






THE TREATMENT OF PARKINSON'S DISEASE

SUMMARY

-  **Levodopa (L-dopa) administered in conjunction with a dopa decarboxylase inhibitor (DDCI) remains the mainstay of therapy for Parkinson's disease.**
-  **New drugs such as entacapone, pramipexole and ropinirole have increased the treatment options available for Parkinson's disease.**
-  **Despite several new agents there is no overall agreed treatment strategy for the management of Parkinson's disease.**
-  **Selegiline remains a useful treatment option despite controversial reports of increased mortality.**
-  **Drug treatment is only part of the multidisciplinary approach to the management of this condition.**

INTRODUCTION

Parkinson's disease (PD) first described in 1817, is a neurodegenerative disorder characterised by the chronic progressive loss of motor function.¹ Presentation is frequently between the ages of 50-80 years of age with a male to female preponderance.^{2,3} It affects approximately 6,000 people in Ireland.⁴

The majority of parkinsonism (approx. 80%) is due to idiopathic PD other causes include drug therapy (**Table 1**), toxins and trauma.

Table 1: Drugs Associated with Drug-induced Parkinsonism⁵

Neuroleptics
Amiodarone
Calcium Channel Blockers
Lithium
Methyldopa
Fluoxetine
Metoclopramide
Phenelzine

The pathogenesis of PD is multifactorial, characterised by a progressive death of heterogeneous populations of neurones particularly in the substantia nigra, resulting in a regional loss of the neurotransmitter dopamine. A 60-70% loss of neurones occurs prior to the emergence of symptoms.⁶

PRESENTATION AND DIAGNOSIS

PD presents as a classic triad of features: tremor especially pill rolling, rigidity and akinesia. Impairment or loss of postural reflex is often a large problem for patients. Diagnosis of PD can only be made on the basis of clinical history and examination.

This can prove difficult especially in the early stages of the disease where the patient may present with vague symptoms. The difficulty is further compounded by the lack of a specific marker for PD.⁷

TREATMENT STRATEGIES

Many patients may not require treatment for some time as their disability may not warrant it. No drug has been unequivocally shown to retard the progression of the disease, however drug therapy has been shown to improve the quality and expectancy of life of most patients. Management issues include withdrawing any drugs that may precipitate PD, when and how to start, stop or switch drug treatment and how best to avoid the long-term unwanted effects of medication.⁸ There are no absolute guidelines for the treatment of PD. Generally treatment begins with low dose levodopa.

Levodopa (L-dopa)& Dopa Decarboxylase Inhibitors (DDCI)

L-dopa remains the most effective symptomatic treatment for PD.^{1,6,9,10} It is converted to dopamine within the central nervous system, and when combined with a DDCI reduces unwanted peripheral effects. This allows a lower dose of L-dopa to be used. Following an initial dose titration a satisfactory response is usually achieved at 200-400 mg/day in 3-4 divided doses.^{9,11} If the patient's dose escalates to >600mg/day with no significant response then the diagnosis of PD should be questioned.⁹ Dose titration should help to alleviate adverse effects such as nausea, vomiting and postural hypotension.^{9,11} Later in the illness and in common with other antiparkinsonian drugs, L-dopa may cause vivid dreams, nightmares and even a toxic confusional state.⁹ The development of problematic dyskinesias and motor fluctuations with chronic L-dopa therapy affects approximately 50% of patients after 6 years treatment, increasing to 70% after 15 years.^{6,12} These effects appear to be associated with "highs and lows" in L-dopa serum concentrations. Methods of minimising these adverse effects include the use of smaller doses at increased intervals, the use of sustained release preparations, or the addition of a L-dopa sparing agent.¹³

