

PARKINSON'S A GENERAL PRACTICE APPROACH

Third Edition

Updated February 2017

PARKINSON'S DISEASE

A General Practice Approach

Third Edition
Updated February 2017

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This Manual has been produced for Parkinson's Australia by Parkinson's Western Australia Inc.

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AIMS

Parkinson's Disease: A General Practise Approach is a concise reference on the most common features and clinically relevant aspects of Parkinson's disease (PD), with an emphasis on the GP's

Boxed sections highlight essential facts and tips for easy reference during consultations.

role in diagnosis and symptom management. Though primarily aimed at GP's involved in the care of Parkinson's disease (PD) patients, others may find the manual useful when suspecting PD (p.13 Could it be PD), or when faced with any patient with tremor (p.17 Diagnosing Tremor). The manual is the result of collaboration between Parkinson's disease (PD) care providers including neurologists, general practitioners (GPs), Parkinson's Nurse Specialists and allied health therapists.

The main aims of this manual are to help GP's:

- recognise PD, particularly in the early stages when signs and symptoms can be non-specific and subtle
- realise the variable impact of PD at different ages and disease stages and adjust treatment plans/goals accordingly
- understand the individual nature of PD, in that symptoms, severity and rate of progression vary from person to person, and require tailored management plans to achieve the best treatment outcomes
- be aware of the most effective drug and non-drug treatments for PD and their availability in the local PD specialist treatment centres.

Summary: The GP's Role in PD Management

- **Early Diagnosis:** *Could this be PD?* Many patients report long, often distressing delays in diagnosis. Arrange specialist referral *before* commencing treatment to confirm diagnosis and establish a management plan
- **Early Stage PD:** Pivotal support role in helping patients cope with diagnosis, particularly given the infrequent contact and minimal role of the specialist at this stage. A rewarding disease stage to treat as many issues can be effectively managed
- **Mid-stage PD:** Co-manage drug and non-drug management issues with specialist.
- **Advanced Stage/Complicated/Elderly PD:** Pragmatic primary care of PD and non-PD issues which may include complex medication regimens, Aged Care Assessment Team (ACAT) review, General Practice Management Plans (GPMP) and nursing home patient management.

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ACRONYMS AND ABBREVIATIONS

AD	Alzheimer's Disease
COMT	Catechol-O-methyl transferase
DBS	deep brain stimulation
DDC, DDCI	dopa-decarboxylase; dopa-decarboxylase inhibitor
DLBD	Diffuse Lewy Body Disease
ECT	Electroconvulsive Therapy
ET	essential tremor
GPi	globus pallidus interna
LID	Levodopa-Induced Dyskinesia
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MSA	Multiple System Atrophy
PD	Parkinson's disease
PET	Positron Emission Topography
PSP	Progressive Supranuclear Palsy
QOL	Quality of Life
SPECT	Single Photon Emission Computed Topography
SNRIs	selective noradrenaline Re-uptake Inhibitors
SSRIs	Selective Serotonin Re-uptake Inhibitors
STN	subthalamic nucleus

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1. INTRODUCTION

Prior to 1960, Parkinson's disease (PD) was considered to be an untreatable degeneration of the brain. There had been little change since James Parkinson wrote in 1817 that Parkinson's disease was considered a natural result of 'declining life'. Patients became increasingly dependent over the course of a decade or two. Medications were non-specific and poorly effective. High-risk, mainly palliative surgery was the only other treatment option.

With the introduction of levodopa in the 1960s, Parkinson's suddenly became a treatable disease. The major symptoms were relieved and overall prognosis improved significantly. However, it soon became clear that levodopa was not a cure-all. While the drug continues to work in the middle to advanced stages of the disease, its effect loses potency and begins to cause movement abnormalities of its own – 'levodopa-induced dyskinesias' (LIDs), which may be as distressing and disabling as the primary symptoms. Furthermore, in advanced PD non-motor and non levodopa-responsive symptoms can add to the burden of disability, such as autonomic dysfunction, speech and swallowing problems, postural instability, cognitive and behavioural abnormalities.

Fortunately there have been many advances in PD treatment since these issues arose, including new drugs and delivery systems, the establishment of solid evidence-based allied health interventions and the rebirth of surgery for advanced PD in the form of Deep Brain Stimulation. It can be rewarding to watch patients respond to treatment and regain function, and their management can be greatly enhanced by the continuity of care that General Practise provides. At times GP's will be faced with problems in their PD patients common to any chronic disease patient, and be comfortable managing these independently. At other times these patient may present with confusing and complex PD-specific issues, and GP's will require the support of specialist medical or allied health services, such as a neurologist or Multidisciplinary PD Clinic which are present in most major centres.

James Parkinson (1755–1824)

James Parkinson was an English geologist, palaeontologist, political activist and physician (who was actually a member of the college of surgeons). In the post-French Revolution period when Britain was in political chaos he published almost a dozen political pamphlets. Writing under his own name and the pseudonym 'Old Hubert', he called for radical changes to the social system. As a member of a secret political society he was hauled before the Privy Council to give evidence on the 'Pop-gun plot', a conspiracy to assassinate King George III with a poison dart, but sensibly refused to testify until he was certain he would not be made to incriminate himself.

Parkinson also contributed extensively to medical journals on subjects ranging from gout to appendicitis and wrote several books and papers on palaeontology. However, his fame sprang from his major opus, 'An Essay on the Shaking Palsy', in which he vividly described the disease and its different stages and gave it the Latin name of 'paralysis agitans' (Parkinson, 1817).

Although he appeared to have substantial first-hand knowledge of the disease, his most important work was, in fact, based on six cases. He gleaned his information from patient history and clinical findings deduced from observation, rather than actual examination of his patients. Indeed, three of the six cases were noticed casually in the street.

Parkinson's wish was that a remedy would be found so that progress of the disease now known by his name would be halted.

2. WHAT IS PARKINSON'S DISEASE?

The Clinical Definition:

PD is the prototypic 'hypokinetic' movement disorder. It is idiopathic, chronic and progressive. It primarily affects the motor system, causing tremor, slowness of voluntary movement, muscular rigidity and eventually postural instability. In addition to motor symptoms, PD can also affect non-motor systems causing autonomic, cognitive, neuropsychiatric, sensory and sleep disturbances. A specific test for PD is lacking and diagnosis remains clinical, with supplementary investigations mainly to exclude secondary causes.

The Neuropathological definition:

Examining the PD brain reveals two main findings:

1. Loss of pigmented dopaminergic neurones in the substantia nigra pars compacta, a midbrain nucleus which projects up to where they release dopamine, maintaining normal basal ganglia function. Only when approximately 70% of these cells are lost do the cardinal signs and symptoms of the disease appear (Figure 1).

2. Remaining nigral neurones contain round intracellular inclusions known as 'Lewy Bodies' (LBs). These are also seen in other brain regions including the cortex in later disease stages. They are not specific to PD, and can be seen in Alzheimers, Multisystem Atrophy and Diffuse Lewy Body Disease (all of which can mimic PD – see p6).

LBs contain large clumps of alpha-synuclein, a protein which like amyloid is thought to be toxic to neurones, but whose function remains otherwise mysterious. Therefore it is believed that LBs are acting as an intracellular 'rubbish bin' for misfolded proteins, protecting the cell from free alpha synuclein. Understanding the Lewy Body and how nigral neurones process toxic proteins appears crucial in unravelling the complex biology of PD. To this end, large multicentre studies are under way searching for 'biomarkers' that will help diagnose PD, quantify its' progression, and hopefully one day lead to novel drug targets to slow or halt the relentless pathological progression.

PD: A Clinical Timeline

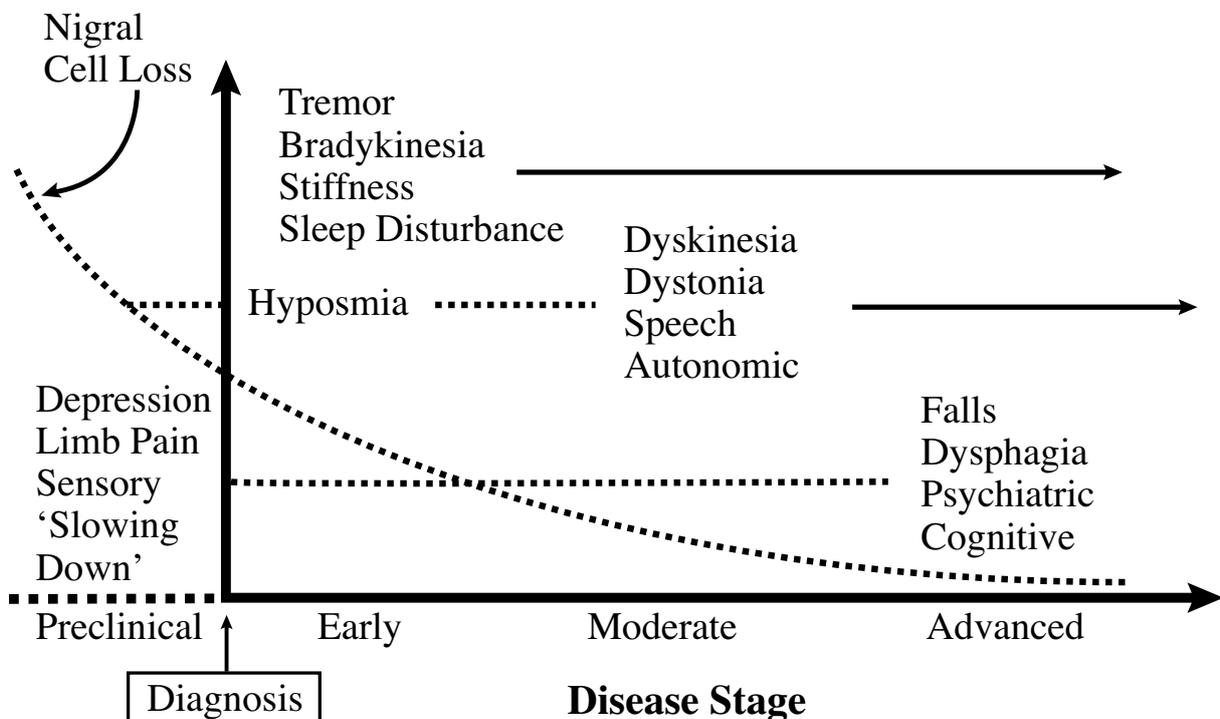


Figure 1. This clinical timeline for PD shows typical symptoms and their development in relation to substantia nigra cell loss. Symptoms occur when approximately 70% of nigral cells have been lost. Disease progression parallels the progressive cell loss. The rate of progression and mix of symptoms vary greatly between patients.

Diagnostic Criteria

The most widely accepted diagnostic criteria for PD are the United Kingdom Parkinson's Disease Society Brain Bank criteria (Table 1), which were developed as part of a study comparing the accuracy of clinical vs. pathological diagnosis (in fact the lead investigator was an Australian neurologist, Hughes et al., 1993). Two major lessons were learnt from study:

1. Other diseases that involve the nigrostriatal system can mimic PD (see p5-6) and be indistinguishable from it in the early stages. With time, atypical symptoms or signs appear, making the diagnosis of PD less likely. This highlights that regular specialist review is essential to monitor patients and confirm that they are responding as expected to dopamine replacement therapy.
2. Diagnostic accuracy can be improved from 80% to 85% to about 99% if a movement disorders specialist assesses patients.

Table 1. United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria*

<p>Step 1–Diagnosis of Parkinsonian syndrome Bradykinesia plus at least 1 of the following: Muscular rigidity Resting tremor - <i>can be absent in some</i> Postural instability - <i>late feature, if present consider alternative diagnosis</i></p>
<p>Step 2–Exclusion criteria History of repeated strokes History of repeated head injury History of definite encephalitis</p>
<p>Step 3–Supportive prospective criteria (at least 3 required) Rest tremor present Unilateral onset Persistent asymmetry Evidence of progression Excellent response to Levodopa <i>minimum 30% improvement in PD Motor scale</i> Levodopa-induced dyskinesias Levodopa response for 5+ years Clinical course of 10+ years</p>

*Note: As with all expert diagnostic criteria, these are designed with research studies in mind and, in a GP surgery, are probably more useful as a checklist after an opinion has been formed, rather than as a diagnostic tool.

How Common Is PD?

PD is the most common neuro-degenerative disease after Alzheimer's disease. It affects about 1% of the population over the age of 60 rising to 5% by age 85. An Australian report (ref: Access Economics Pty Ltd., 2011) estimated that 64,000 people had PD, and that this number would double in 20 years as the population ages. The incidence ranges from 10 to 20 per 100,000 per year (ie approximately 4000 newly diagnosed patients per year). An Australian General Practice of 1700 patients would have, on the average, four patients with PD and a new case of PD every four years.

Who does PD affect?

Though the mean age of onset is 60 years, 5 to 10% of all cases present before age 40 (Young Onset PD). The gender ratio varies across studies, but overall there is a slight male preponderance. The disease is more common in Europe and North America than in Japan, China and Africa. Ten per cent of cases have an affected relative, though the disease is not inherited in the typical sense of the word.

Prognosis

If left untreated, PD produces severe disability in ten to fifteen years. Although dopaminergic therapy does not alter the underlying pathology, it markedly improves quality of life and increases the time to development of dependency by four to five years.

The prognosis of PD depends on the age of onset, severity of symptoms and co-morbidities. It is hard to generalise, and even harder to answer patients questions about their likely future, but as a guide:

1. The disease always progresses, but at different rates in different people. 'Keeping up' with the disease by increasing medication also masks the true progression rate
2. Presenting with a bradykinetic/rigid syndrome and older age at onset usually means more rapid progression.
3. When it presents with tremor alone, the rate of progression is slower.
4. Postural instability, falls and dementia are poor prognostic factors which increase the risk of dependence and death.

Mortality

Mean survival in the pre-levodopa era was only 10 years, or an age adjusted mortality of 3:1. Since its introduction, death rates have fallen substantially. Age adjusted mortality has fallen but still remains greater than normal, ranging between 1.2 to 1.8:1 depending on the age range and disease stage of the study population. The most common cause of death in the end-stage, immobile patient is pneumonia.

Parkinson's Disease and Parkinsonism

Parkinsonism defines the cluster of signs found in the numerous conditions that affect the nigrostriatal system and cause symptoms and signs similar to those seen in PD.

Apart from PD, a number of conditions may present with parkinsonism. These may be difficult to differentiate from PD, particularly in the early stages.

Secondary Parkinsonism

Vascular parkinsonism

This clinical syndrome closely mimics PD and can be seen in the setting of the elderly patient or vasculopath with multiple subcortical infarcts. Imaging of the brain may show numerous discrete lesions in the deep white matter or basal ganglia, or a diffuse confluent deep white abnormality typical of small vessel disease. One can think of the parkinsonism in this case as being due to a 'disconnection' of frontal pre-motor areas from the basal ganglia. The most prominent clinical feature is the gait disorder. There may be a partial response to levodopa so a trial of treatment may be justified.

Drug-induced parkinsonism

Most will be familiar with the parkinsonian effects of major tranquillisers and antipsychotic drugs. Adverse effects are more common with the elderly, with females and with patients on higher doses. The newer antipsychotic agents have a lower but not insignificant incidence of extrapyramidal adverse effects, particularly in the elderly. Of these, quetiapine (Seroquel™) seems to have the lowest risk.

Many other drugs have been implicated as causing parkinsonism (Table 2), but none can be said to cause PD.

Management points

- If the symptoms are truly drug-induced, they will resolve on stopping the offending medication, but be prepared to wait 12 to 18 months for full recovery.
- In some cases the patient is significantly disabled to warrant levodopa treatment.
- It is important to note that in some patients the drug is actually unmasking subclinical PD, and this is only realised retrospectively. Treat as for PD.

Prochlorperazine (Stemetil™) used for non-specific dizziness seems to be the greatest offender. Problems can present insidiously in people on chronic therapy. Patients may forget to mention it so it needs to be specifically asked for.

If you tell the GPs one thing in this book, tell them not to use long-term Stemetil in the elderly.
(a Perth Neurologist)

Table 2. Common drugs known to cause parkinsonism

Dopamine Blocking

Metoclopramide (Maxolon™)

Prochlorperazine (Stemetil™)

All antipsychotics, including ‘atypicals’)

Dopamine Depleting

Tetrabenazine

Mechanism Unknown

Amiodorone

Multi-agent chemotherapy

Calcium channel blockers

Lithium

Phenytoin

Selective Serotonin Re-uptake Inhibitors (SSRIs)

Valproate

Note: See also Appendix I ‘Medications to be used with caution for people with Parkinson’s Disease’.

Atypical Parkinsonism or ‘Parkinson’s Plus’ Syndromes

Atypical Parkinsonism or ‘Parkinson’s Plus’ syndromes are neurodegenerative conditions (most of them rare) in which parkinsonian features form only part of the clinical picture. Although the differentiation of these syndromes from PD in the early stages may be difficult, most present with bilateral symptoms and signs. Few respond to levodopa but it is usually trialled.

