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MANAGEMENT OF PARKINSON'S DISEASE

- **The prevalence of Parkinson's Disease (PD) is increasing due to increasing life expectancy**
- **Levodopa remains the single most effective symptomatic treatment but is associated with motor complications in up to 70% of patients**
- **Other treatment options have less motor complications, but are also less effective**
- **Due to difficulties in diagnosis and deciding when to initiate therapy, specialist advice is recommended**

INTRODUCTION

Parkinson's Disease (PD) is a chronic, progressive, neurodegenerative disease characterised by the classical signs of bradykinesia, rigidity and resting tremor with postural instability developing at a later stage.[1,2,3] It is associated with significant morbidity and disability and mortality rates are higher than in the general population.[1] It is a substantial burden not only on patients but also on their families and carers.[1,3]

The prevalence of PD increases with age. It affects 1-2% of people ≥ 65 years increasing to a prevalence of 4% in those >80 years.[1,2,4] It is the most common neurodegenerative disease after Alzheimer's disease[5] and its incidence is increasing due to the longer life expectancy in many populations.[1]

Up to 90% of idiopathic PD cases are sporadic with no clear aetiology, however 10% have a genetic origin, which are more frequently seen in young-onset PD.[1] Parkinsonism can also be caused by drugs (e.g. phenothiazines) and medical conditions including multiple cerebral infarction and degenerative conditions (e.g. progressive supra-nuclear palsy).[1,3]

This bulletin, which is an update on a previous bulletin [NMIC 2000 Vol 6, No. 2] will focus primarily on the pharmacological management of the motor symptoms of PD.

PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

The main histological feature in PD is degeneration of dopaminergic neurons in the substantia nigra (SN), resulting in reduction of striatal dopamine, which is involved in the regulation of excitatory and inhibitory outflow of the basal ganglia.[1] This results in depigmentation of dopamine producing neurons and the presence of Lewy bodies in the cytoplasm of the remaining neurons.[6] It is estimated that patients are asymptomatic until there is a loss of 70-80% of SN neurons.[6] Neuroimaging studies suggest that compensatory responses such as up-regulation of dopamine synthesis and downregulation of synaptic dopamine reuptake occur as adaptive mechanisms, which may explain why PD is almost asymptomatic until the relatively profound depletion of SN neurons has occurred.[6]

CLINICAL PRESENTATION

The clinical presentation of PD varies from patient to patient and includes both motor and non-motor symptoms.[1]

Motor symptoms - The most common initial symptom, particularly in younger patients is asymmetric rest tremor. Bradykinesia is the most disabling symptom and is more prominent in older patients. The classical "cogwheel pattern" of rigidity is best detected in the distal part of the limbs. Postural instability is a sign of more advanced PD. Table 1 summarises the motor features of PD.

Table 1: Motor features of PD[1]

Resting tremor	Affects 70-90% of patients initially unilateral, becoming bilateral as the disease progresses More commonly distal and "pill rolling" in nature May also involve jaw, tongue or leg and may have postural component
Bradykinesia	Affects 80-90% of patients and is the most disabling symptom of PD Extreme manifestation is akinesia (inability to initiate movement)
Rigidity	Affects >90% of patients, which may be "cog-wheel" or "lead-pipe" Occurs in both flexor and extensor muscles throughout entire range of movement
Postural instability	Reflects progression to advanced stages of PD, which predisposes to falls and injuries Early onset is atypical for PD and suggests other cause of parkinsonism

Non-motor symptoms are common in PD and significantly affect a patient's quality of life.[1] Surveys in PD patients suggest that 90% have at least 1 non-motor symptom and 10% exhibit 5 non-motor symptoms.[1] Non-motor manifestations comprise autonomic dysfunction (prevalence varies from 2% for urinary incontinence to 72% for constipation), sleep disorders (affects two thirds of

patients) and neuropsychiatric symptoms (affects up to 60% of patients).[7] Depression, which can pre-date the motor manifestations, affects up to 40% of patients and is usually mild to moderate but can be severe.[3,7] Psychotic symptoms are also common affecting up to 50% of patients; which may be due to the neurotransmitter disturbances of PD, but may also be caused by the drugs used to treat PD.[3] Dementia develops in 40% of patients.[8] Non-motor symptoms can often be more disabling than motor symptoms and are generally not responsive to dopaminergic therapy.[7]

