which drug has proved neuroprotective properties?
- (5) Which drug that relieves parkinsonian symptoms has recently been shown to improve dyskinesias?
- (6) What are the benefits of COMT inhibitors?
- (7) Why should L-dopa therapy be delayed, particularly in young patients?
- (8) Which drug can effectively and reliably reduce refractory "off" periods?
- (9) What is the most effective drug for symptomatic treatment of psychosis and delusions?

be very severe and are often refractory to medical treatment. They are more common in young onset Parkinson's disease.³⁰ Adding an agonist sometimes helps. Overlapping L-dopa doses can be useful. Amantadine has recently been shown to be effective in reducing L-dopa induced dyskinesias without altering the antiparkinsonian effects of L-dopa.⁶³

"Off" period dystonia commonly occurs in the morning and can sometimes be avoided by taking a dispersible L-dopa preparation on waking or can be overcome by apomorphine injections. Lithium is also sometimes helpful¹⁰⁷ and patients often benefit from botulinum toxin injections into dystonic muscles.¹⁰⁸

During "off" periods patients may experience dysphoria¹⁰⁹ including panic attacks, depression, and occasionally delusions or hallucinations. These symptoms resolve when patients turn "on" again and are best managed by reducing the time the patients spends in an "off" state. When sustained depression develops, which is the case in about one third of patients, treatment with antidepressants is warranted. Selective serotonin reuptake inhibitors have the potential to worsen parkinsonism¹¹⁰ and can adversely interact with selegeline.¹¹¹

In case of an organic confusional states or psychosis antiparkinsonian drugs should in principle be discontinued following the rule "last in, first out". If that rule is not applicable as the patient has not changed his medication recently the following order is suggested: anticholinergics, selegeline, amantadine, dopamine agonist. L-dopa has the best therapeutic index and should therefore be stopped last. If antipsychotic treatment is necessary clozapine is probably the drug of choice.^{112 113} It appears to be specific for the subclass of dopamine receptors mediating psychosis and does not worsen parkinsonian symptoms.^{112 113} Full blood count has to be monitored regularly as agranulocytosis may occur under clozapine treatment.

Alternatively, olanzapine, the newest atypical neuroleptic drug, has become an option to treat psychosis in Parkinson patients.¹¹⁴ It has not been associated with agranulocytosis but may worsen parkinsonian symptoms.¹¹⁵ Ondansetron, an antagonist of the 5-hydroxytryptamine₂ receptor, has also been shown to be effective for visual hallucinations and delusions without worsening parkinsonian symptoms.¹¹⁶

Dr Alexander Münchau was supported by the Ernst Jung-Stiftung für Wissenschaft und Forschung in Hamburg, Germany and by the Eugene Brehm Bequest, UK.

Answers

- (1) Essential tremor, drug induced parkinsonism, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration.
- (2) This is probable due to non-physiological pulsatile stimulation of dopamine receptors in the basal ganglia. In early stages exogenous L-dopa is taken up by remaining neurons in the substantia nigra and L-dopa release is more or less continuous. This changes in later stages when an increasing number of dopaminergic neurons die. Consequently L-dopa can no longer be stored and L-dopa levels fluctuate according to plasma levels. Dyskinesias do not occur when L-dopa is administered continuously by intravenous infusion supporting this concept.
- (3) Dopamine agonists have a longer mode of action and therefore resemble physiological continuous dopamine receptor stimulation. They have a L-dopa sparing effect and may have neuroprotective properties.
- (4) None of the currently available drugs.
- (5) Amantadine.
- (6) COMT inhibitors reduce "off" periods, prolong the "on" time and allow a reduction of the L-dopa dose. They do not, however, have a L-dopa sparing effect.
- (7) There is theoretical concern that L-dopa may be neurotoxic. Moreover, and more importantly, L-dopa invariably induces motor complications after chronic use.
- (8) Apomorphine that can be given as single subcutaneous injections or as a continuous infusion via a pump.
- (9) Clozapine. Full blood count must be monitored regularly when using this drug as it may cause agranulocytosis.

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