‘Red flag’ signs and symptoms which raise the suspicion of the Parkinson’s Plus diseases

1. Postural instability and falls within two years of symptom onset.
2. Early and severe autonomic dysfunction, e.g. postural hypotension, bladder dysfunction.
3. Cerebellar signs.
4. Early dementia or neuropsychiatric problems.
5. REM sleep behaviour disorder: vivid nightmares ± violent limb movements due to loss of REM sleep atonia. This often impacts on the bed partner more than the patient.
6. Lack of/loss of levodopa responsiveness.

Progressive Supranuclear Palsy

Progressive Supranuclear Palsy (PSP, Steele Richardson Olziewski syndrome) is a sporadic disorder caused by degeneration of a number of brainstem and subcortical areas in which deposits of Tau protein are found. This is in a different form than the Tau seen in Alzheimer’s disease. It is the most common cause of primary parkinsonism after PD, with a prevalence of approximately one in 1000. It usually presents in late adulthood.

The parkinsonism can be severe though upright posture is preserved. Patients develop a gaze palsy and typically downgaze initially (ask about messy eating), with mild dementia, dystonia and bulbar dysfunction. Falls are common and occur within the first one to two years.

There is a poor levodopa response and although median survival from diagnosis is approximately seven to nine years some patients can live well beyond a decade from diagnosis.

Multiple System Atrophy

Multiple System Atrophy (MSA) is a rare sporadic neurodegenerative disorder where parkinsonism, autonomic insufficiency and cerebellar signs are seen in any combination. The cause is unknown, but alpha-synuclein deposition occurs along with degeneration of striatonigral and olivopontocerebellar pathways. The term MSA-P is used when parkinsonism dominates. MSA-C is used where cerebellar signs dominate or MSA-mixed where both are prominent. These terms have replaced the old terms 'Olivopontocerebellar atrophy', 'Shy-Drager syndrome' and 'Striatonigral degeneration'. Postural hypotension can occur in any of the forms.

There may be a response, albeit incomplete, to levodopa, and drug-induced dyskinesias may even occur. The prognosis is poor with a median survival of seven years.

Other diagnoses to consider

Diffuse Lewy Body disease

Diffuse Lewy Body disease is considered by most pathologists to be a pathologically distinct entity from Alzheimer's disease and Parkinson's disease dementia. Clinically, the situation can be tricky, as it occurs in an older population (onset usually over age 70) where multiple pathologies often coexist. Widespread subcortical and cortical Lewy Bodies are found. The clinical hallmark is the **early development of dementia with fluctuating cognition after the onset of parkinsonism**. This develops within a few years as compared to after 10 or more years in those who develop so-called Parkinson's disease dementia. The parkinsonism itself is similar to PD, but rest tremor is less common, postural stability and gait disorders are more common and the rate of progression is faster.

While the disease is levodopa responsive, psychotic symptoms may occur and require treatment with atypical antipsychotics or anticholinesterase inhibitors.

Normal Pressure Hydrocephalus

Normal Pressure Hydrocephalus classically presents as a triad of dementia, gait disorder and urinary incontinence. It can mimic PD when the gait disorder is the dominant feature, as short shuffling steps, start hesitation and freezing of gait can all occur. The gait disorder is believed to relate to cerebrospinal fluid pressure in the frontal horns compressing corticospinal fibres to the legs. There may be pyramidal signs but most importantly there is no response to levodopa. The pressure can be high enough to cause a transudate and striking periventricular white matter changes on MRI. The radiologist needs to take care to differentiate this from small vessel disease (see vascular parkinsonism above). Ventricular enlargement on CT is obvious and should raise the possibility of this condition, which responds to ventriculoperitoneal shunting if treated early.

Alzheimer's disease

Alzheimer's disease can present a diagnostic dilemma, especially where the dementia in the early stages may be less obvious than the parkinsonism. Twenty per cent of patients with Alzheimer's disease have extrapyramidal signs.

Wilson's disease

Wilson's disease (an autosomal recessive disorder of copper metabolism) presents in adolescence with a postural tremor and dystonias. Seizures and dementia gradually supervene.

Huntington's disease

Huntington's disease may also have features of parkinsonism, although it usually manifests with hyperkinesia, cognitive and neuropsychiatric problems and a family history.

Parkinson's Disease: Establishing the Cause

Despite an enormous amount of work, the cause of Parkinson's disease has eluded researchers. The search is more than academic; specific treatment directed at a known cause might slow or even prevent the disease if a preclinical marker was found.

- The only unequivocal risk factor for PD is increasing age.
- There is little difference between racial groups or socio-economic status, although, interestingly, smokers seem less likely to develop the condition.

Trauma?

Head trauma as a risk factor is controversial. Firstly, the issue of boxing and dementia pugilistica confuses things. This is not the same as idiopathic PD, as dementia is more common than parkinsonism and the brain pathology differs. Studies have reported an increased prevalence of PD in people with a past head injury, but not with simple mild concussion, rather with more serious injuries causing prolonged loss of consciousness or requiring hospitalisation. It is difficult to know what to make of this data in the light of the large number of people with serious head injuries who do not develop PD.

Genes?

Sir William Gowers, a famous English neurologist and inventor of the tendon hammer, was the first to note in 1888 that PD patients often had an affected first degree relative. Despite advances in the field of PD genetics, sorting out the role and significance of genes in PD remains a work in progress. At this time most PD is still considered sporadic rather than of genetic aetiology.

The key point to arise from work to date is that the younger the age of onset, the more likely genetic factors are to have played a causative role in the disease. Other forms of evidence support this, such as a twin studies showing no difference in incidence between monozygotic and dizygotic twins if the disease started after age 50, but a higher concordance in monozygotic twins if the age of onset was below 50.

The scientific discoveries to date have not altered clinical practice in terms of genetic testing and counselling. It is hoped that studies of rare genetic forms of the disease may discover the cellular mechanisms underlying the vastly more common, sporadic form of the disease. This would hopefully lead to the development of new treatments, such as effective neuroprotective agents.

The search for the 'Parkinson's Gene'

My grandfather had Parkinson's. Does that mean it runs in our family? Can I pass it on to my kids?

The clearest answers at present are 'probably not' and 'not likely' for the majority of patients.

In 1997 the first gene for familial PD was reported in a large Italian family. The excitement of this discovery was increased when the mutation was found within the gene for alpha-synuclein, the main protein component of the Lewy Body. Since then the number of genetic loci for monogenically inherited PD has risen to 12 and is sure to keep growing. As most PD is sporadic and familial PD is rare, testing for these genes in most patients is not warranted. The function of these genes is not fully understood, but some mutations cause a defect in the intracellular machinery that disposes of waste proteins. In this scenario, the protein 'rubbish bin' mechanism malfunctions, causing an accumulation of proteins, perhaps in a toxic form, which cause slow neuronal death.

There are also genetic susceptibility factors, which implicate enzyme systems (CYP2D6, monoamine oxidase B, nitric oxide synthase), cytokines (Interleukin 1), the Tau gene and mitochondrial genes. As with other diseases there is a complex interplay of genetic and environmental factors underlying the development of PD which we do not understand. Susceptibility factors may provide important and perhaps modifiable gene - environment links by explaining the greater vulnerability of certain individuals to environmental toxins that damage the substantia nigra.

Infection?

Most GPs would be aware of the incidence of PD in survivors of encephalitis lethargica. There are still a few survivors from this consequence of the 1910–1920 influenza pandemic. Their disease was slow in onset and showed little progression, and no new outbreaks have been reported. However, there have been rare reports of parkinsonism as a consequence of HIV infection and related diseases.

Autoimmunity?

There is pathological evidence of immune activation in the Parkinson's brain. Some have hypothesised that this may play an important role in its pathogenesis. The case remains circumstantial at present, as it is difficult to know if the inflammation is primary and causes the neuronal death, or is simply a reaction to a primary degenerative process.

Toxic?

MPTP or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine is one intriguing chemical cause of parkinsonism. This occasional contaminant of certain designer drugs can produce irreversible full-blown parkinsonism within a few days. This now rarely occurs, but the main relevance of MPTP is its use in primate models of PD. The drug is toxic to the substantia nigra and has similarities to several pesticides in common use. The drugs selegiline and rasagiline were originally designed to simply enhance dopamine neurotransmission by inhibiting monoamine oxidase-B. They have been studied for their role in slowing the progression of PD, as both seem to protect against the toxic effects of MPTP and other models of neuronal damage. The discovery of MPTP has given weight to research efforts into an environmental cause of PD. A naturally occurring environmental toxin or toxins, structurally similar to MPTP, may gain access to the nervous system in some individuals and cause the disease. Despite the epidemiological evidence it is unlikely that these agents cause the disease in isolation, but rather in combination with other toxins and genetic influences. Numerous case control studies have indicated that PD is associated with rural residence, farming, well water drinking and herbicide/pesticide exposure. Furthermore, families have been identified in which age of onset in parent and child correspond to a past common environmental trigger. Parkinsonism in manganese-exposed workers has been reported all over the world.

3. HOW IS PARKINSON'S DIAGNOSED?

The Value of Early, Accurate Diagnosis

Early, accurate diagnosis is important.

- The patient has access to clinical trials and participation in research projects.
- Patients are relieved to have an explanation for their perplexing symptoms.
- Physical therapy, self help and education can commence.
- If the patient is working, vocational rehabilitation can be explored.

Geoff is a 45 year old storeman. He noticed a stiff arm and a mild tremor. His mates thought he was grumpy, although he said he just felt tired. He has responded very well to pramipexole and has learned a great deal about the disease from the Parkinson's Association.

The doctor's challenge

Few GPs would have problems with diagnosing the well established case of PD. The flexed posture, shuffling gait and pill-rolling tremor are classic signs in clinical medicine. However, its vague, slowly progressive signs and symptoms make it one of the masquerades of general practice.

I hit age 70 and thought my arthritis had caught up with me—I just couldn't seem to walk as fast, my left knee hurt and I thought that's why my leg would drag on that side.

Common factors which delay diagnosis in early PD

- Symptoms can be mild, non-specific (e.g. fatigue, pain), or even non-motor (depression).
- The gradual onset of symptoms can make it hard for the GP and family, who see the person regularly, to notice a difference until signs become obvious.
- Unfamiliarity with making the diagnosis of PD – there is no harm in a neurological opinion.

The patient's perspective

Patients with PD often describe a prolonged phase of disturbing symptoms, unrewarding referrals and expensive investigations preceding diagnosis.

I had problems with a very sore shoulder. I couldn't write, and I wasn't really swinging one arm. I couldn't even play the piano anymore. I initially saw a rheumatologist who diagnosed RSI and suggested I retire. A pain specialist suggested I wear a TENS machine. A psychologist tried to treat my tremor with bio-feedback; when he thought I needed to see a psychiatrist, I gave up. My chiropractor told me to get a referral to a neurologist. When I was diagnosed with PD, my GP was very surprised.
(Rosemary, age 48)

Clinical Presentation

Non-specific early features

The preclinical syndrome of PD is poorly understood, but there is no doubt it exists, as prior to the onset of definite motor symptoms patients report a range of non-specific symptoms. These may be due to intermediate levels of dopamine deficiency, or perhaps result from compensatory changes required to maintain normal motor function. Depression, constipation, hyposmia and sleep disturbance are the more common problems predating diagnosis. Patients may complain of tiredness, lethargy, mild depression or restlessness. Many will have non-specific limb pain, aching muscles and vague paraesthesias. The earliest motor manifestations of PD are subtle and gradual and, not surprisingly, may be attributed in the older patient to ageing.

Rate of onset

A sudden onset of symptoms is not at all typical, and should raise the possibility of alternative diagnoses. The exception to this is the unmasking of incipient PD by anti-dopaminergic drugs (e.g. Stemetil™) or major intercurrent illness (e.g. surgery).

Early features of Parkinson's Disease

- Resting tremor
- 'Slowing down'
- Non-specific limb pain
- Tiredness, lethargy
- Handwriting difficulty
- Mild depression

Primary or 'Cardinal' Clinical Features

Tremor

Found in about 75% of patients at presentation, tremor is the most common early symptom. Tremor is absent in some or may disappear with time, leaving an akinetic rigid syndrome. In early PD it tends not to interfere with movements, particularly pure resting tremor which disappears when performing activities. Some patients without overt limb tremor report an annoying internal tremor.

Tremor in PD

- Tremor usually starts unilaterally in the upper limb.
- Typically it is a resting tremor that decreases with limb movement, though postural and action tremor may coexist.
- Tremor increases with anxiety, excitement, mental activity and walking.
- It disappears during sleep.
- When tremor occurs in isolation for many years without significant bradykinesia or rigidity (tremor-dominant PD), the prognosis is better.

Bradykinesia

Several movement abnormalities are seen in PD (Table 3), which have different characteristics. Despite the literal meaning of each term, unless in a pedantic crowd, one can use any of the terms to broadly describe the motor deficits of PD.

Bradykinesia can affect:

- large voluntary movements: standing up, walking, turning in bed
- fine voluntary movements: difficulty fastening buttons or cutting food; smaller and more cramped writing (micrographia)
- 'automatic' movements: slow blinking, reduced arm swinging, loss of facial expression
- autonomic movements: constipation, dysphagia.

Table 3. Movement abnormalities in Parkinson's Disease

Symptom	Definition	Example
Bradykinesia	slowed movement	slowed finger tapping, walking speed
Hypokinesia	small movement	small steps, soft speech
Akinesia	difficulty initiating movement / lack of movement	start hesitation when getting up to walk, 'freezing' when walking through doorway

Rigidity

Rigidity is an increase in muscle tone, present in limb and trunk muscles. As well as being an objective sign, patients may experience rigidity as discomfort, stiffness, cramping or pain.

There seems to be a perception that PD is painless—that has not been my experience. That ‘interesting’ cogwheel effect that health professionals love to detect becomes for me taut muscles that not only ache of their own accord, but also cause poor posture with all of its attendant backaches. Rigidity also robs me of true relaxation. I can remember what it was like to sit back in an armchair and feel the tension drain out of my body; I can remember the feeling of my limbs going floppy, but I no longer experience it. Instead, when sitting on a chair now, I experience the curious sensation of pulling away from the chair even as I sink into it as a dead weight.

(Dennis, age 56, diagnosed age 37)

Postural instability

Postural instability is not useful as a diagnostic sign as it appears several years into the disease. While present to some degree in all advanced PD patients, its onset and severity varies. It is due to a primary disturbance of postural control mechanisms, and no effective treatment exists. Falls are so frequent in the elderly PD patient that anyone with a fractured neck or femur should be examined for PD.

I was surprised to find a hip fracture patient still not mobile two weeks post-op, instead of the usual two days. His GP of 10 years was present and thought that he was not walking as his hip was too painful. I went to assess the patient who was hunched over and very difficult to understand. His facial expression was solemn and he was drooling. He had a prominent resting tremor, and on passive movement his body was clearly rigid. When I asked him to stand he looked frustrated and just shook his head. I asked his GP how long ago he had been diagnosed with Parkinson’s. He stated that his patient did not have Parkinson’s, at which point his wife broke her silence and informed me that she thought something had been wrong with him for the last two years. I spoke to the registrar who organised a neurology consult. Six days after being prescribed levodopa the patient was discharged fully ambulant and independent.

(Perth physiotherapist)

PD and balance problems

- The impaired balance seen in advanced PD is unresponsive to medication, and in fact medication can make falls more likely by allowing the patient the ability to get up and fall, or by exacerbating postural hypotension.
- The risk of falls is increased by sudden freezing episodes, the ‘walking while talking’ (dual task) phenomenon and dementia.
- An experienced physiotherapist may be able to improve safety by gait training, or at least by teaching proper use of an appropriate walking aid.

Secondary Clinical Features

Postural hypotension

Postural hypotension is a result of the autonomic dysfunction caused by degeneration of sympathetic ganglia, where Lewy Bodies are also found. **It is exacerbated by most antiparkinsonian drugs so warn of this when starting or increasing medication.**

Restless legs

Restless legs is a characteristic syndrome with the following features:

- leg discomfort (of any description)
- onset after a stereotyped latent period when the patient lies down to go to sleep
- relief upon standing up and walking around.

Restless legs is thought to be a primary dopaminergic problem. The symptoms respond well to dopamine agonists, e.g. pramipexole, though benzodiazepines or gabapentin can be used as second line treatment if dopamine agonists are not tolerated.

Speech difficulty

Speech difficulty may be an early problem. Bradykinesia of the speech mechanism makes the voice quiet, monotonous and often slow despite patients feeling that they are speaking normally.

They find it hard to shout and have difficulty using the phone. Paradoxically, some patients may have rapid, almost festinating speech. Stuttering is also common.

A 63 year old university professor with a history of previous anxiety became rapidly disabled by inability to raise his voice and express himself while lecturing. His anxiety over this symptom made it worse. He responded very well to levodopa, and was able to return to work with confidence restored.

Other ‘Soft’ Symptoms

Problems with body functions other than movement are frequent. Hyposmia (poor sense of smell) is common as the olfactory system is under dopaminergic control. Fatigue, even with optimally treated PD, occurs in up to 50% of patients. Sufferers sometimes have dysphagia and take a long time to eat their meals. Impotence is not unusual.

I wasn't able to cope with even things like getting family meals without great difficulty – I was just flopping about the place. The other things that I thought were relatively minor things, and related to the menopause, were incontinence, bowel problems, constipation and bleeding. It was only when my left leg started to behave strangely that I was diagnosed. (Sarah, age 46)

4. COULD IT BE PD?

Once having suspected PD, how can the GP confirm it?