DIAGNOSIS OF PARKINSON'S DISEASE

The diagnosis of PD is clinical and the most widely accepted criteria for the diagnosis of PD are those introduced by the UK Parkinson's Disease Society (PDS) Brain Bank Criteria.[1,2,3] Guidelines recommend that patients with suspected PD should be referred to experts in secondary care for the diagnosis and management of the condition.[2,3] There is a diagnostic error rate associated with PD, which is higher in community settings (47%) than in standard neurological and geriatric practice (26%); in tertiary referral centres the error rate is only up to 8%.[3] Table 2 gives the criteria for the diagnosis of PD, which is made in 3 consecutive steps.

Table 2: UK PDS Brain Bank Criteria for the diagnosis of PD[3]

Step 1. Diagnosis of a parkinsonian syndrome

Bradykinesia and at least one of the following:

- Muscular rigidity
- Rest tremor (4-6Hz)
- Postural instability unrelated to primary visual, cerebellar, vestibular or proprioceptive dysfunction

Step 2. Exclusion of other causes of parkinsonism including:

History of:

- Repeated strokes with stepwise progression
- Repeated head injury
- Antipsychotic or dopamine-depleting drugs
- Definite encephalitis and/or oculogyric crises on no drug treatment
- Exposure to known neurotoxin

Step 3. Supportive criteria for PD

The presence of ≥3 other features including:

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the side of onset most
- Excellent response to levodopa

In addition there are different methods used to assess patient's motor symptoms and clinical status, however the Unified Parkinson's Disease Rating Scale (UPDRS) is the most commonly used and is used both in clinical practice and research.[1]

MANAGEMENT OF PARKINSON'S DISEASE

There is currently no cure for PD[9] and no existing therapy has been shown clearly to halt or slow the progression of the disease.[2,6,9] The most important goals of management are to preserve the patient's functional independence and health-related quality of life (HRQoL). This is achieved by symptomatic treatment of the motor and non-motor deficits, with minimisation of adverse effects, using both pharmacological and non-pharmacological interventions.[6] The decision when to begin treatment and which treatment to commence should be tailored to the individual patient[10] and be made ideally in a specialist setting.

In patients with non-motor symptoms it is necessary to ascertain if the symptoms are related to the dopaminergic medication, to the disease state or a combination of both.[7] Many patients with advanced PD are sensitive to small changes in plasma levodopa and may suffer adverse reactions to anti-parkinsonian drugs.[7] Non-motor symptoms should be treated in the individual patient on a case-by-case basis ideally in a multidisciplinary setting.[3]

NON-PHARMACOLOGICAL MANAGEMENT

A multidisciplinary approach is important in the management of PD. The use of nurse specialists, physiotherapy, occupational therapy and speech and language therapy are valuable in the management of a patient with PD.[3,6] Education of patients and carers is an important aspect of management and they should be encouraged to participate in treatment by recording information on drug administration times, as well as "on" and "off" times.[6] Patients should also be encouraged to exercise. The Parkinson's Association of Ireland provides support and information to both patients and carers (www.parkinsons.ie).

PHARMACOLOGICAL MANAGEMENT OF MOTOR SYMPTOMS

The timing of initiation of drug therapy in patients with newly diagnosed PD has been the subject of considerable debate. Many physicians adopt a "wait and see" strategy initiating therapy only when there is a perceived symptomatic or functional need.[11] The degree of functional impairment is highly variable among individual patients and factors including employment, co-morbidities, previous treatment for PD, lifestyle, and patient desires must be considered when starting pharmacotherapy.[6]

Pharmacological treatment is based on increasing dopamine either directly with levodopa (dopamine precursor), by decreasing its breakdown (MAO-B inhibitors, COMT inhibitors) or by stimulating the striatal outflow neurone (dopamine agonists).[6,9,12] Uncertainty still exists as to which class of drug is the most effective in the treatment of PD [3,5] and the decision must take into account the individual patient. A large trial is currently underway in the UK to study the effects of the different classes of drugs on PD, to determine which class of drug provides the most effective control, with fewer side-effects, for both early and later PD.[13]

It is important that anti-parkinsonian medication is not withdrawn abruptly to avoid the potential for acute akinesia or **neuroleptic malignant syndrome**. The practice of withdrawing patients from their medication (drug-holidays) to reduce motor complications should be avoided because of the risk of neuroleptic malignant syndrome.[3] Table 3 summarises the main classes of drugs, which are used in the symptomatic management of the motor symptoms of PD.