The goal of treatment is to improve mobility and function, provide maximal comfort and improved quality of life while limiting reversible but long term side effects.⁶ L-dopa increases life expectancy if started before the patient has begun to lose their postural reflex and are at risk of falling.⁸ The optimum time of initiation is undecided as the use of L-dopa containing preparations is associated with the development of irreversible motor problems. Young patients (<50 years) have been found to develop motor fluctuations and dyskinesias more rapidly than older patients in response to L-dopa.⁵ Current practice suggests that L-dopa sparing strategies may be preferred in the initial treatment of young patients if the symptoms of PD are not too severe.¹⁴ Treatment of older patients (>70 years) aims at prolonging life, improving symptoms and maintaining cognitive status.¹⁵ The use of dopamine agonists, amantadine, and anticholinergics as L-dopa sparing agents in the elderly is undesirable as they can contribute to confusion.¹⁵

The main role of sustained release preparations lies in simplifying regimens, relieving nocturnal akinesia and minimising on/off episodes.⁹ When compared with immediate release preparations, sustained release preparations have been found to provide a longer "on time" when the patient experiences beneficial therapeutic effects. In

addition, they may also prevent the appearance of wearing off fluctuations and delay the onset or reduce the severity of “on-off” fluctuations.¹⁶ However bioavailability is reduced and a 30-50% increase in L-dopa dose may be required.¹¹ If treating “off” periods the delayed onset of action of sustained release preparations means that supplementation with immediate release tablets may be warranted until the sustained release preparation achieves its effect.^{12,13,17}

Clinically relevant interactions with L-dopa include hypertensive crises with MAOIs. Therapy should be avoided for at least two weeks after stopping an MAOI.¹⁸

Selegiline

Selegiline selectively inhibits monoamine oxidase B (MAO_B) which is responsible for the breakdown of dopamine. A dose of 2.5-5mg daily, is recommended initially titrated up to a maximum of 10mg as necessary. Adverse effects of selegiline include insomnia, vivid dreams and hallucinations which may be symptoms of dopamine excess.¹¹ Interactions have been reported with MAOIs e.g. tranylcypromine, and selective serotonin re-uptake inhibitors (SSRIs), and these should be avoided.¹⁹

The proposed neuroprotective effect of selegiline remains unproven.⁹ Selegiline is a helpful addition to levodopa for end of dose fluctuations. The data suggesting increased mortality remains controversial as the study involved criticised on many grounds including the methodology used.^{2,9,11}

Dopamine Agonists

Dopamine agonists e.g. ropinirole, pergolide may have two roles; firstly in the initial treatment of PD (for which bromocriptine and ropinirole are licensed) or secondly as adjunct to L-dopa therapy (“L-dopa sparing”). They differ in dopamine receptor specificity and a lack of efficacy with one does not preclude benefit with another dopamine agonist. It is recommended that all dopamine agonists should follow the **“START LOW, INCREASE SLOW”** dose escalation rule, to reduce unwanted effects and increase tolerability.²⁰

The dopamine agonists are licensed as adjunctive treatment of PD with L-dopa, and a potentiation of effect allows a 20% reduction in L-dopa dose.²¹ Most long term studies of dopamine agonist monotherapy have shown that the use of L-dopa can be delayed for 2-5 years, but only approximately one-third of patients have a good response.⁶ Dopamine agonists are less effective than L-dopa in reducing symptoms, but cause less dyskinesias and motor problems.²⁰

Nausea and vomiting may occur initially with the use of dopamine agonists. The administration of domperidone twenty-four hours prior to initiation of treatment may help to alleviate this although tolerance usually develops. Pleuropulmonary/retroperitoneal fibrosis has been associated with the long term use of the ergot derivatives e.g. bromocriptine, patients should be monitored for signs of this condition.⁹ Acute and unpredictable sleep attacks have been associated with the use of the non-ergot derivatives pramipexole and ropinirole and patients should be informed to exercise caution when driving or operating machinery.²² Dopamine agonists interact mainly with dopamine antagonists e.g. neuroleptics, metoclopramide.¹⁹

Apomorphine

Apomorphine is a dopamine agonist administered as an intermittent or continuous subcutaneous infusion. It is reserved for troublesome dyskinesias in advanced PD as well as improving akinesia and rigidity.⁹ Apomorphine is highly emetogenic and must be preceded by 3 days therapy with domperidone which is continued for several weeks to six months before usually being gradually withdrawn.²³ A licensed preparation of apomorphine is not currently available in Ireland however this agent is used in a hospital setting.