The Patient's History

Ask the patient and spouse about:

- slowing down, fatigue and difficulty with performing work or home duties (writing, preparing meals and dressing)
- shakiness, falls and dizziness on standing
- symptoms favouring one side (early PD is almost always unilateral).

Drug history

A careful drug history should cover:

- antipsychotics, sometimes used as sedatives
- gastrointestinal drugs (e.g. Stemetil™ and Maxolon™)
- street drugs in younger patients.

Important negatives

A positive family history is unusual, but is common in essential tremor.

Check for multiple previous strokes, hydrocephalus, CNS infections, tumours or trauma.

See also 'Red Flag signs and symptoms' about atypical parkinsonism on page 5.

The Examination

Early motor symptoms and signs in PD are usually unilateral due to greater dopamine depletion in one side of the substantia nigra. This asymmetry usually persists as the disease progresses and becomes bilateral. In later stages levodopa-induced dyskinesias develop earlier and are typically worse in the more dopamine-depleted side.

Consciously look at the patient

Facial expression shows stillness from the lack of activity in the muscles of facial expression.

PD patients blink slowly. Normally we blink 20 times per minute. Patients with early PD may blink once every ten seconds.

Note the voice

Is the voice quiet, slow or monotonous? The voice can be reasonably normal in early PD.

Watch the patient getting out of the chair and walking

Posture may be stooped and flexed. During walking consider speed (reduced), stride length (shortened), base (normal or reduced, not wide), arm swing (asymmetrically reduced) and turning ('by numbers', as in those on a clock face, a lovely analogy used to describe the small rotatory steps PD patients need to make to turn around). Resting tremor worsens on walking, or even appears for the first time during the examination.

The 'pull test'

When standing, test postural stability with the 'pull test', a quick and easy test of postural reflexes and stability. If the patient's response is abnormal both on and off medication, it indicates a greater fall risk that medication is unlikely to improve, and non-drug strategies such as a walking aid should be used. In PD, righting reflexes to posterior displacement (retropulsion) are lost earlier than those for anteropulsion (pulling them forwards) or lateropulsion. The old 'push test' gives the same results, but is unsafe as the patient is at risk of falling unless two people are present.

Warn the patient what you are about to do—the aim is not to ‘surprise’ the patient but to test their ability to recover from an expected and reasonably standardised perturbation.

- The patient stands up straight with feet shoulder width apart and eyes open.
- Tell them to try to stop you pulling them over. Tell them that if they feel they are going to fall backwards, to try to take a step to recover.
- Stand behind them, and give a sharp tug on the shoulders.
- Be prepared to catch them, but allow enough space to assess for three to four backward steps, as more than two is considered abnormal.

Sit the patient on the examination couch

Observe tremor

Observe tremor at rest, with hands outstretched (postural) and performing finger to nose testing (action/intention). Resting tremor can be provoked by mental arithmetic, e.g. ask them to ‘count backwards out loud from 100 by threes’.

Pyramidal screen

- Tone is best assessed at the wrist in PD. The muscle tone feels increased with resistance to movement throughout the range of movement. This should be differentiated from the spastic ‘catch’ of pyramidal disorders when a brisk passive stretch is applied.
- Cogwheel rigidity occurs wherever increased tone and tremor coincide (e.g. essential tremor with incomplete relaxation) and is not pathognomonic of PD.
- Power and sensation should be normal, but one must allow the bradykinetic patient time to develop maximum force, or ‘weakness’ will be found.
- Reflexes can be brisk but only abnormally so with the atypical parkinsonism syndromes or with other co-existing neurological disease. Slightly brisker reflexes may be found in PD on the more symptomatic side due to enhancement of the spinal reflex arc.

Extrapyramidal screen

- Rapid movements (uncoordinated pronation/supination, hand clenching).
- Fine movements (slowness and difficulty tapping finger and thumb together rapidly).
- Finger to nose test (negative).

Primitive reflexes include Glabellar tap (normally habituates after three blinks). Other frontal lobe reflexes (grasp, pout) are more common in the demented patient, but have low specificity.

Check eyes

Kayser-Fleisher rings are greenish yellow or brown rings seen at the edge of the cornea. They are best seen on slitlamp examination and signify Wilson’s disease, which can cause parkinsonism.

Eye movements should be full range and are a critical factor in differentiating PD from other syndromes.

- Restricted eye movements, especially downgaze, in Progressive Supranuclear Palsy (PSP).
- Involuntary movements (jerks, nystagmus) as can be seen in Multiple System Atrophy (MSA).

Lying and standing blood pressure

- A systolic/diastolic blood pressure drop of greater than 20/10 mmHg defines postural hypotension which may or may not be symptomatic.

At a Later Visit

Micrographia

Micrographia (small cramped handwriting) is typical. Ask the patient to bring in some old letters to compare handwriting. An old family photograph or video may confirm the changes in posture and mobility.

Mini mental state exam

The presence or absence of dementia is important in treatment and in differentiating PD from other mimics.

Check for depression (see p27 Depression and Dementia)

Depression is common in PD and in some patients can impact more on QOL than the motor symptoms of PD. It may be missed in the examination as the lack of facial expression can mask the usual cues that remind doctors to ask about mood. Monitor for reactive depression in the newly diagnosed patient.

Laboratory examinations

Several tests should be done to screen for coexisting disease.

- Urinalysis and blood sugar (in the surgery).
- Full blood count.
- Urea and electrolytes.
- TSH (hypothyroidism can produce tiredness, lethargy and gait disturbance; hyperthyroidism can produce anxiety and tremor).
- The young patient with signs of PD should be checked for Wilson's disease (serum copper, caeruloplasmin and Liver Function Tests).
- All patients with parkinsonism should have brain imaging, at least a CT scan to exclude the occasional cerebral tumour, subdural haematoma or normal pressure hydrocephalus. An MRI may show specific abnormalities in atypical parkinsonism.

Supplementary tests

Again, it should be stressed that NO TEST is diagnostic in PD, but they can be reassuring in difficult clinical situations. Some of these are still at the research stage of development, or are not widely available.

- Olfactory testing such as the UPSIT (a quantifiable 40-point 'scratch and sniff' test) may demonstrate severe hyposmia in PD, not seen in PSP or MSA, but significant overlap exists.
- Dopaminergic imaging (Dopamine transporter SPECT, Fluorodopa PET): a normal scan makes PD very unlikely, but differentiating PD from other syndromes is more difficult.
- Cardiac MIBG scan, a widely available nuclear medicine test, demonstrates the peripheral sympathetic denervation of PD, not seen in MSA where only the central sympathetic centres are affected. Results can be normal in early PD.
- Transcranial ultrasound testing is only performed in expert centres. Changes in the substantia nigra can be seen.

The levodopa challenge: using the response to dopaminergic treatment as a diagnostic aid

The levodopa challenge refers to the supervised acute administration of a large dose of levodopa (e.g. 250mg PO or apomorphine subcutaneously or by IV to assess the short-term effects of supramaximal dopaminergic stimulation. It should be performed by a Parkinson's specialist who will assess the patient before and after the challenge, looking for objective changes in clinical signs. Typically, a formal motor rating scale is used, with a minimum 30% improvement defining a positive response. Some indications for performing the test include:

- differentiating PD from other forms of parkinsonism
- clarifying issues relating to potential drug toxicity
- assessing dyskinesia severity
- 'tracking' a dose cycle in a patient where it is uncertain whether certain symptoms relate to the 'on', 'off', or transition state. This can be enlightening for both doctor patient, and also helps set realistic goals of what can be achieved with medication.

Pitfalls

The problem with using this as a diagnostic test is that while most patients with PD will respond acutely, some may fail the challenge but respond to chronic treatment, so a longer treatment trial is always warranted if in doubt. Conversely, some conditions may show a positive response to such a large dose, but the effect is not sustained with chronic therapy.

Specialist Role

Once a diagnosis of PD is suspected, referral to a neurologist or PD physician before commencing treatment is recommended. If the patient is not disabled, treatment is not an issue and a non-urgent appointment will suffice. There will be times when you are concerned that the patient is significantly disabled to warrant treatment and they cannot be seen by a specialist within an appropriate time, e.g. six weeks. Contact the specialist and ask if they would like you to start treatment. Most neurologists will prefer to see the patient untreated and your call will hopefully result in an earlier appointment.

Benefits of early specialist referral in early PD

- Confirmation of the diagnosis and likely prognosis.
- Establishing a shared management plan.
- Access to some of the excellent allied health resources in PD.
- Access to research programs including new drug trials.

5. DIAGNOSING TREMOR

Definition

Tremor is simply a **rhythmical involuntary oscillatory movement of a body part**. It is periodical and involves movement around an axis. James Parkinson described the typical PD tremor as ‘involuntary tremulous motion in parts not in action’.

Subdivisions of tremor

Resting	occurs when muscles are at complete rest
Postural	occurs when muscles are working against gravity, e.g. holding out hands
Action/kinetic	occurs with movement
Intention	action tremor that increases in amplitude when nearing target (absent in PD)
Orthostatic	leg and trunk tremor occurring only when standing upright (rarely in PD)

Approach to Tremor

Ask about the onset of tremor

If rapid, consider drugs or non-organic causes.
A positive family history suggests essential tremor.

Take a drug history

It is important to include alcohol, antiepileptics, antiemetics, antidepressants and antipsychotics.

Examine the tremor

Resting tremor? Try a distraction manoeuvre while watching the tremor. Ask the patient to perform a calculation or tap their leg with the other hand. This usually worsens PD tremor, but reduces psychogenic tremor.

Postural tremor? Hold the hands out straight ahead and in front of the mouth.

Action tremor? Perform the finger to nose test.

Check

Gait	normal in essential tremor. Even in early PD the arm or arms often do not swing.
Reflexes	increased in hyperthyroidism
Sensation	invariably normal in isolated essential tremor and PD
Eyes	exophthalmos in thyroid disease, reduced blink in PD
Thyroid enlargement	

Table 4. Differentiating tremor clinically

Tremor	Parkinsonian tremor	Physiological tremor	Essential tremor
speed (Hz)	4 to 5 per second	8 to 12 per second	6 to 9 per second
laterality	unilateral initially	bilateral	bilateral
increases	at rest ‘resting tremor’	with anxiety, beta agonists, thyrotoxicosis	with movement or posture holding
family history	no	no	yes
head tremor	no	no	sometimes
type	resting (‘re-emergent’ postural)	action	action (postural)
neurological exam	increased tone, bradykinesia	normal	normal

Types of Tremor

Parkinsonian tremor

The typical tremor of PD is a resting tremor, decreased by activity, and usually unilateral in its early stages (Table 4). It never starts in the head, but once present can involve any body part. The rest tremor can re-emerge with posture holding and interfere with activities in some people. Action tremor can coexist but is much less prominent.

Beware patients that call any abnormal involuntary movement ‘the shakes’, when they are in fact experiencing dyskinesia – attempts to fix this problem with more medication will only make it worse.

Physiological tremor

Physiological tremor is the most common tremor detected in general practice. It is a fine low amplitude tremor which accompanies any voluntary activation of muscle. It is usually only noticed on fine precise movements (e.g. threading a needle). Enhanced physiological tremor is seen with anxiety, hyperthyroidism, some drugs and caffeine.

Essential tremor

The typical presentation of essential tremor is a very slow, progressive bilateral action or postural tremor

Essential tremor (ET) is the most common movement disorder in adults.

that starts in the hands. With time the tremor can spread to the forearms, head, chin, voice and legs. Incidence is bimodal, presenting most commonly in late adolescence or older adulthood. The tremor worsens very gradually and is not disabling in the majority of cases. The pathophysiology is unknown but PET (Positron Emission Topography) scans show increased activity in cerebellar and brainstem nuclei which probably represents an abnormal oscillatory neural network. Structural brain imaging is normal.

Supporting historical features

Tremor reduction with one to two standard alcoholic drinks, positive family history in 50% to 70% (the disease has a genetic basis with autosomal dominant inheritance, but the gene has not been found).

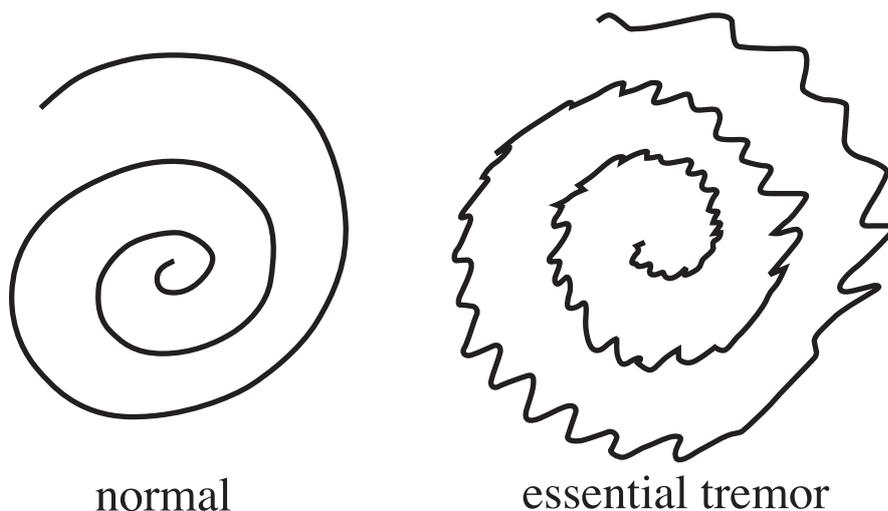


Figure 2. Drawing an Archimedes spiral can be a useful way of monitoring the severity of a patient's essential tremor and their response to treatment.

Supporting examination findings

The postural tremor appears immediately on holding up the hands, as opposed to the re-emergent postural tremor of PD which reappears several seconds after the hands are held up. The action tremor does not have an intention component. ‘Cogwheeling’ can be detected, particularly in older patients, but true rigidity is absent. Head, lip and voice tremor can occur. Handwriting is large and looping as opposed to the small and cramped writing of PD patients. To demonstrate and monitor the severity of essential tremor (ET), ask the patient to draw an Archimedes spiral (Figure 2) without resting their elbow on the desk. When drawn in the patient’s notes, it is a quick and simple way to track the progression over years.

Pitfalls

While usually bilateral and symmetrical, essential tremor can be asymmetric or even unilateral early in the disease. Resting tremor occurs in up to 10% of cases. Tandem gait is abnormal in a subset of patients.

Essential tremor and PD

Essential tremor (ET) is the most common misdiagnosis given to PD patients who present with isolated tremor. This occurs at all levels of expertise, including specialist movement disorders clinics. Time is the best test to distinguish the two, and one should remain vigilant for the development of parkinsonism, especially in the older patient or where features atypical for ET are present. As both ET and PD are more common in the older patient, some patients may have both conditions (treat dominant syndrome, or treat for both).

Management

Management involves exclusion of other disease(s), reassurance as to the benign course and use of drugs to decrease the tremor. Propranolol (optimal dose usually between 120 mg to 160 mg bd but can be helpful at lower doses and is more effective than selective beta blockers) or primidone (up to 250 mg bd) are reasonable first choices. Gabapentin and topiramate (both unavailable for ET on the PBS) may benefit some patients, and the newly released pregabalin may be more effective, but trials are in the early stages. All drugs only partially reduce tremor, and patients should not expect complete relief. Thalamic deep brain stimulation is reserved for cases of severe disabling tremor and is very effective.

Essential tremor and alcoholism

Patients with alcohol sensitive ET may self-medicate with one or two drinks before important social or business events. There are conflicting reports on the association of ET and secondary alcoholism based on this practice, and one should not assume that such patients are at risk of excess alcohol intake if common sense prevails.

Drug-induced tremor

There is an exhaustive list of drugs associated with tremor that usually cause an action or postural (less commonly resting) tremor. The drugs most commonly seen in clinical practice are listed below (Table 5). Remember that drug interactions may cause previously well tolerated drugs to become toxic and cause adverse effects such as tremor. See Appendix 1 for more details.

Table 5. Common drugs known to cause tremor

Drug	Action or postural tremor	Resting tremor
Amiodarone	x	
Amitriptyline	x	
Cyclosporine, tacrolimus	x	
Caffeine, theophylline	x	
Co-trimoxazole		x
Haloperidol	x	x
Lithium	x	x
Metoclopramide	x	x
SSRIs	x	x
Tamoxifen	x	
Thyroxine	x	
Sodium valproate	x	x

Cerebellar tremor

Diseases of the cerebellum or the connections form the classic action tremor which increases at the end of active movement (intention tremor). While subtle cerebellar disease may manifest as isolated limb tremor, examine for gait or limb ataxia, nystagmus and dysarthria.

Metabolic tremor

Asterixis is found when the arms are extended with wrist hyperextension. It is found in the ‘organ failures’ (respiratory, hepatic or renal) as well as in Wilson’s disease or lesions of the red nucleus.

Unusual tremors

Odd causes of tremor include minor head trauma, major head trauma (post-traumatic tremor) and tremors confined to odd sites and certain activities (e.g. task-specific tremor, orthostatic tremor).

6. MANAGING EARLY PD

Being given a diagnosis of PD can be a devastating experience for patients. It is often said that in early PD the greatest impact of the disease is fear of the disease itself. This can be helped by support and education, but also depends on the individual's coping strategies, as with any traumatic event.