Table 3: Indications and main adverse effects of drugs for the treatment of motor symptoms [6,9]

Drug class *	Clinical Indication	*Main adverse effects & complications [9]
Levodopa • *Dopamine precursor* Used in combination with dopa decarboxylase inhibitor (carbidopa/benserazide)	Treatment of all stages of PD – the most effective agent for the treatment of motor symptoms May be considered as first line agents in older patients	Initially nausea, sedation, vomiting, orthostatic hypotension Chronic use – delusions, hallucinations Impulse control disorder Motor complications occur in up to 70% of patients after 9 years of treatment
Dopamine agonists • *Bind to post-synaptic dopamine receptors*	As monotherapy in early PD, possibly in younger patients, to delay levodopa therapy Used in combination with levodopa in advanced PD	Adverse effects more common than with levodopa Nausea, somnolence, postural hypotension, hallucinations, sudden sleep attacks Impulse control disorder (gambling) Motor complications - less likely than with levodopa Serosal reactions with ergot agonists
MAO-B inhibitors • *Prevents metabolism of dopamine in the brain, enhancing its availability*	As monotherapy in early PD – to delay levodopa therapy Used in combination with levodopa in advanced PD	Nausea and orthostatic hypotension Important drug interactions – check SPC Increased levodopa effects, especially in elderly
COMT inhibitor • *Reduces the metabolism of levodopa*	Adjunct treatment with levodopa (not to be used unless patient is on concomitant levodopa) Useful in patients with motor fluctuations and wearing off, may need to reduce levodopa	Diarrhoea, nausea, dyskinesias, urine discolouration Serious hepatoxicity with tolcapone (not to be used first line and needs regular liver function tests)
Amantadine • *Weak dopamine agonist*	Useful for dyskinesias in advanced PD Also improves mild bradykinesia, tremor and rigidity[14]	Nausea, confusion, insomnia, hallucinations and oedema Dose reduction in renal deficiency Severe psychosis reported in elderly, with high plasma levels
Anticholinergics	Reduce tremor and rigidity but may have little effect on bradykinesia[15] Reserved for younger patients	Constipation, dry mouth, vomiting, tachycardia, confusion, hallucinations[15]

***Please check the Summary of Product Characteristics (SPC) for complete information on each medicine, including potential drug interactions**

Levodopa – has been the standard symptomatic therapy for > 30 years and remains the single most effective symptomatic therapy for the treatment of PD.[6,9] The question of when to start therapy with levodopa remains controversial due to its long-term use being associated with motor complications.[9,16] Initial therapy with other agents is often recommended for younger patients (<65 years) or patients who are considered functionally young, whereas for older patients, therapy is usually initiated with carbidopa-levodopa.[6] However as PD progresses, all patients will require levodopa.[6] Initially patients have a good and sustained response (honeymoon period) which can last for up to 5 years and a "post-honeymoon" period, initially characterised by a change in the pattern of responsiveness which may occur abruptly or more gradually.[17] Motor complications occur in up to 70% of patients after an average of 9 years of treatment with levodopa[9,18] [this will be discussed in a later section].

Levodopa has a short half-life of approximately 1 hour which increases to 1.5 hours with the addition of carbidopa or benserazide and to 2-2.5 hours with the addition of a COMT inhibitor.[6,9] With progressive disease the benefits of each dose become shorter with a "wearing off" of benefit before the next dose.[9] Controlled-release formulations of carbidopa-levodopa are used in patients with motor fluctuations and nocturnal akinesia,[3,17] however erratic absorption may occur in some patients, resulting in a slower and unpredictable onset of action and possible worsening of dyskinesias.[9,19] A dispersible formulation is also available for patients who require a more rapid onset of action.