Catechol -O-Methyl Transferase (COMT) Inhibitors

COMT is an enzyme responsible for the bulk of extracerebral metabolism of L-dopa in the presence of a DDCI.²⁴ Entacapone is licensed as adjunctive therapy in the treatment of end of dose motor fluctuations for patients with moderately advanced disease.⁹ A 10-30% reduction in L-dopa dose is recommended.²⁵ Studies demonstrate that entacapone increases “on time” by an average of 1.2 hours, with efficacy demonstrated following the first dose.²⁶ Adverse effects include dyskinesias, hallucinations and red/brown discolouration of urine.¹¹ Entacapone chelates iron and should be administered 2-3 hours apart from oral iron supplements.²⁵ There have not been any clinically significant interactions reported to date.^{18,19} However, caution is advised with drugs metabolised via the same route e.g. apomorphine, selegiline.^{11,25}

Others

Amantadine may be classified as a dopamine agonist although its mode of action is unclear.^{6,7} It provides only mild relief of symptoms in the treatment of PD. Adverse effects include hallucinations, peripheral oedema and livedo reticularis. It is usually reserved for younger patients due to the risk of cognitive effects especially in the elderly.^{8,14}

Anticholinergics e.g. procyclidine, benzhexol, benztropine have frequently been used in PD, as they have mild antiparkinsonian effects. They are more effective for treating tremor than for other features of PD and have well recognised adverse effects including dry mouth and blurred vision.^{11,17} Choice is dependent on patient tolerability. Use of anticholinergics in PD is generally not recommended, except in younger patients to delay the onset for L-dopa therapy. They should be avoided in the elderly or dementing patients as they can contribute to confusion both acutely and chronically.¹⁷ It has been suggested that Vitamin E may have some protective effects however the data is very limited.

A resurgence of neurosurgical treatment for severe and refractory dyskinesias has occurred following refinements in procedure, improved accuracy and safety.⁶ Electrode implantation and stimulation is used for the treatment of severe disabling parkinsonian tremors that are inadequately controlled by optimal drug therapy, or in young patients with severe tremor to delay the introduction of high dose L-dopa.¹³

Apart from drug therapy there are other practical issues which must be taken into account in the management of this condition e.g. compliance issues, swallow disorders, respite care etc. Due to the long-term progressive nature of this disorder patients require a continuum of care which is best provided by a multidisciplinary team

approach. Physiotherapy has a role in maintaining mobility and posture. Occupational and Speech therapist consultations may also be useful for certain patients.²⁷ The Parkinson's Association of Ireland, Carmichael House, North Brunswick St., Dublin 7 (Tel: 1800 359 359) provides support to both PD patients and their carers.

Table 2: Treatment Costs of Parkinson's Disease Therapies (GMS March 2000)

	Daily Dose	Cost per 28 days
L-dopa/benserazide	187.5mg (Madopar®)	£7.00-
L-dopa/carbidopa	300mg (Sinemet Plus®)	£11.47-
Selegiline	2.5mg-10mg	£7.58-£30.33
Pergolide	50mcg-50mg	£10.76-£220.28
Bromocriptine	1.25mg-40mg	£2.79-£80.30
Ropinirole	0.75mg-24mg	£1.13-£316.75
Pramipexole	0.264mg-3.3mg (base)	£7.92-£284.20
Entacapone	200mg-2g	£19.71-£197.10
Amantadine	100mg-200mg	£5.14-£10.28
Biperidan	2mg-16mg	£1.42-£10.66
Benzhexol	1mg-15mg	£0.24-£2.88
Benztropine	0.5mg-6mg	£0.11-£1.31
Procyclidine	7.5mg-30mg	£2.63-£10.50

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