What seems to happen when people are diagnosed fairly early and are not suitable for medication is that at that point the doctor seems to say, "OK, I've done my bit, I know what you've got, I've told you what you've got, there's nothing I can do about it in the next two years. Go away and come back and see me when you've got a problem". The problem is that although you may not be feeling physically sick at the time, you start to feel pretty miserable about the future. It's at this point that patients need some sort of counselling contact with their GP or through Parkinson's Associations.
(Donald, age 47)

GPs are ideally placed to coordinate lifetime holistic care in those diagnosed with PD. Once the diagnosis has been made, a plan of management should be designed, and the patient given an idea of what the future may hold.

Aims of management

- to encourage a healthy lifestyle
- to help the patient and their family understand the disease
- to manage the disabling symptoms as they arise.

Helping the Family Understand the Disease

Few other non-terminal diseases require such understanding as PD. Patient and family are often overwhelmed following diagnosis.

My husband was only 37 years when he was diagnosed. I'd just had my second child. He was pretty low, and I was pretty low and I had the new baby. I didn't really have anybody to talk to. I was finally put in touch with a support group facilitator, and I burst into tears, and she said "It's all right, get a tissue, I'm still here, and when you've calmed down I'm still here". It was so fantastic to have someone on the end of the phone, because you feel so very alone.
(Jenny, age 47)

There is a huge amount of patient information on the condition. Families can benefit from the educational resources and group support provided by the Parkinson's Associations and various carers groups (see Chapter 13 Self Help and Information, for patient resources).

Encouraging a Healthy Lifestyle

Regular exercise and a sensible diet are necessary in maintaining a healthy lifestyle. It is important for the PD patient to continue normal activities—physical, mental and social.

With the high risk of falling in PD, early prevention of osteoporosis should be a priority. Encourage exercise, consider calcium replacement and, in women, offer HRT. Other strategies may be required.

Excess weight adds to the work of maintaining mobility. Encourage overweight patients to lose weight now, rather than later when their capacity for aerobic exercise may be limited by motor disability.

Managing the Disabling Symptoms with Medication

Some patients present with symptoms so mild that they do not need drug treatment. Patients with minor tremor in the non-dominant hand may have few other symptoms and no significant progression.

It can be a difficult decision deciding when to start medication for PD. Treatment can be extremely rewarding for all involved in early Parkinson's disease, where many of the drugs work well and in low doses, the so-called honeymoon period. Patients may need to be reminded that the disease is progressive, and that medication adjustments are inevitable. These adjustments should not be seen as a step backwards, but rather a means of keeping up with the disease and focusing on maintaining good health.

Treatment of mild PD

Patients are usually seen more often by their GP who can gauge the overall impact of PD on their lifestyle and alert the specialist to the development of significant disability. At this point a reassessment review by the specialist or clinic is preferable to commencing medication.

Treatment of moderate PD

Treatment of early / mild PD 'Watch, wait, support and protect'

In all patients with PD:

- conduct a baseline clinical review to establish severity
- provide information on the disease
- refer to neurologist, consider allied health referral
- review every three to six months for functional disability.

The rule is: 'Drugs when functionally disabled: not before'.

In many young patients and nearly all elderly patients, there will be actual disability which justifies treatment with medications.

Jane is 53. Her PD was diagnosed two months ago and she was rapidly deteriorating. She had stiffness, fatigue, shoulder pain and found it difficult to walk. She was unable to work. With neurologist advice, it was decided to commence pramipexole. Within two weeks she could return to her teaching job.

Choosing a drug in PD

Drug treatment in PD is reasonably straightforward initially, with the aim being to treat the dopamine deficiency. Options include:

- Levodopa is the prototypic antiparkinsonian drug. It crosses the blood–brain barrier and is converted to dopamine and taken up by remaining substantia nigra neurons. Dopa decarboxylase inhibitors (carbidopa in Sinemet™ and Kinson™; benserazide in Madopar™) inhibit peripheral levodopa metabolism. They do not cross the blood–brain barrier. Their main function is to block unwanted peripheral levodopa effects such as nausea and postural hypotension. As they are always combined with standard levodopa preparations they do not need to be considered separate to the levodopa dose. Stalevo™ (levodopa/ carbidopa/ entacapone) contains two peripheral enzyme blockers, thus ensuring the half-life of levodopa is maximised.
- Dopamine agonists are synthetic agents that mimic the effect of dopamine by binding to receptors downstream from the substantia nigra. Pramipexole (Sifrol™) is mainly used at present.
- COMT inhibitors (entacapone/Comtan™) inhibit dopamine breakdown, thereby prolonging the effect of a levodopa dose. They have no anti-PD effect on their own.
- Selective MAO-B inhibitors (selegiline/Eldepryl™/Deprenyl™ and rasagiline/Azilect™) work centrally to inhibit dopamine. They provide mild symptomatic benefit.
- Non-dopaminergic drugs (amantadine, anticholinergics, beta blockers) have a limited role but may benefit some patients for a limited time.

Principles Behind Choosing a Drug

Where to start?

There is no best, first choice drug for all patients. The choice should take into account age, lifestyle, occupation and co-morbidities. Patients may wish to be involved in the choice of drug after being informed of the typical benefits and short and long-term adverse effects of the drugs.

There seem to be as many recipes for treating PD as there are celebrity chefs, in part, because no one regimen can be defined as the prototypical script for the disease. General principles are followed and the doctor and patient decide what will best suit the patient in terms of benefits and adverse effects. Drug therapy may appear confusing with its array of pills, strengths and slow release formulations. **Pill charts, such as on the inside cover of this manual**, can help bewildered patients to identify their medication and help caregivers reinforce prescribing instructions.

Levodopa – The Mainstay of PD Medical Treatment

Levodopa is dramatically effective in early PD. Though it remains effective throughout the disease course for the motor symptoms of PD, its potency and duration of effect wane after several years as the disease progresses. Motor fluctuations (‘wearing off’, ‘on-off’ phenomenon and levodopa-induced dyskinesias) occur in 50% of patients after five years. They can become disabling, but are amenable to medication adjustments. Other non-levodopa responsive symptoms such as falls and cognitive problems can be the main cause of disability in later stages.

Levodopa Dosage – more is not necessarily better

Keep levodopa doses at the minimum level required to maintain good motor function as this reduces the risk of adverse effects.

Initiating treatment with dopamine agonist monotherapy is recommended, especially in younger patients, as it delays (but does not prevent) the onset of motor fluctuations.

Medication Compliance

A critical aspect of PD management, especially in patients with:

- motor fluctuations is that they often become frustrated with the unpredictability of their symptoms and out of desperation concoct their own regimen, often worsening the situation.
- adverse effects is that they are at risk of developing a reluctance take effective medication, even when solutions are readily available to overcome the problem e.g. domperidone for nausea.

Good compliance is best achieved by thoroughly educating people about their disease and ensuring their expectations of medication are appropriate. This knowledge gives them a sense of personal control over their disease, and has been shown to improve quality of life.

Treating doctors should do their best to provide this education, and are well placed to do so given their key role in the eyes of their patients. Some GPs will have detailed knowledge of PD and wish to handle the education aspect themselves. Those who do not will be pleased to know there are good resources available for patients. These include the local PD Association, PD Nurse Specialists, pharmacists and other informed PD patients.

While poor compliance usually means forgetting to take medication, in PD it can also mean the opposite: self over-medication. Some patients are so impressed with the motor (and in some cases neuropsychiatric) effects that they supplement their prescribed regimen with extra doses. This can get out of hand, and two situations are especially important to look out for:

- **‘The Fiddler’** - advanced patients who fluctuate randomly due to overlapping doses. Patients often use combinations of strengths and formulations to try to tailor each day to suit them. This may work for a period of time, but is destined to fail, resulting in erratic motor function and more adverse effects.

- **‘Levodopa High’** - patients who report a euphoric feeling on medication. They are intolerant of the slightest sign of the drug wearing off, and take extra doses despite florid dyskinesia. These are warning signs that the patient is at risk of levodopa addiction (also known as dopamine dysregulation syndrome). Behavioural changes can occur and become more debilitating than the disease itself, including impulse control disorders (gambling, substance abuse, hypersexuality) and punding (repetitive purposeless activities that may appear to be ‘hobbies’ but consume the patients’ waking hours).

The drugs used in PD are fully discussed in Chapter 12 Drugs.

When To Start Treatment? Ask Four Questions

The following guidelines broadly outline early drug management in PD. Although the indications are not absolute, the principles are reasonably well accepted. The decision to use medications should be determined by considering the following questions:

1. What are the main symptoms and their severity?

Pure resting tremor is often more of a nuisance than a disability, since it usually goes with active movement. If they are accepting of this and not distressed by it, patients are often pleased not to ‘have to’ commence regular medication. Others will become embarrassed, withdraw socially or even develop depression due to this most visible symptom, and require treatment for this aspect alone.

Similarly, bradykinesia, if mild, may go unnoticed or not limit patients usual activities. The onset of significant gait symptoms (marked slowness, shuffling, start hesitation) usually prompts patients to return to clinic requesting help. Rigidity may cause discomfort or pain, but is usually accompanied by other significant symptoms which tip the balance towards commencing treatment.

Nonmotor symptoms that may present early in the disease include depression, constipation, sexual dysfunction, vivid dreams (REM sleep disorder) and should be promptly treated with appropriate specific drug and non-drug measures rather than PD medications.

2. Does the patient have functional impairment?

In general, patients should not be treated until their motor deficits begin to impact on their ability to perform their usual daily activities or fulfil occupational or domestic duties.

Is the patient working?

Depending on their occupation, the working patient is more likely to require treatment than someone who is not, particularly those who provide the primary financial support for their family.

Is the dominant hand affected?

The effect of PD on work performance may be especially significant if writing or fine motor tasks are frequently performed.

3. How old is the patient?

Levodopa is the most effective drug, but a subgroup of patients will develop troubling motor fluctuations after 5-10 years of therapy. It is not possible to predict which patients will develop these problems and there is some evidence to suggest that using dopamine agonist monotherapy delays their onset and severity for months to years. Generally speaking, this is less of a concern when treating the older patient.

Less than 60?

Dopamine Agonist Monotherapy

Dopamine agonists are considered first-line treatment for younger PD patients. Although less potent than levodopa, its main practical advantage is the ability to prescribe once-daily treatment (e.g. Sifrol™ ER), improving compliance and pill burden. Transdermal and subcutaneous formulations are also available, although not typically used as initial therapy

Disadvantages of dopamine agonists include greater incidence of nausea and postural hypotension than levodopa. This class of drugs can also cause limb edema, sedation, sleep attacks and neuropsychiatric symptoms such as confusion, behavioural changes, hypomania, visual hallucinations, frank psychosis and impulse control disorders). The older class of ergot-derived drugs (bromocriptine, pergolide, cabergoline) were found to cause fibrotic effects (heart valve, lung and retroperitoneal) in a small number of patients, and have since been superseded by the newer 'non-ergot' drugs (see. P 42).

Non-dopaminergic Drugs

These are now less used since dopamine agonists were developed, but still have a role in selected patients. The glutamate antagonist Amantadine (Symmetrel™) has modest effects, but is poorly tolerated at the higher doses required as the disease progresses, particularly in older patients. Anticholinergics such as Benzhexol (Artane™) improve mainly tremor but can have modest benefit on other symptoms. The usual adverse effects occur, and cognitive deficits may develop insidiously as the patient ages.

Older than 60?

Levodopa is the drug of choice and although dopamine agonists may still be used the incidence of adverse effects is higher than in younger patients.

4. Is there cognitive impairment?

The prevalence of dementia in PD is as high as 20% in advanced disease. Its presence means extreme care must be taken with medications. If present in younger onset patients, it makes the possibility of one of the Parkinson's Plus syndromes more likely.

7. ADVANCED PARKINSON'S DISEASE

Major Manifestations

Bradykinesia

Bradykinesia means that movements become increasingly slow, and hand dexterity worsens. It may take several attempts to get out of a chair. The patient may begin to experience freezing attacks when walking, especially when turning or walking through doorways.

Rigidity

With rigidity, the increased muscle tone becomes painful, especially in major muscle groups such as trunk muscles.

Tremor

Tremor can become disabling, interfering with activities and providing a source of social embarrassment. In some patients tremor fades or even disappears, leaving an akinetic-rigid syndrome.

Postural instability

Unsteadiness evolves to become a major problem in walking, turning and getting in and out of cars and buses. Falls become more frequent.

Levodopa-Induced Dyskinesias (LIDs) and on-off motor fluctuations

After several years of treatment, due to a complex interaction between disease progression and the long-term administration of levodopa or dopamine agonists, all patients develop the well-known 'motor fluctuations' of PD.

While initially patients blame the medication, they need to be advised that these symptoms are an inevitable consequence of treating the disease with highly effective dopaminergic medication. If such treatment was withheld in fear of developing such complications, they would have suffered years of disability instead.

Although dopaminergic therapy is always of some benefit, over time the magnitude of benefit declines, the response may fluctuate unpredictably, or adverse effects may limit the use of effective dosing. Drug-induced involuntary movements (LIDs) occur, appearing choreoathetoid or dystonic, and initially can be dismissed as 'fidgeting' or restlessness by patients or people around them.

Oral problems

Saliva problems, most commonly drooling, can occur and be embarrassing and distressing. Reduced swallowing frequency and flexed neck posture are to blame, rather than excessive salivary production. Treatments to reduce saliva production can provide significant benefit (anticholinergic medications, botulinum toxin injections to the parotid glands) but good dental surveillance is necessary.

Dysphagia

Dysphagia (swallowing problems) occurs in 40% of patients with PD and results from bradykinesia of the swallowing muscles. Aspiration may be a problem.

Skin problems

Sweating is often troubling, as is seborrhoea and dandruff.

Autonomic problems

Postural hypotension, constipation, urinary problems, sexual problems.

Neuropsychiatric Problems

Sleep problems

There are many causes of disturbed sleep in PD. See ‘sleep problems’, page 35 for the differential diagnosis.

Confusion

Confusion in advanced PD has a wide differential diagnosis, and thorough assessment is indicated, especially in the elderly patient. Some antiparkinsonian drugs can cause confusion and may need to be stopped, especially anticholinergics.

Depression

Recent studies have shown that 40% of the PD population will experience significant depression.

Dementia

The risk of dementia is about five times the normal population, with the main risk factor being increasing age.

The 15-Minute PD Review

While it may seem like a daunting task, the 15-minute PD review is very important. Covering the following aspects ensures that GP's does not miss anything crucial, and helps educate patients regarding symptoms to watch for. The 15-minute PD review emphasises aspects that most commonly impact on quality of life.

- **Disability** – is there anything you can't do by yourself?
- **Mobility** – when is it bad? Is there any consistent relationship to medication timing? How do you know when your medication is working/wearing off?
- **Tremor** – distinguish persistent tremor due to under medication from breakthrough tremor which occurs with excitement or anxiety during ‘on’ periods, as the latter in isolation does not warrant an increase in medication.
- **Sleeping and nocturia** – most patients with more than mild disease get up to pass urine at least once a night. Ask about bradykinesia and rigidity interfering with sleep, and remind them of the risk of falling at night.
- **Swallowing and constipation** – choking episodes are distressing and need intervention by speech and diet therapists. Many patients are unaware that constipation can impair drug absorption and cause nausea.
- **Work or hobbies** – get an idea of physical and social functioning – people who continue with their pre-morbid lifestyle, including exercise, are doing well. Watch out for withdrawal from activities due to depression, anxiety, disease stigma or physical issues.
- **Thinking or mood** – are there any problems?
- **Prescriptions** – does the patient need any prescriptions? This is a good time to ask about any medication adverse effects.
- **Examination** – much can be gained by simply watching the patient get up from the waiting room and walk into the office. Hand function can be quickly assessed with finger tapping or doing up buttons. There is no need to perform a detailed examination unless directed to it by a particular symptom.

Be prepared for the introspective patient who arrives with a carefully diarised list of problems, as well as those who insist everything is fine as they try not to fall off their chair with florid dyskinesia. Try and get the patient to focus on the symptoms that are causing the most disability or distress. If outstanding issues remain, they are best dealt with at another appointment

8. MANAGING ADVANCED PD

In the pre-levodopa era, Parkinson's disease progressed steadily to produce increasing disability and dependency. Levodopa treatment delays this substantially but does not halt the underlying pathology. After about five years of levodopa treatment, most patients have regressed to their pre-treatment levels of disability despite continuing with medication.

It is important (but not always easy) to distinguish between the symptoms of the advancing disease and the adverse effects of medication.

Movement Problems

The first four major manifestations of advanced Parkinson's disease—bradykinesia, rigidity, tremor and postural instability—result in various types of movement problems. Some areas of particular concern are discussed below.

Freezing attacks

Freezing refers to the patient's feet feeling stuck to the ground with an inability to move for seconds to minutes. This can occur when initiating walking, during walking (especially if distracted), walking through tight spaces such as doorways or when turning. Freezing attacks are increasingly common as the disease progresses.

Management

- If occurring during 'off' periods, try a higher levodopa dosage.
- 'On' period freezing can also occur, and is a major problem as it does not respond to medication.
- Many patients find behavioural techniques helpful in 'unfreezing'. These include whistling, clapping, side- or back-steps, visual cues or other external cues such as a tap on the shoulder.
- Specialised physiotherapy and neurological advice should be sought.
- Antiparkinsonian drugs may help. Subcutaneous apomorphine (Apomine™) can be used for freezing attacks and this requires a review at a specialist level.