Continuous levodopa is authorised for patients with severe motor complications not controlled with other combinations of drugs.[20] It is administered via a permanent catheter implanted into the duodenum in a specialist centre.[2,21,22] It has been shown to provide more continuous plasma levels than oral administration with a reduction in dyskinesia and "off time" in clinical studies.[21]

Dopamine agonists - consist of ergot derived (bromocriptine,[23] pergolide,[24] cabergoline[25]) and non-ergot derived (pramipexole,[26] ropinirole,[27] rotigotine[28] and apomorphine[29]) agonists, of which the non-ergot derived agonists are the preferred option.[3] Many specialists use dopamine agonists in younger patients to delay the onset of motor complications,[2,3,6,30,31] however virtually all patients will eventually require the use of levodopa.[9] A recent Cochrane review comparing dopamine agonists versus levodopa, concluded that while motor complications are reduced with dopamine agonists, symptom control is poorer and other important side-effects are increased, leading patients to withdraw from therapy.[5] When given as adjunctive therapy to levodopa in advanced PD, dopamine agonists improve the symptoms and enable lower doses of levodopa to be given.[9]

The ergot derived dopamine agonists are known to cause serosal reactions including: pleural, pericardial and peritoneal effusion and/or fibrosis.[3] Recent studies suggest an increased incidence of cardiac valve disease with pergolide[32,33,34] and cabergoline; cardiovascular monitoring is required.[32,33] Pergolide should only be initiated under specialist supervision, following cardiovascular evaluation[35] and as second-line therapy in patients who are intolerant of or fail treatment with a non-ergot derived agonist.[24] In certain specialist centres, it is considered good practice to get written consent from patients prior to commencing ergot agonists especially cabergoline and pergolide.

Impulse control disorders are reported with all dopamine agonists (e.g pathological gambling or shopping, and hypersexuality).[24-28]

Ropinirole is available in a prolonged release formulation providing continuous delivery over 24 hours.[36] Rotigotine is given by a transdermal patch delivery system administered once daily.[28,37] [At the time of printing of this bulletin the European Medicine Agency (EMEA) has recommended that the patches should be stored in a refrigerator and no new patients should be commenced on rotigotine until further notice, due to reports of crystallisation of the active substance.[38] The company hopes to resume normal supply as soon as possible. (Personal communication)]

Apomorphine is a powerful dopamine agonist used as adjunctive treatment in patients with severe motor complications not controlled with other combinations of drugs.[12,29] It is administered as intermittent bolus subcutaneous (S/C) injections for severe off-periods or as a S/C infusion for patients with frequent off-periods.[3,12,21] It is a powerful emetic and should be used initially with domperidone until tolerance develops.[17] It should be initiated in a specialist clinic setting.[29]

Monoamine-oxidase-B (MAO-B) inhibitors are used as monotherapy in early PD or as adjunctive treatment with levodopa in more

advanced PD.[39,40,41] Some experts recommend that MAO-B inhibitors should be considered as initial therapy in patients with PD.[6] Selegiline when used as monotherapy produces modest improvements in motor function and when used as adjunctive therapy may provide up to 1 hour of extended "on" time for patients.[6] Rasagiline is more potent than selegiline and has exhibited disease-modifying effects in experimental models.[41,42] Clinical studies suggest that it may have disease-modifying effects, and further studies are underway in this area.[41-43]

There are important **drug interactions** in relation to the MAO-B inhibitors and their use is contraindicated with certain drugs[39,40] including other monoamine oxidase inhibitors and pethidine. Antidepressants should be administered with caution as serious adverse reactions have been reported with their use.[39,40] In addition concomitant administration of sympathomimetics are not recommended. Prescribers should review the SPC for full details of the prescribing information. At therapeutic doses selegiline is unlikely to induce a "cheese reaction", however dietary restrictions are recommended with concomitant use of moclobemide.[40] Tyramine challenges with rasagiline indicate that it can be used safely without tyramine restrictions.[39]

Catechol-O-methyltransferase (COMT) inhibitors – are indicated as adjunctive therapy with levodopa, however **they have no effect on PD in the absence of levodopa.**[6] The two COMT inhibitors are entacapone[44] and tolcapone[45] which lead to a 30-50% increase in levodopa half-life. COMT inhibitors should be considered to extend the duration of activity of levodopa if motor fluctuations develop.[6] Tolcapone is only authorised for those who have failed on entacapone and should not be considered first line due to the risk of potentially fatal, acute liver injury.[3,45] Liver function tests are required both prior to starting treatment and at specific intervals during treatment.[45] If benefits are not seen within 3 weeks of the initiation of treatment, treatment should be discontinued. Entacapone is not associated with hepatotoxicity[6] and is considered (as is rasagiline) a first-line choice for management of motor fluctuations,[6,41] particularly "off-time".[19] Entacapone has been formulated with levodopa and carbidopa making a triple combination, which may be convenient for patients.[6,46]

Amantadine – has demonstrated efficacy in relieving tremor in early PD[9] but would not be considered first choice. It is also used for the treatment of levodopa-induced dyskinesias.[3,6,9] Amantadine is no longer marketed in Ireland, however it is available on a named patient basis.

Anticholinergics – have been used for the treatment of PD for over 100 years, however their use is limited by the frequent development of intolerable adverse effects.[6] They are used for the symptomatic treatment typically in young people with early PD and severe tremor, but would not be considered first choice due to limited efficacy and propensity to cause adverse effects.[3] The anticholinergics authorised include biperiden and procyclidine. They are typically reserved for younger patients (<60 years) with predominant tremor illness and preserved cognitive function, who are better able to tolerate the adverse effects.[6,9]

Motor complications

Motor complications occur in virtually all patients, especially if on levodopa, and they impair quality of life and cause significant functional and social disability.[3,6,9] They are difficult to treat which has led to maximising treatment with other agents for as long as possible before using levodopa. Factors associated with earlier development of motor complications are cumulative dose of levodopa, younger age at onset and more severe disease at diagnosis.[18,19]

Younger patients are more prone to motor fluctuations and for these patients dopamine agonists are considered first line by many clinicians.[9,18] The most common motor complications are end-of-dose "wearing off" and levodopa peak dose dyskinesias. "Wearing off" is thought to result from a reduced duration of clinical effectiveness of levodopa and less often, of dopamine agonists.[12] "On-off" phenomena describes the abrupt and mostly random and unpredictable loss of benefit, which can occur during a successful "on" period.[17] "On" periods are associated with dyskinesias, which can be violent and incapacitating. Table 4 gives examples of some of the options for treating motor complications.

Table 4: Management of motor complications[19,22]

Motor fluctuations
- Provide more frequent smaller doses of carbidopa-levodopa
- Addition of a MAO-B inhibitor or COMT inhibitor or dopamine agonist to prolong levodopa response
- Consider controlled-release levodopa/carbidopa
- Consider use of carbidopa/levodopa plus entacapone

Dyskinesias
- Reduce each dose of carbidopa-levodopa
- Add amantadine
- Reduce or stop anticholinergic therapy

Advanced PD patients are faced with increasing periods of "off time" with rigidity, bradykinesia and freezing problems resulting in them being unable to perform normal daily activities such as sitting, eating or walking.[21] When patients have reached this stage there are currently only three treatment options: subcutaneous apomorphine (in combination with oral levodopa), continuous duodenal levodopa administration and deep brain stimulation of the subthalamic nucleus (STN).[21]

Surgery

Deep brain stimulation of the STN is an effective surgical procedure in appropriate candidates for treating medically resistant motor symptoms of PD and improving HRQoL in patients with advanced disease.[9,47] The advantage of STN deep brain stimulation over medications is that symptoms are controlled continuously with reduced motor complications and a decrease in levodopa requirements resulting in a reduction of dyskinesia, hallucinations and other adverse effects.[47] Side effects of surgery include haemorrhage, stroke, infection and psychiatric adverse events.[9,47] Evidence from several studies has also suggested a risk of suicide.[48] Outcomes are better in younger patients. There is an ongoing surgical trial reviewing this form of treatment.[48]

SUMMARY

PD is a chronic neurodegenerative condition associated with substantial morbidity, increased mortality and high economic burden. There is ongoing research for neuroprotection therapies. The goal of management remains the maintenance of acceptable functional control with minimal treatment-emergent complications. Patients with suspected PD ideally should be referred to a specialist prior to initiation of treatment due to the diagnostic error rate associated with PD. Patients ideally should also have access to a multidisciplinary team. Pharmacotherapy can significantly improve a patient's quality of life and functional status, however there is much debate as to which drug should be first line treatment. While levodopa remains the most effective agent for symptomatic control and virtually all patients will ultimately require it, it is associated with motor complications with long-term use. The optimal time to start pharmacotherapy varies but in general treatment should be started between the time of diagnosis and when the disease begins to interfere with activities of daily living, employment or quality of life.

List of references available on request. Date of preparation: August 2008

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