Dystonias

Dystonias consist of cramp-like posturing of the limbs, often affecting the feet and calf muscles, and may be painful. They are related to the progression of the disease. Different types exist (off-period, peak-dose, end-of-dose, early morning) with different management strategies for each.

Management

- If other signs of under-treatment are present, increase the dose of levodopa.
- Slow release levodopa at bedtime can help morning dystonias.
- For stereotyped focal dystonia, botulinum toxin injections can be used to temporarily weaken the muscles involved and improve pain and limb function.

Tremor

Tremor worsens with anxiety and excitement. When this occurs during 'on' periods, it is termed breakthrough tremor, as opposed to that seen during 'off' periods or when a levodopa dose is wearing off.

Management

Management is similar to that of the other major manifestations, with the exception that beta blockers and benzodiazepines can help tremor without changing bradykinesia and rigidity. Neurosurgery is an option in selected patients where medication is ineffective. Breakthrough tremor is not an indication for increased medication, as even at toxic doses of levodopa complete tremor control is unlikely.

Speech problems

Bradykinesia affects the muscles of speech, and the problems present in various ways. The voice may become monotonous, slow, quiet and muffled, with distorted articulation. At times it may be difficult to initiate speech. Sometimes the rate can become so fast as to make the voice unintelligible.

Management

Early referral to speech therapy is indicated.

Falls

The risk of falling is high in advanced PD. Bradykinesia, postural instability, postural hypotension and sudden motor fluctuations can all contribute. Advanced age, cognitive impairment and length of disease are further risk factors.

Any PD patient with falls should have:

- postural hypotension excluded
- a home occupational therapy assessment (checking for bathroom design, loose rugs and dangerous steps)
- a careful review of his/her antiparkinsonian and other vasoactive drugs
- physiotherapy assessment to consider gait and balance training, strategies to manage freezing episodes and a walking aid.

Levodopa Problems

‘Wearing off’ effects

The patient finds that levodopa effects begin to fade or wear off before the next dose.

Management

- Give levodopa more frequently, possibly in smaller doses.
- Consider switching to Stalevo™. The addition of entacapone has been demonstrated to increase the half-life of levodopa by up to 85%.
- Add a dopamine agonist. Most patients will already be on a dopamine agonist, especially those with younger onset disease. Adding a dopamine agonist in the older patient can be rewarding but, as with most psychotropic drugs, the incidence of dose-limiting adverse effects is higher (nausea, postural hypotension, edema, drowsiness, confusion, hallucinations). Dyskinesias may worsen and require smaller levodopa doses.
- Substituting slow release levodopa (Sinemet™ CR or Madopar™ HBS) has not been shown to reduce ‘off’ time compared with standard immediate release preparations. These drugs can still be useful for night-time symptoms.
- If the patient is woken by symptoms of stiffness, pain or tremor, take slow release levodopa just before retiring. If on cabergoline, try taking the dose at night if not already doing so.
- If sleep initiation is difficult because of the wearing off of the last levodopa dose of the day, take a dose of standard or slow release levodopa an hour before retiring. The problems can be motor (tremor, stiffness) or non-motor (restlessness, malaise).

Delayed or poor quality ‘on’ response

If the patient is experiencing a delayed or poor quality ‘on’ response, make sure the drug isn’t taken with a large amount of dietary protein and is taken 30 to 60 minutes before meals (Figure 3). Individual levodopa doses can be taken dissolved to make it easier to swallow. Some patients also use this method to shorten the time it takes for a dose to work, as absorption is quicker.

Plasma levels after single oral dose of levodopa

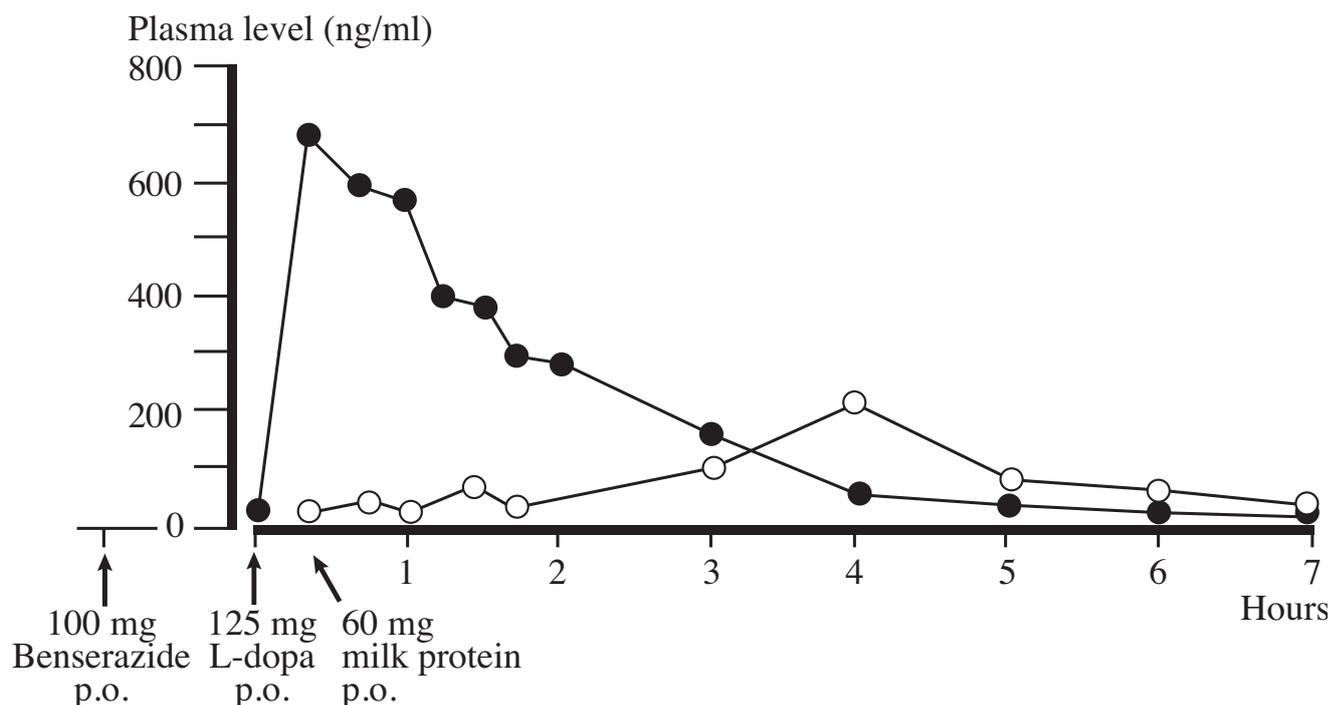


Figure 3. Plasma levels of levodopa with and without the equivalent of a glass of milk. It is easy to imagine the patient experiencing a poor quality 'on' response or even a dose failure in such a situation.

Fluctuations or 'on-off' attacks

Fluctuations in response to levodopa occur in almost 50% of patients. Instead of the usual rapid onset and four-hour duration of levodopa, unpredictable swings from normality to profound hypokinesia occur. The brain seems to become more sensitive to small changes in the plasma levodopa concentration.

If the levodopa effect is wearing off:

- ensure maximal absorption (take on empty stomach, treat constipation)
- give levodopa more frequently
- add a dopamine agonist (e.g. pramipexole, ropinirole, rotigotine).

Management

Once recognised, 'on-off' attacks should be managed with neurological advice. Many strategies have been developed, but in simple terms they all aim to keep dopaminergic stimulation above a certain threshold and as stable as possible. This can be achieved by changing dose strengths or timing of levodopa and dopamine-agonists, or prolonging the effect of levodopa with drugs like entacapone (Comtan™) or Stalevo™ (levodopa/carbidopa/entacapone).

Liquid levodopa

Levodopa does not come in a liquid presentation, but one can easily be made up. Its use is reserved for advanced PD where fine dose titration is required. The hourly dosing schedule is wearing on patients and carers and requires great motivation. There are those who find it manageable and obtain important benefits over standard preparations. Consider a trial when all other strategies have failed.

To prepare an oral levodopa solution, 1000 mg must be crushed and dissolved in water with 2 g of vitamin C (acts as a preservative). The mixture must be prepared each day and kept in a fridge or thermos as it is stable for only 24 hours. The effect of each dose lasts only for an hour or so.

Calculate the total daily dose of levodopa and give D/24 ml of the solution per hour.

NOTE: A bigger dose (e.g. 100 mg to 200 mg levodopa) needs to be taken at the start of the day to kick off the liquid regimen. Otherwise, the liquid dose may not be enough to get the patient to their turning on threshold.

Abnormal involuntary movements or dyskinesias

Almost all patients with advanced PD will have dyskinesias. They are more common in the young patient with a good early response to levodopa. To maintain mobility and independence one often needs to accept at least some dyskinesia, as long as it is not disabling. They are typically choreo-athetoid but may be myoclonic or dystonic. Peak dose dyskinesias occur in 'on' periods. They can be embarrassing and unpredictable. They may interfere with balance and represent a major impediment to quality of life.

For many patients this is one of the major management issues. There are a variety of responses among patients. Some find them tiring and irritating, while others appreciate the mobility in 'on' periods, even with dyskinesia, in contrast to the immobility of the 'off' periods.

Management

Although changing the amount and timing of levodopa dosing helps, neurologist input is recommended.

Levodopa Induced Dyskinesias (LIDs)

Dyskinesias are involuntary movements caused by high doses or long exposure to levodopa. In the early stages they tend to affect a single limb but can progress to affect all four limbs and the head, neck and trunk. The movements associated with dyskinesia bear a superficial resemblance to tremor. Look for the following points to identify dyskinesia:

- occurs only during the 'on' phase or the 'on-off' syndrome
- appears first in the side that the PD symptoms initially presented, then spreads to other limbs
- typically writhing/twisting/rocking movements but can be mistaken for tremor if rhythmic
- any shaking of dyskinetic origin feels different to the true PD tremor experienced during the 'off' phase. An insightful patient can learn to pick one from the other.

It is important to be able to distinguish dyskinesia from tremor. Tremor is a symptom of PD. Dyskinesia is a reaction to excessive dopaminergic stimulation in a dopamine-depleted brain, hence increasing the dose of levodopa (or dopamine agonist) will make dyskinesia worse.

Deep Brain Stimulation for Advanced PD

Deep brain stimulation (DBS) is now available in most Australian states and is considered routine surgery. It is rightly regarded as a major breakthrough in management, but it suits only a minority of patients with advanced PD, and has no place in the management of early or moderate PD. Long-term data is starting to appear, showing benefits on motor symptoms lasting at least five years, and quality of life at least two years. Further development is in progress, refining the technology and exploring new targets.

Background

Neurosurgery for PD is not a modern phenomenon, being performed as far back as the 1950s, the frontier time in neurology and neurosurgery when men like Penfield and Jasper were busy mapping the sensorimotor homunculus in awake patients as part of epilepsy surgery. In fact, Jasper was the first to perform single cell recordings from the basal ganglia of PD patients undergoing stereotactic surgery in 1964. Morbidity and mortality was high, but the fact that there was still demand for it highlights the desperate situation of patients at the time.

The discovery of levodopa suddenly made PD surgery irrelevant (or so people thought), as finally even severely disabling symptoms could be treated with pills. It took less than a decade for people to discover the limitations of the drug, and only two decades for the revival of neurosurgery in the early 1980s. By this time major advances in stereotaxy reduced complication rates to acceptable levels and enhanced targeting capabilities. Treatment consisted of the focal destruction of small brain volumes by heating the tip of a probe (known as 'lesioning'), the main two targets being the thalamus and globus pallidus. Many patients underwent successful life-changing surgery, but problems arose when it was discovered that bilateral lesions caused unacceptable effects such as severe dysarthria, dysphagia or cognitive dysfunction.

Fortunately, a breakthrough came in the late 1980s in the form of deep brain stimulation, a procedure that can safely be performed bilaterally. This was the result of a serendipitous discovery by a French group, who noted that when electrically stimulating a patient's thalamus to check for adverse effects prior to making a lesion, the patient's tremor was abolished. They devised a temporary setup using leads left in the brain connected to an external stimulator and found the effect was durable.

Work began to develop the procedure into what is now a widely practised and accepted form of management for advanced PD, with an estimated 40,000 patients worldwide having undergone DBS. Parallel improvements in understanding and modelling of basal ganglia dysfunction in PD allowed a third target, the subthalamic nucleus (STN), to be explored. STN DBS is now the most widely performed surgical procedure for PD.

Procedure

Surgery is performed while the patient is awake to allow an assessment of the response to test stimulation. This requires full cooperation and a certain amount of mental resolve to undergo surgery. Targeting is performed using a combination of MRI, CT, test stimulation and micro-electrode recording of cell firing patterns. After the brain lead is inserted and fixed in place, a general anaesthetic is given and the leads connected to a pulse generator which is implanted in the same way as a cardiac pacemaker. Post-operative programming via handheld telemetry takes place over subsequent months with a number of settings being adjusted to optimise the therapeutic effects and minimise adverse effects. Battery life is currently four to five years but technology is improving and rechargeable devices are also available.

Indications

Given that DBS improves motor function and quality of life when compared with best medical management, why is it not offered to all patients at any stage of the disease? There are many reasons, not least of which is the small (approximately 1%) risk of serious complications including intracerebral haemorrhage and hardware infection. Other reasons become evident when looking at the specific effects of different types of DBS.

- 1. Subthalamic nucleus (STN)** has a levodopa-like effect, improving all the cardinal symptoms by 40% to 70% in the 'off' state. It allows a 30% to 50% reduction in levodopa dosage, with resulting reduction in levodopa-induced dyskinesia. 'Off' symptoms and fluctuations are less noticeable as the stimulation provides round-the-clock cover. STN must be bilaterally implanted. It can cause or exacerbate cognitive impairment and mood disorders.
- 2. Globus Pallidus Interna (GPi)** directly suppresses levodopa-induced dyskinesias when in the medication 'on' state, and improves the severity of cardinal PD symptoms in the 'off' state by 30% to 40%. GPi can be performed unilaterally. Medication generally remains unchanged though, in some patients, doses can now be increased without fear of disabling dyskinesias, and others are able to take fewer or smaller doses. There is no effect on cognition or mood.
- 3. Ventralis intermedius of the thalamus** provides excellent tremor suppression (the other main indication is severe essential tremor) but has no effect on other PD symptoms. It is the least commonly performed procedure, reserved for those with severe tremor without major disability from other disease features, e.g. so-called tremor dominant PD. Ventralis intermedius of the thalamus can be performed unilaterally. Medication remains unchanged.

Adverse effects

Adverse effects can be stimulation related (e.g. unwanted stimulation of nearby structures such as the internal capsule causing facial contraction/tingling; dysarthria), hardware related (e.g. low risk of lead infection; fracture; device failure) or medication related (cognitive or mood symptoms due to excessive antiparkinsonian medication reduction).

There is an individual adverse effect profile for the three DBS sites which is beyond the scope of this summary, except to say that it does impact on the patient selection process.

Deep brain stimulation: the future

At the present time there does not appear to be any other therapy to supplant the role of deep brain stimulation (DBS), which in theory is a reversible treatment which can be removed when the next best thing arrives (e.g. stem cells, growth factors). A promising new target is being explored, the little known basal ganglia nucleus called the pedunculo-pontine nucleus which is involved in postural control and gait, and which may become an important treatment for the otherwise untreatable postural instability/gait disorder that arises in some patients.

Deep brain stimulation

Who decides which patient is suitable?

Movement disorders specialists with DBS experience

Inclusion criteria

- levodopa responsive symptoms
- when the patient is disabled by motor fluctuations (esp. ‘on-off’ phenomenon) and/or peak dose dyskinesias, despite best medical management
- severe drug-resistant tremor.

Exclusion Criteria

- alternative medical management (refer to movement disorder specialist clinic)
- dementia
- active psychiatric illness
- dominant non-levodopa responsive problems.

Relative exclusion criteria

Age (over 75; probably greater risk of haemorrhage), gross cerebral atrophy (accurate targeting is difficult due to intraoperative brain shift), cognitive impairment (risk of worsening), marked postural instability/gait disorder (unlikely to improve), co-morbidities that preclude surgery or negate any of the likely benefits of DBS.

About GPi or STN DBS

GPi or STN DBS do not have any impact on disease progression. They are by no means curative or neuroprotective.

GPi or STN DBS do not provide any improvement over the best effect of levodopa, i.e. the best ‘on’ from medication will be the same after surgery. It will, however, be more useful without disabling dyskinesias.

GPi or STN DBS do not improve major non-motor symptoms such as cognition, poor balance, pain and autonomic dysfunction.

Non-motor Problems

Postural hypotension

Always monitor postural hypotension in the patient with advanced PD.

Prevention

Check standing and lying blood pressure at each visit. Postural hypotension’s link with falls is significant. Make sure the home is safe.

Management

Treat when symptomatic.

- Review medications. If pre-existing treated hypertension is present, consider a reduction of the antihypertensives. Dopamine agonists and levodopa can compound the problem.
- Increase salt and water intake.
- Recommend compressive stockings.
- Where drug treatment is necessary, the options include domperidone / Motilium™ 10-20mg tds, fludrocortisone 100 to 400mcg daily or Midodrine (requires specialist prescription, and caution in those with a history of cardiovascular disease).

Oral and dental care

Oro-dental problems arise due to drooling, swallowing problems and other factors such as inability to care for teeth and dentures. Levodopa may cause 'burning tongue' and altered taste sensations. Dopamine agonists and anticholinergic drugs are implicated in the cause of dry mouth. The incidence of dental caries and dental plaque is increased as is oral candidiasis. A dental examination is recommended every six months and using an electric toothbrush may be helpful.

Dysphagia

Ask about choking spells with food or fluid. Check clinically (and radiologically, if concerned) for aspiration.

Management

- Recommend a soft diet, and advise patients to eat during levodopa 'on' times. More aggressive treatment involving the pro-kinetic agents may eventually be contemplated.
- Early referral to a speech pathologist or dietician may be of benefit.

Constipation

Constipation is common and distressing in Parkinson's disease, and is one of the leading causes of hospitalisation. Autonomic dysfunction, immobility, diet and medication may all contribute to decreased intestinal motility.

Management

- Prevention: Advise about diet (roughage and bran), fluid intake, exercise and stool-bulking agents. A dietician may assist. Warn patients of the consequences of severe constipation, which include nausea and delayed onset or failure of levodopa efficacy.
- Treatment: If preventive measures are unsuccessful, give patients a graded management plan to follow until they regain regular bowel activity, e.g. coloxyl ± senna/Osmotic agents (lactulose, sorbitol)/Microlax enema.

Urinary problems

The most common urinary symptom in PD is nocturia. This clearly increases the risk for night-time falls. Detrusor instability is not uncommon in moderate and advanced PD, and can manifest as urgency and frequency. The combination of urgency and poor mobility creates an additional challenge for patients.

History and examination/investigations

Men: screen for prostatism as per usual.

Women: note history of pelvic floor injury/surgery.

If complex, refer to urologist for consideration of further investigations including urodynamic flow studies.

Management

- Involve a community continence service where available. They are invaluable in performing assessments including mobile bladder scans, and can provide ongoing support and monitoring of treatment.
- Fluid restriction at night-time often helps.
- Toilet design and location is important, especially at night.
- Prevent constipation.
- If detrusor instability is suspected, a trial of a peripheral anticholinergic (e.g. propantheline 7.5 mg to 15 mg nocte) may be worthwhile. Continence aids may be required.

Nocturia increases the risk for falls in PD. Make sure the patient can reach the toilet or commode safely. Night-time levodopa can help.

Sexual problems

Impotence in men is common. Sexual problems can also arise from the physical slowness and tiredness of Parkinson's disease. It should always raise the question of depression.

Levodopa treatment may improve sexual functioning by reducing bradykinesia. Dopaminergic therapy can increase libido, producing hypersexuality in a minority of patients.

Management

- Consider the partner.
- Assess for depression.
- Exclude a drug cause:
 - Beta-adrenergic blockers are prime offenders
 - Some antihypertensives, thiazide diuretics, anxiolytics, cimetidine and digoxin also have the potential to cause problems.
- Otherwise treat as normal for impotence. PDE5 inhibitors agonists (e.g. Viagra™, Cialis™ and Levitra™) can be used.

Skin problems

Sweating is often a problem and may respond to levodopa. Many PD patients also complain of oily facial skin, seborrhoea and dandruff. The usual treatments work but Nizoral (ketoconazole) shampoo is effective and can be used for scalp and face. Hydrocortisone 1% can be used for facial seborrhea.

Neuropsychiatric Problems

Neuropsychiatric problems can be as troubling as the motor disabilities of PD. As in many chronic diseases, the problems may be related to the condition or to its treatment or may be unrelated to either.

Sleep problems

One needs to keep an open mind when considering causes of insomnia in PD, which may be related to restlessness, nightmares, nocturnal hallucinations, restless legs syndrome, dementia, depression or drug-induced dyskinesias. Excessive day-time sleepiness can be due to poor night-time sleep, but may also occur as part of the primary disease process or secondary to medication.

Insomnia

- Selegiline and amantadine appear to be the significant offenders of the excitatory drug effect, and may require dosage reduction and encouragement to take the tablets earlier in the day. Selegiline should not be taken after midday, as one of its metabolites is the stimulant metamphetamine.
- If the night is disturbed by choreiform movements, reduction of night-time levodopa will often help. Compulsive restlessness (akathisia) can be a problem in PD.
- Day-time medications often wear off by night-time, leading to trouble getting comfortable. Try patients on a bedtime dose of Sinemet™ CR, Madopar™ HBS or Stalevo™, or recommend they to take a dose of Sinemet™ or Madopar™ if they are woken by PD symptoms during the night.
- Restless legs syndrome (see page 12).

- Nightmares can often be induced by antiparkinsonian medication, and may be relieved by decreasing the night-time dose.
- Conditions other than PD: Anxiety, depression and dementia (sometimes including nocturnal hallucinations) should always be considered as significant causes of sleep problems, especially in the elderly.

Cognitive impairment

Long-term mental impairment may result from changes in frontal lobe cognitive processing, affecting aspects such as executive function. This causes difficulties in planning and initiating tasks that involve a sequence of activities such as getting ready to leave the house, or organising a grocery shopping trip. Apathy may also occur as part of this process. Drug-induced confusion can also occur, with anticholinergic drugs being the principal offenders.

Two Major Problems—Depression and Dementia

Depression

Depression is common and often difficult to diagnose in PD. Sleep disturbance, slow movement, blank facial expressions and cognitive impairment can be found in both conditions. It seems not to have the familial link found in idiopathic depression. **Diagnosis and treatment of depression is critical in PD, as it can present at any disease stage and impact on QOL more than the motor symptoms themselves.**

Risk factors

- Early onset (under 65 years). Females may be at greater risk.
- Those with bradykinesia and gait instability.

Characteristics

Depression in PD is different to the typical depression seen by the family doctor. Patients tend to be anxious, sad and pessimistic about the future, but generally have little guilt or self reproach. Although suicidal ideation is common, suicide itself is rare.

Note that facial masking may mimic a depressed affect. ‘On-off’ phases may affect mood significantly.

Management

- As with all depressions, attention to context, family and, in particular, the patient’s fears for the future form a fundamental part of treatment.
- Levodopa and the other antiparkinsonian drugs have no positive effect on mood.
- Tricyclic antidepressants are effective. Those with anticholinergic properties may help the motor symptoms. SSRIs are also used. ECT is reserved for medication-resistant severe depression and has the added benefit of improving motor symptoms for two to three months.

The SSRIs and SNRIs have potentially dangerous interactions with selegiline. Moclobemide interacts with levodopa.

Dementia

Dementia at diagnosis is rare, and when present should alert us to alternative diagnoses (DLBD, ‘Parkinsons Plus’ syndromes, coincident AD). However, 15%-20% of advanced PD patients have dementia, a poor prognostic feature. The nursing home patient with PD is a common general practice concern.

Risk factors

- Increasing age
 - Long disease duration
 - More severe disease
- } not seen
} in all studies

Pathology

High numbers of Lewy Bodies outside the substantia nigra are found in PD patients with dementia. The pathological changes are typically more subcortical than cortical, as in Alzheimer's and Diffuse Lewy Body disease, but involvement of the hippocampus and other cortical areas has been linked to hallucinations, cognitive impairment and dementia.

Characteristics of Parkinsonian dementia

- Memory loss is significant as is unusually slowed thinking. Levodopa may improve the bradyphrenia (slowed thought) that some PD patients experience during 'off' periods.
- Visual hallucinations are common in advanced PD. They are usually nocturnal and occasionally drug-related, but in general are a manifestation of the dementia associated with advanced PD. Some of the new antipsychotics (clozapine and risperidone) have been useful in their control.

Treatment issues

- Be careful that the drugs don't cause hallucinations or confusion in the deteriorating brain. Conservative use of levodopa is recommended. The patient will find it much harder to report any wearing off of the drugs or adverse effects from their use.
- Gait impairment and postural instability are more of an issue in the demented patient, so if these exist they should be treated.
- Referral to a memory clinic can be beneficial for a multi-disciplinary assessment and management approach.
- Treatment with anticholinesterase drugs (donepezil, rivastigmine or galantamine) can be beneficial, though as they increase brain levels of acetylcholine may in some cases worsen parkinsonism.

Claire is 78 and lives in a nursing home. She is confused and disorientated. Her GP discovered PD after she had been falling for a few months. Sinemet™ tds increased her independence and stability. She is more settled at night. The physiotherapist has helped her walking.

End Stage PD

Epidemiology

The mortality of the condition is nearly twice normal in the later stages.

Causes of death

The terminal stage of the disease is not so long-drawn out as it was a few decades ago. Many patients remain mobile enough to die from a fall and fracture or heart attack. Some die from prolonged immobility, while others have terminal dysphagia and weight loss, perhaps with aspiration pneumonia.

Symptom management

The patient may be on a variety of drugs, many of which cause confusion. These drugs can slowly be withdrawn and the minimum used to maintain patient comfort and mental awareness. Stemetil™, Maxolon™ and the phenothiazines should continue to be avoided. The benzodiazepines are useful for confusion or agitation.

9. WHO CAN HELP THE GP?

Specialist Neurologist

Neurologists have a vital role to play in PD. Early referral can confirm the diagnosis and help forge an ongoing relationship between patient, carers and medical staff. The complexities of the drug regimes in late PD make input from a neurologist or movement disorder clinic mandatory. Many are happy to discuss patients with GPs on the telephone. It can be frustrating for neurologists when other doctors:

- precipitate drug-induced parkinsonism from treatment of conditions such as dizziness in the elderly
- alter drug regimens in the complex PD patient.

Geriatricians

Geriatric units, which take a special interest in PD, exist in many states. With both inpatient and day hospital facilities, these are good places for the stabilisation of drug regimes, rehabilitation and ongoing management. Respite care, usually in community settings such as hostels or nursing homes, can be organised by geriatric unit staff. Aged Care Assessment Team (ACAT) reviews can be performed at the patient's home to assess the need for community support or placement. Parkinson's Associations can be useful sources of information on the location of these units.

PD Nurse Specialists

PD Nurse Specialists are community or hospital-based nurses who have a special interest and expertise in all aspects of PD, including drug and non-drug management. They perform important roles which include:

- education of patients, family, carers and nursing staff
- liaison with treating doctors
- community/home visits
- counselling and support.

Allied Health Professionals

There are few chronic conditions so reliant as Parkinson's on a knowledgeable, coordinated health team. State Parkinson's associations may be able to assist with contacts for therapists with expertise in the condition.

Physiotherapy is aimed at prolonging the patient's ability to remain independent, mobile and safe. Rigidity, posture and gait can all be helped by intensive, individually tailored physiotherapy. Freezing attacks can be helped by distraction techniques. Flexor muscle stretching and extensor strengthening help the flexed posture so common in established PD.

A good **occupational therapist** will do more than install shower rails and wall handles. They can assess the safety of the home and make structural changes to increase independence. Simple utensils can make eating less tedious. Furthermore, practical advice can significantly help slow and clumsy dressing (Velcro as clothes fasteners; using loose clothing like tracksuits) and bed mobility (satin sheets and/or pyjamas; bed rails). Vocational counselling can encourage the patient to take an interest in former hobbies, or to develop new skills.

Speech pathology can help the almost universal communication and swallowing difficulties experienced by people with PD. The Lee Silverman Voice Treatment is a technique which successfully combats the disabling speech disorder of PD and is provided by most speech therapy services. The initial therapy is intense but rewarding, and improvements in volume and clarity can be expected. Though benefits can last up to six months, patients should be reminded that to maintain these benefits they need to keep practising the exercises over the long term.

Anosmia is an early feature of PD. Its association with loss of taste makes eating, already slow, even more of a chore. Depression may decrease appetite and inactivity encourages demineralisation of bone. It is not surprising that patients with PD are at risk of malnutrition and weight loss.

Dietician input can be valuable in menu planning, the use of supplements and the management of constipation.

10. OTHER MANAGEMENT ISSUES

Counselling

Continuity of care is perhaps the greatest contribution that the GP makes to a chronic illness. The establishment of rapport in the doctor/patient relationship is important in order to:

- develop a clear plan of treatment with the patient (and partner/carer)
- address concerns of patient realistically without overemphasising optimistic or pessimistic outcomes
- provide information.

A double appointment may be useful shortly following diagnosis.

Continuing to Work

For younger patients, employment and financial stability may be of concern. Early retirement issues may arise due to increasing disability. This may be particularly difficult if the patient is relatively young and could have reasonably expected several years of working life ahead.

How can the GP help?

- Be more inclined to treat aggressively if the patient is working, and affected on the dominant hand.
- Consider early vocational rehabilitation.
- Discuss financial implications. Some patients and carers may be eligible for Social Security benefits.
- When the patient faces early retirement because of PD, be aware of the emotional impact of this change, and the potential for depression. Counselling can help.

General Practice Management Plans

A recent government initiative, the General Practice Management Plan (GPMP) is an attempt to recognise the importance of the GP's role in coordinating the management of patients with complex medical problems. A GPMP is drawn up, and the patient benefits from the holistic approach and interdisciplinary communication between GP, specialists and allied health staff.

Help for Carers

All who work with PD patients have a responsibility to listen to and care for the carer. Carers need to be acknowledged, offered respite and above all given clear information about the condition. The GP is in a unique position to offer this support. Naturally, it will be most needed at times of change such as stopping work, increasing dependency or moving to institutional care.

The federal government has designed and produced a free kit specifically for carers, 'Carer Support: Practical Information on Caring at Home'. Carers associations in each state are able to discuss individual needs and supply information. (Chapter 13. Self help and Information provides contacts for state and territory carer associations).

Continuing to Drive

As the population ages, GPs regularly need to assess the fitness of their elderly patients to drive. PD produces a set of extra dilemmas. The loss of a driving licence magnifies the loss of independence faced by all with PD.

What is the problem?

Dyskinesia and dystonia may interfere with the patient's reflexes and ability to initiate movement. 'On-off' fluctuations can be hazardous when controlling a vehicle. A study showed that patients with Parkinson's disease tended to drive slowly and avoid driving at night. Although patients with advanced PD are more likely to have accidents than age-matched controls, the greatest accident risk factor was cognitive impairment.

Risk factors

Risk factors for drivers with PD include:

- increasing bradykinesia
- substantial hand and foot coordination deficit
- significant cognitive impairment
- uncontrolled ‘on–off’ attacks and abnormal movements.

Guidelines

National guidelines on driving with PD do not exist. The question of when to give up driving is usually subjective and relates to the degree of disability and impairment. GPs concerned about the driving fitness of their patients can get advice from occupational health physicians at police departments. Schools of Occupational Therapy in some states conduct driving assessments.

Hospitalisation

Hospitalisation has hazards for the person with PD. The stress of surgery and acute illness leads to a potential increase in symptoms. Furthermore, doctors, nurses and allied health professionals who do not have regular contact with PD often lack a good understanding of the condition. As a result:

- finely tuned drug regimes and diets can be challenged by inflexible hospital routines
- the hour-to-hour variability of treated PD is potentially misunderstood
- commonly used medications can interact with antiparkinsonian drugs or significantly worsen symptoms.

When the Parkinsonian patient goes to hospital

- Ask the patient or family to notify their usual PD specialist.
- Give them a list of drug interactions (Appendix I).
- Suggest to hospital staff that the patient be allowed to self medicate with levodopa, if they are able.
- Warn the hospital staff about deterioration with surgery, the importance of regular drug regimes and diets and the hour-to-hour variability of treated PD.

General practitioners who do not have inpatients can help by stressing in referral letters the importance of regular drug doses. Photocopying the information sheet ‘Medications to be Given With Caution to People with Parkinson’s (for Health Professionals)’ (Appendix I) could be helpful to hospital staff.

Medic Alert Bracelet

People with Parkinson’s disease should obtain a Medic Alert bracelet. This assists in the emergency situation, especially where potentially interacting medication may be required. Forms are available from most pharmacies and GPs.

11. THE FUTURE

Sadly, despite much effort, there have been no breakthroughs in the search for ways to slow, stop or reverse the neurodegenerative process that underlies the inevitable progression one sees in PD patients. This has resulted in PD patients and their families being enticed by unproven and potentially dangerous therapies in the search for a ‘cure’. These therapies and procedures may be broadly grouped as low-risk (e.g. long term administration of putative neuroprotective/ neurorestorative biologic agents, low intensity magnetic field therapy) or high-risk (e.g. stromal stem-cell transplant). Regardless of the methods used and theories invoked, such therapies have failed the basic test of credibility for the medical profession by declining to report outcomes in peer-reviewed literature. While the centres offering such treatments may criticise aspects of the process used to validate the efficacy of their treatment, such criticisms cannot be taken seriously when patients are offered such unproven therapies, often procured in distant countries usually at great expense compared with standard treatment widely available in Australia.

Neuroprotection and Neurorestoration in Parkinson’s Disease

The following section outlines the current situation regarding research into novel strategies to slow or reverse PD. Readers are reminded that this section of the manual is the least likely to be up to date though it is our sincere hope that this will become the case before the next edition is published.

Neuroprotection

Numerous agents that have shown promise in animal or in vitro models of the disease have failed to show definitive slowing of disease progression. The most well-known and controversial of these are the MAO-B inhibitors, selegiline and rasagiline. These agents maintain dopamine levels in the brain by inhibiting its metabolism, but also have antioxidant and other effects. It has remained difficult to prove whether the improvement in motor function is simply due to higher dopamine levels rather than increased survival of nigral neurons.

New Drugs

Background

Though there have been advances in neuropharmacology in recent decades, for the large part this has involved discovering a bewildering array of substances that the CNS uses not only to send signals between cells (i.e. the classic ‘neurotransmitter’ function), but also to modulate activities on longer timescales, such as neural network plasticity and trophic activity.

Most PD drug development has been narrowly focused on the dopaminergic system, but there is increasing recognition that non-dopaminergic neurotransmitter networks become deranged in PD, contributing to non-motor and non-levodopa responsive symptom. Drugs such as growth factors have been used in an attempt to stimulate dopaminergic and non-dopaminergic function, neuronal connectivity, and neuronal regeneration, Studies showing abnormalities in adenosine, AMPA, serotonin and cannabinoid function have led to some success in treating experimental animal models of PD, but translation to efficacy in clinical trials has been disappointing.

The view that PD is simply a disease of the motor system caused by loss of a specific set of dopamine-producing cells, and would therefore be ‘cured’ by dopamine replacement, has long been discarded. The first evidence for this was the appearance of ‘motor fluctuations’ and LIDs in long-term LD treated patients in the 1970’s. It is now accepted that the primary problem in PD is not *just* dopamine deficiency due to loss of dopamine-producing SN cells, but that over time, non-dopaminergic neural networks become affected, as evidenced by the emergence of ‘LD resistant symptoms’ and non-motor symptoms. Future drug development will need to address these issues.

There are no truly novel drugs for PD planned for release in the near future. What is badly needed is a drug which improves ‘off’ symptoms without causing dyskinesias, or an effective anti-dyskinetic drug that does not impair dopaminergic function. Such agents are currently in the early phases of development.

Most ‘new’ drugs in the past decade or so fall into two categories:

- ‘New versions’ of old drugs:
 - ‘Non-ergot’ dopamine agonists, developed in the 1990’s in an attempt to improve on drugs such as bromocriptine and cabergoline
 - Rasagiline, the ‘new selegiline’, which has failed to conclusively demonstrate a neuroprotective effect in large carefully designed trials.
 - Stalevo, simply sinemet and comtan combined in a single tablet.
- Novel delivery systems:
 - Duodopa™, an intraduodenal infusion of concentrated levodopa/carbidopa gel via an enterostomy tube
 - Rotigotine/Neupro™, a transdermal ‘patch’ formulation of a non-ergot dopamine agonist therapy
 - continuous subcutaneous apomorphine infusion using a miniaturised external pump.

Foetal Brain Implant Surgery

Implantation of embryonic neural tissue has been performed in over 300 patients. Open trials showed a clinically significant improvement in symptoms, a reduction in medication and a benefit lasting years in some cases. Only one trial used sham surgery as a control, showing foetal cell transplant provided a definite but modest benefit over the placebo effect. An unforeseen and alarming situation arose in some patients who developed runaway dyskinesias. These involuntary movements were in some cases severe and persisted even off medication, presenting a whole new management problem. Due to this, as well as issues of ethics and limited supply, the treatment is unlikely to be further developed. Also, the dose is difficult to standardise, and only 5% to 20% of transplanted neurons survive.

Stem Cell Therapy

Stem cell therapy is a highly misunderstood and controversial area of medical research. It does hold promise for PD sufferers, but it is hard to predict when any meaningful therapeutic intervention will appear. Issues of embryonic vs. adult stem cell use will be largely resolved by the development of tissue banks derived from the patient’s own stem cells. One new technique involves a simple endoscopic nasal biopsy to obtain olfactory neural tissue which can be grown into various cell lines including dopaminergic neurons. Regardless of the source of stem cells, even if a stable functional cell line is derived, issues of where and how to deliver them and how to stimulate physiological connectivity and function will become the next challenge.

Neural Growth Factors and Cell-based Implants

A trial of intrastriatal Glial-derived neurotrophic factor infusion which initially showed promise has failed a randomised controlled trial, but other agents are likely to be studied in future. Spheramine™, a preparation of dopamine-producing cells grown on ‘microsphere’ support medium and injected into the striatum, is currently in the advanced stages of the extended clinical trial process. Whether or not these types of agents will provide long-term symptom control or neuroprotective effects remains to be seen.

12. DRUGS

Levodopa

Levodopa revolutionised the treatment of PD following its introduction in the 1960s. If a patient shows no response to levodopa, the diagnosis should be reconsidered.

Realistic treatment goals should be discussed with the patient when medication is commenced. The doctor's aim is to get the patient as mobile and functional as possible while minimising adverse effects.

Actions

The effects of levodopa are related to the primary deficiency of dopamine in the basal ganglia of patients with PD. Several other facts are important:

- Dopamine does not cross the blood–brain barrier.
- Levodopa is converted in the brain to dopamine by dopa-decarboxylase (DDC).
- Other sources of DDC are found in the gut and liver.

If dopamine is given orally, it can't gain access to the brain. If given in the form of levodopa, it is broken down peripherally and only 1% reaches the brain. The problem was resolved by giving the levodopa with a dopa-decarboxylase inhibitor (DDCI).

Dopa-decarboxylase inhibition

- Increases the amount of levodopa available to the brain
- Decreases the nausea and vomiting caused by excess peripheral dopamine
- The first DDCI was carbidopa followed closely by benserazide. Neither have toxic or therapeutic effects in the normal therapeutic range. They don't cross the blood-brain barrier
- Carbidopa + levodopa is Sinemet™, Sinacarb and Kinson
- Benserazide + levodopa is Madopar™
- Carbidopa, entacapone + levodopa is Stalevo™

Indications

Patients with functional impairment from PD. Chapter 6 Managing Early PD has a detailed discussion.

Administration

The drug can be taken after food to minimise risks of nausea or vomiting, though this is not a problem for many people. If there are problems with delayed or poor 'on' responses or motor fluctuations, take 30 minutes before or 60 minutes after food (especially protein) as this maximises GI absorption.

Preparations

All levodopa preparations come with a DDCI, and this is denoted by the number after the slash on the label. This often causes confusion, e.g. Madopar™ 200/50 may be written as Madopar™ 250, leaving one wondering if the prescriber means 200 mg or 250 mg.

Levodopa/carbidopa (Sinemet™, meaning literally ‘without emesis’)

Sinemet™ M	Levodopa 100 mg/carbidopa 10 mg
Sinemet™t100/25	Levodopa 100 mg/carbidopa 25 mg
Sinemet™	Levodopa 250 mg/carbidopa 25 mg
Sinemet™ CR#	Levodopa 200 mg/carbidopa 50 mg controlled release

Levodopa/benserazide (Madopar™)

Madopar™ Q	Levodopa 50mg/benserazide 12.5 mg
Madopar™ M	Levodopa 100mg/benserazide 25 mg
Madopar™	Levodopa 200mg/benserazide 50 mg
Madopar™ HBS#	Levodopa 100 mg/benserazide 25 mg controlled release

Levodopa/carbidopa/entacapone

Stalevo 50™ 75mg	Levodopa 50 mg + carbidopa 12.5 mg + entacapone 200 mg
Stalevo 100™ 125mg	Levodopa 100 mg + carbidopa 25 mg + entacapone 200 mg
Stalevo 150™ 200mg	Levodopa 150 mg + carbidopa 37.5 mg + entacapone 200 mg

Slow release levodopa

Levodopa pharmacokinetics

Onset 20 to 60 minutes
Duration 1 to 4 hours

Note These are simply plasma levels, and the numbers need to be taken in the context of the disease stage. Patients with mild PD may not notice an ‘on’ response from each dose of medication, or one dose may seem to last several hours. This is because of the patient’s preserved endogenous dopamine production. The advanced patient has little remaining endogenous dopamine production and is highly sensitive to plasma levodopa changes.

Slow release levodopa pharmacokinetics

Onset 1 to 2 hours
Duration 4 to 6 hours
Bioavailability approximately 75% of standard levodopa preparations

These formulations were designed to smooth out plasma levels of levodopa by embedding the drug in a matrix which slows uptake across the gut wall. While this occurs in controlled conditions, in reality this makes the absorption even more erratic. As the drug spends longer in the gut it is more prone to interference by ingested protein and other factors such as gut motility. Their use in reducing ‘off’ periods in patients with motor fluctuations has fallen out of favour as trials have shown no difference to standard levodopa. They are still useful for troubling nocturnal symptoms.

Pregnancy B3

Contraindications

Patients on non-selective monoamine oxidase inhibitors should stop this medication two weeks before levodopa is commenced. Take care with selective monoamine oxidase inhibitors (e.g.moclobemide). They will require a decreased dose of levodopa. Major interactions also occur with the major tranquillisers and antihistamines.

Dosage

Starting dose of levodopa

Most people are started on 50 mg to 100 mg tds of levodopa. The dose is titrated upwards until functional improvement or symptom relief is obtained. Some patients with mild or early PD respond to single doses of the drug. It is worth waiting at least a week before deciding whether a regimen is successful or not, as the drug effects take some time to even out.

Initial Response

Levodopa has its most dramatic effect on bradykinesia. Tremor shows less dramatic but substantial improvement. Rigidity, pain and stiffness also improve. The patient moves more quickly and freely. Fine motor tasks such as doing up buttons and shoelaces once again become semi-automatic. Posture improves and arm swinging may return.

Maintenance dose

It is rare for a patient's dose of levodopa to remain stable over long periods of time. Regular follow-up and reassessment is important. A four or five times daily dose regimen may eventually be necessary (Figure 4).

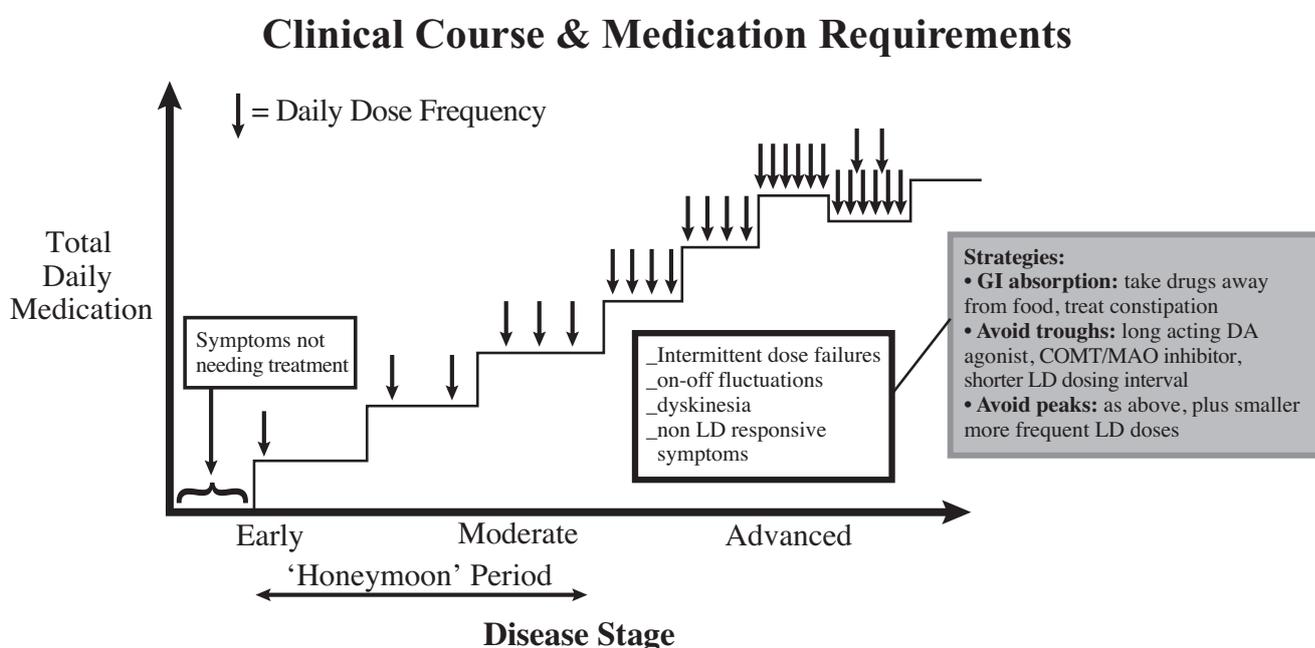


Figure 4 shows typical changes in medication over the clinical course of the disease. Initially, the patient may do well on a daily dose of dopamine agonist. Eventually, the patient will require the introduction of levodopa in larger and more frequent doses to maintain motor function and treat other symptoms. The so-called honeymoon period ends when the motor fluctuations and dyskinesias of advanced PD start to impact on the patient's life. The total daily dose may even need to be cut when dyskinesias cause disability, at the cost of increasing the chance of significant 'off' symptoms.

Adverse effects

Nausea and vomiting

- Start with a low dose.
- Suggest the patient take medication with meals or a light snack, e.g. crackers and juice.
- Domperidone / Motilium™ 10-20mg tds as an anti-emetic will help. **Do not use Maxolon™ or Stemetil™** as they will worsen the parkinsonism.
- Increase the amount of decarboxylase inhibition, e.g. change Sinemet™ M (100/10) tds to Sinemet™ 100/25 tds (Chapter 12 Drugs).

Postural hypotension

Postural hypotension should be anticipated, and checked with standing and lying blood pressures. Consider reducing antihypertensives.

Monitoring the response to levodopa

Realistic treatment goals should be discussed with the patient when medication is commenced. The doctor's aim is to get the patient as mobile and functional as possible, ideally without adverse effects

No response

The patient who does not respond to levodopa probably does not have PD, but instead one of the atypical parkinsonian syndromes. Refer back to diagnosing physician.

The patient who responds partially

Refer back to diagnosing physician, who may suggest:

- increasing the levodopa slowly up to 250 mg per dose (one tablet of Sinemet™ 250/25 or 1 + ¼ Madopar™ 200/50 tablet), which is considered the maximally effective dose beyond which a further increase will only result in more adverse effects without added motor benefits
- adding a dopamine agonist (e.g. pramipexole, ropinirole, rotigotine)
- when the response wears off
- add a dopamine agonist
- add a COMT inhibitor (entacapone/Comtan™), or consider switching to Stalevo™(levodopa/carbidopa/entacapone)
- give levodopa more frequently.

Synthetic Dopamine Agonists

The most commonly used drugs in this class are known as 'non-ergot' dopamine agonists (ropinirole/Repreve™, pramipexole/Sifrol™, rotigotine/Neupro™, apomorphine/Apomine™). In reference to the older 'ergot-derived' compounds, (Cabergoline/Cabaser™, bromocriptine/Parlodel™/ Krypton™), are still available but rarely used now due to risk of irreversible cardiac valve, lung and retroperitoneal fibrosis, which does not occur with non-ergot drugs.

Synthetic Dopamine Agonists antiparkinsonian effects are less potent than levodopa (except for apomorphine, which requires subcutaneous injection and specialist input). Adverse effects are more common, especially in the elderly. If treatment with dopamine agonist monotherapy is maintained, the development of dyskinesias and motor fluctuations is delayed by one to two years compared to levodopa-treated patients. This comes at the expense of slightly worse motor benefit, but is a reasonable trade off in younger patients in whom disease duration is longer and motor complications more problematic.

Actions

Synthetic dopamine agonists directly stimulate the post synaptic dopamine receptors in the striatum, the area to which the substantia nigra neurones project, as opposed to levodopa which is released pre-synaptically by remaining nigral neurones. In practical terms their effect is similar to levodopa.

Indications

Monotherapy in early disease, especially younger patients where initiation with levodopa is associated with an earlier onset of motor fluctuations.

As an adjunct to levodopa therapy at any disease stage. May allow reduction in levodopa dosage or smooth out motor fluctuations. Despite many trials attempting to show a disease-modifying or neuroprotective effect there is no evidence to support this.

Administration

For reasons of tolerability and to allow careful monitoring for adverse effects, dopamine agonists are commenced at low dose and gradually titrated up to an effective dose. This may take several weeks, and the patient should be advised that the goal is to introduce the drug as gently as possible. Otherwise, an important drug in their management regimen may be prematurely discarded due to inappropriate dose escalation. While standard recommendations exist, the dose increments may be tailored to the patients age and comorbidities.

The older agents have been largely superseded by Sifrol ERTM (pramipexole extended release) a once-daily drug with a long half-life. You may come across some patients on older regimens, as these have suited them and there is no need or desire to change treatment on either the patient or doctors' part. For example, although patients are often switched to extended-release pramipexole from cabergoline (approximately equivalent in mg dosages) due to concerns regarding fibrotic complications, some patients do badly when switched to newer non-ergot compounds and choose to remain on cabergoline and thus require careful monitoring for serious, albeit rare, adverse effects by their physician.

Dopamine agonist drugs available in Australia

- Pramipexole / Sifrol™: Immediate-release - 0.125mg, 0.25mg, 1mg; Extended Release - 0.375mg, 0.75mg, 1.5mg, 3mg, 4.5mg (available on PBS Restricted Benefit for PD as monotherapy or adjunctive therapy with levodopa; also available on PBS Restricted Benefit for severe Restless Legs Syndrome).
- Ropinirole / Repreve™: 0.25, 0.5, 2mg tabs (TGA registered for Restless Legs Syndrome only).
- Rotigotine / Neupro™ transdermal patch: 2mg/24h, 4mg/24h, 6mg/24h, 8mg/24h; (TGA registered for PD as monotherapy or in combination with levodopa and severe Restless Legs Syndrome).
- Cabergoline / Cabaser™: 0.5, 1, 2 mg tabs (less commonly used, available on PBS Restricted Benefit for PD).
- Bromocriptine / Parlodel™: 2.5 mg tab: 5, 10 mg caps (rarely used, available on PBS Restricted Benefit for PD).

Dosage

Initiation and dose escalation information should be clearly specified by the treating physician, however the following schedules usually suit most patients. If taking levodopa, the dose may need to be reduced. The aim, as with levodopa, is to titrate the dose to maximum therapeutic effect.

- Pramipexole Immediate-release (Sifrol™) – Week 1: 0.125mg tds; Week 2: 0.25mg tds; Week 3: 0.5mg tds; Week 4: 0.75mg tds; Week 5: 1mg tds; Week 6: 1.25mg tds; Week 7: 1.5mg tds (max dose). If switching from immediate to extended release the same dosage will suffice for most patients, though in some cases a lower or higher dose may be needed.
- Pramipexole Extended-release (Sifrol ER™), single daily dose – Week 1: 0.375mg ; Week 2: 0.75mg tds; Week 3: 1.5mg tds; Week 4: 2.25mg; Week 5: 3mg; Week 6: 3.75mg; Week 7: 4.5mg (max dose).
- Rotigotine (Neupro™), single daily dose – early stage PD commence at 2mg/24h and titrate at weekly intervals by 2mg/24h to therapeutic effect (maximum 8mg/24h); advanced PD commence at 4mg/24h and titrate at weekly intervals by 2mg/24h to therapeutic effect (maximum 16mg/24h).
- Cabergoline (Cabaser™), single daily dose – commence 0.5 to 1mg, increase by 0.5 to 1 mg increments at 1-2 week intervals. Target dose is 2-3mg. Previously doses up to 6mg were used before it was recognised that the fibrotic adverse effects are related to dose and duration of use.

With long-acting dopamine agonists, nocte dosing generally minimises the chance of patients noticing adverse effects, and may help with bed mobility due to the slight peak in plasma levels.

Combination with levodopa

Combined treatment with levodopa and a dopamine agonist requires very careful adjustment if optimal results are to be obtained. Careful note of the timing, response, adverse effects and ingestion of medication is necessary.

Adverse effects

Compared to levodopa, more patients are unable to tolerate synthetic agonists in a dose adequate to achieve a therapeutic effect. The most common adverse effect is nausea, while postural hypotension is a significant risk in the elderly. Ankle swelling is common but not usually a reason to stop the drug.

Confusional states (ranging from disturbing dreams to hallucinations and frank psychosis) are perhaps the most serious complications. These appear to be idiosyncratic and are more likely in the elderly. The mental state of the patient may recover only slowly after withdrawing the drug.

‘Sleep attacks’, episodes of sudden onset of sleep without warning can occur, and effect safety during operation of machinery and while driving.

Compulsive behaviours may emerge or become exacerbated e.g. pathological gambling, hypersexuality, excessive spending during treatment.

The older ergot-derived dopamine agonists have been largely withdrawn from use, due to the rare occurrence of pulmonary, heart valve or retroperitoneal fibrosis. Although this usually resolves when the drug is ceased, some patients developed severe irreversible complications such as valvular heart disease requiring cardiac surgery. These are now only used in patients who idiosyncratically benefit from the specific drug with regular surveillance of cardiac and lung function.

Pregnancy

Cabergoline	B1
Bromocriptine	A
Pramipexole	B3
Ropinirole	B3
Rotigotine	Unlisted

Contraindications

Known hypersensitivity to ergot compounds.

COMT (catechol-O-methyl transferase) Inhibitors

The COMT class of drugs (catechol-O-methyl transferase) inhibits another major enzyme pathway involved in dopamine metabolism, thus prolonging the effect of levodopa. They have no symptomatic effect of their own. They have become a widely used and useful adjunct to levodopa treatment. Tolcapone was the first such drug to be released, but has been withdrawn in Australia due to the occurrence of severe idiosyncratic hepatotoxicity. Entacapone is now the only COMT inhibitor in use, either alone as Comtan™ or in a combination pill called Stalevo™ (levodopa/carbidopa/ entacapone).

Actions

When taken with a levodopa dose, the levodopa plasma concentration area under the curve is increased by 50%. Time to peak concentration and maximum concentration are not affected, which theoretically should not result in an increase in dyskinesias. However, in clinical use an increase in dyskinesias is seen and a levodopa dose reduction of up to 25% may be necessary. When taken with each levodopa dose a greater amount of time is spent in the ‘on’ state, equating to about an extra hour of ‘on’ time a day in patients experiencing wearing off.

Indications

Add to levodopa in patients experiencing ‘wearing off’ of the levodopa response, which is a return of their typical PD symptoms prior to taking the next levodopa dose. In patients with motor fluctuations and dyskinesias, the smoother levodopa plasma concentration profile results in better symptom control. Its use in early PD is not yet established. Trials are under way to assess whether early treatment with such drug regimens can delay the onset of motor fluctuations in a similar manner to dopamine agonists.

Administration/Dosage

Patients are commenced on one tablet of entacapone taken with each dose of levodopa. If already on a stable levodopa dose this can be substituted with one of the Stalevo™ formulations. A maximum of ten doses/day is recommended.

Comtan™ (entacapone)	200 mg tablets; cannot be divided
Stalevo™ (levodopa/carbidopa/entacapone)	preparations containing 50, 100 or 150 mg of levodopa available

Adverse effects

Entacapone potentiates all the adverse effects of levodopa. If patients are already experiencing peak dose dyskinesias, a review two to three weeks after drug commencement is recommended to see if a levodopa dose reduction is required.

Diarrhoea can occur and may be severe enough to warrant withdrawal of the drug. A metabolite of the drug is excreted in the urine, giving it a deep red colour which can alarm patients if not warned of this harmless effect.

Pregnancy B3

Contraindications

Known hypersensitivity to the drug.

Non-selective MAO inhibitor use within 14 days.

Apomorphine

Apomorphine (Movapo®) has been known to be beneficial in Parkinson’s disease for many years. It has primarily been used as a rescue therapy of severe, unpredictable ‘offs’ in the form of intermittent subcutaneous injections. More recently, it has been used as a continuous subcutaneous infusion to manage selected patients who are having difficulties controlling their PD with oral medications.

Actions

Apomorphine is a dopamine agonist which acts by stimulation of the post-synaptic dopamine receptors. Apomorphine relieves all the major symptoms of PD, and is the only dopamine agonist that does so as well as levodopa. With continuous subcutaneous infusion (via a miniaturised pump) it can be highly effective at treating off-period fluctuations, even in those with significant dyskinesia, where these disabling involuntary movements can subside over a period of months.

Indications

Apomorphine is indicated for the management of patients who are suffering motor fluctuations, particularly difficult to control and unpredictable ‘off’ periods. While its use in patients with dyskinesia requires careful monitoring, such patients may experience a gradual reduction in dyskinesia severity with continued treatment, presumably as a result of a partial reversal of the abnormal brain plasticity that underlies this state.

Administration

Apomorphine should be administered under specialist medical supervision. It is poorly absorbed from the gastrointestinal tract and is therefore administered subcutaneously either as single injections (usually using a 'penject' syringe) or via an infusion pump. Onset of action occurs within five to fifteen minutes of an injection and duration of action is approximately one to two hours. Sublingual administration is also possible and special preparations are available for administration via this route.

Adverse effects

Nausea and vomiting are severe if patients are not pre-treated and maintained on the peripheral dopamine antagonist domperidone /Motilium TM(10-20 mg tds). Otherwise its adverse effect profile is similar to other dopamine agonists. Cellulitis may accompany repeated subcutaneous injections. Injection sites should therefore be varied and used in rotation, and local ultrasound treatment is used to break down troublesome nodules.

Contraindications

Morphine allergy.

Concomitant use of drugs of the 5HT₃ antagonist class e.g. ondansetron is contraindicated.

Pregnancy B3

Amantadine (Symmetrel™)

Amantadine was introduced as an anti-viral agent and noted fortuitously to have anti-parkinsonian properties. Generally safe, it is useful in the treatment of the mild case. Major drawbacks are its weak action and the short duration of its efficacy.

Actions

A glutamate antagonist, its mode of action in PD is uncertain but probably relates to an ability to increase dopamine release.

Indications

The young patient with mild symptoms who is yet to need levodopa.

Administration

Most younger patients tolerate amantadine very well. Response to amantadine is usually noticeable within one week. Benefits then usually decline. In many cases the improvement has been lost within three to six months. In some patients benefit may be maintained substantially longer.

Dosage

Start at 100 mg per day for one week, then increase to 100 mg bd. Target dose is 200 to 300 mg daily, higher doses are of no benefit.

Adverse effects

These are common in the elderly and include restlessness, confusion, hallucinations and livedo reticularis (a mottled lower limb appearance). Dependent oedema may be exacerbated and care should be taken in those with congestive cardiac failure.

Contraindications

Care should be taken in those with narrow angle glaucoma or prostatism.

Pregnancy B3

Anticholinergics

This group of drugs was introduced in the 1940s when they superseded the belladonna alkaloids in the treatment of parkinsonism. Although useful in relieving tremor in the young patient early in the disease, they cause significant problems in the elderly.

Actions

Early in the development of physical symptoms from Parkinson's disease, there is an increase in cholinergic activity. The action of anticholinergic drugs is to diminish this activity and improve the chemical imbalance between dopamine and acetylcholine.

Indications

Most younger patients with mild early symptoms. Although traditionally said to be most effective in relieving tremor, they can also be mildly effective against bradykinesia and rigidity, and have the added benefit of reducing dribbling of saliva. Given at night they can improve the poor sleep often associated with PD.

Administration

Generally start with a low dose once or twice day. Maintenance doses need to be individualised.

Adverse effects

Common amongst all anticholinergics, particularly when dosages are escalated too quickly. Tolerance to therapeutic dosages is improved by slow titration. Nausea and postural hypotension are common problems. Dry mouth, urinary outflow obstruction, and constipation and blurring of near vision also occur but these symptoms decrease with continued use. Neuropsychiatric adverse effects are potentially debilitating in the elderly, in whom these drugs are best avoided or withdrawn if such symptoms appear.

Contraindications

Anticholinergics are contraindicated in narrow angle glaucoma, prostatism and patients with a history of mental confusion or dementia.

Pregnancy

Benzhexol/Artane™ B1

Orphenadrine/Disipal™, Benztropine/Cogentin™ B2

Anticholinergic drugs

Benzhexol (Artane™) 2 mg, 5 mg tabs

Orphenadrine (Disipal™) 50 mg tab

Benztropine (Cogentin™) 0.5 mg, 2 mg tabs

Selegiline

Selegiline (Eldepryl™, Deprenyl™) acts centrally to inhibit dopamine metabolism, and has a mild symptomatic effect in PD. It also supplements the effects of levodopa, but the effect is subtle and COMT inhibitors are much more effective in this regard.

Actions

Selegiline is a selective inhibitor of monoamine oxidase subtype B (MAO), one of the major enzymes necessary for the breakdown of dopamine. Its symptomatic effect is well established, but its potential neuroprotective effects are less clear, with conflicting results from large studies. It may prevent the production of antioxidants associated with the increased turnover of dopamine, and can block the action of MPTP-induced parkinsonism in animal models. There is ongoing research attempting to establish whether rasagiline, a second generation MAOI-B inhibitor, prevents neurodegeneration in Parkinson's disease. While these drugs delay the need for levodopa, it is unclear whether this is due to the symptomatic effect rather than enhanced survival of dopaminergic neurons.

Indications

In the later stages of Parkinson's disease to reduce 'off' time. The dose of Sinemet™ or Madopar™ can usually be reduced by about 20% to 25% when selegiline is added.

Administration

Selegiline has a mild alerting effect and should not be given after the middle of the day due to its effect on sleep.

Dosage

Starting dose

Commence at 5 mg bd with food. Its alerting effects mean the last dose should be taken no later than 1 pm.

Maintenance dose

5-10mg bd.

Adverse effects

Rarely severe, but may include nausea, dizziness and insomnia. Confusion has been reported.

Contraindications

Pethidine (see Appendix 1, 'Medications to be used with caution for people with PD')

Pregnancy B2

Other medications used in Parkinson's Disease

Domperidone

Domperidone (Motilium™) is a dopamine agonist which does not cross the blood-brain barrier and therefore does not exacerbate PD symptoms (unlike the contraindicated antiemetics metoclopramide / Maxalon™ and prochlorperazine / Stemetil™). It acts on the chemoreceptor trigger zone to block the emetic effects of levodopa and dopamine agonists. It is also effective for treatment of gastroparesis. It is well tolerated, although it does cause elevation of prolactin secretion by the hypothalamus, usually without clinical sequelae.

Propranolol

When postural tremor is severe, it may respond to treatment with beta-blocking drugs such as propranolol, commonly used in essential tremor. The effect is seldom dramatic but may increase the improvement in tremor achieved by levodopa.

13. SELF HELP AND INFORMATION

It is helpful to have leaflets for patients to take away which answer some of the questions about the illness.

Each patient should carry the information brochure, 'Medications to be used with caution for people with Parkinson's Disease' (copy attached as Appendix 1).

Websites have good information for the computer literate patient and GP. See page 54 for a list of recommended websites.

Parkinson's Associations provide a range of information for the person with PD, including information packs and special seminars for newly diagnosed patients and their families or friends. State and Territory Associations are listed below.

Parkinson's Organisation

The national body, Parkinson's Australia, serves as an umbrella organisation for the State Organisations.

GPs should contact the office of their local Parkinson's organisation (see contact details below) for patient referral and in order to obtain access to the wide range of services provided.

Under the auspices of Parkinson's Australia, a national multi-disciplinary conference on Parkinson's disease is held biennially.

Services provided by state Parkinson's organisations

- Support and information by phone and in person, and referral to other resources, such as respite care, where appropriate.
- Written and taped information on PD for loan or sale.
- Regular newsletters.
- Educational seminars with expert speakers, including special seminars for the newly diagnosed.
- Network of support groups for people with Parkinson's and their partners/carers.
- Support for local researchers.
- Educational talks on PD to health professionals and community groups.
- Some organisations offer counselling or Parkinson's Nurse Specialist services.

Contact details for Parkinson's organisations

Australian Capital Territory
Parkinson's ACT Inc
PO Box 717
MAWSON ACT 2607
Phone (02) 6290 1984
Fax (02) 6286 4475
Email parkinsons@shout.org.au
Website www.parkinsonsact.org.au

New South Wales
Parkinson's NSW Inc
PO Box 71
NORTH RYDE NSW 1670
Phone (02) 8051 1900
Fax (02) 8051 1999
Email pnswn@parkinsonsnsw.org.au
Website www.parkinsonsnsw.org.au

Queensland
Parkinson's Queensland Inc
PO Box 1684
SPRINGWOOD QLD 4127
Phone (07) 3209 1588
Fax (07) 3209 1566
Email pqi@parkinsonsqld.org.au
Website www.parkinsonsqld.org.au

South Australia
Parkinson's SA Inc
PO Box 466
UNLEY SA 5061
Phone (08) 8357 8909
Fax (08) 8357 8876
Email info@parkinsonssa.org.au
Website www.parkinsonssa.org.au

Tasmania
Parkinson's Tasmania Inc
PO Box 608
KINGSTON TAS 7051
Phone (03) 6229 2509
Email pdomeney@netspace.net.au
Website www.parkinsons.org.au

Victoria
Parkinson's Victoria Inc
Po Box 239
SURREY HILLS VIC 3127
Phone (03) 8809 0400
Email info@parkinsons-vic.org.au
Website www.parkinsonsvic.org.au

Western Australia
Parkinson's Western Australia Inc
Suite B, The Niche
11 Aberdare Road
NEDLANDS WA 6009
Phone (08) 6457 7373
Fax (08) 6457 7374
Email info@parkinsonswa.org.au
Website www.parkinsonswa.org.au

Northern Territory
Please contact Parkinson's Western Australia Inc.

National Office
Parkinson's Australia Inc
PO Box 108
DEAKIN WEST ACT 2600
Phone 0407 703 328
Email info@parkinsonsaustralia.org.au
Website www.parkinsons.org.au

Carers Australia National Free Call number 1800 242 636

Internet Sites

World Parkinson's Association

www.wpda.org

Parkinson's Australia

www.parkinsons.org.au

Parkinson's New Zealand

www.parkinsons.org.nz

European Parkinson's Association

www.epda.eu.com

National Parkinson Foundation USA

www.parkinson.org

The Movement Disorder Society

www.movementdisorders.org

Michael J. Fox Foundation

www.michaeljfox.org

Parkinson's UK

www.parkinsons.org.uk

Australian Brain Foundation

www.brainfoundation.org.au

Worldwide Education & Awareness for Movement Disorders

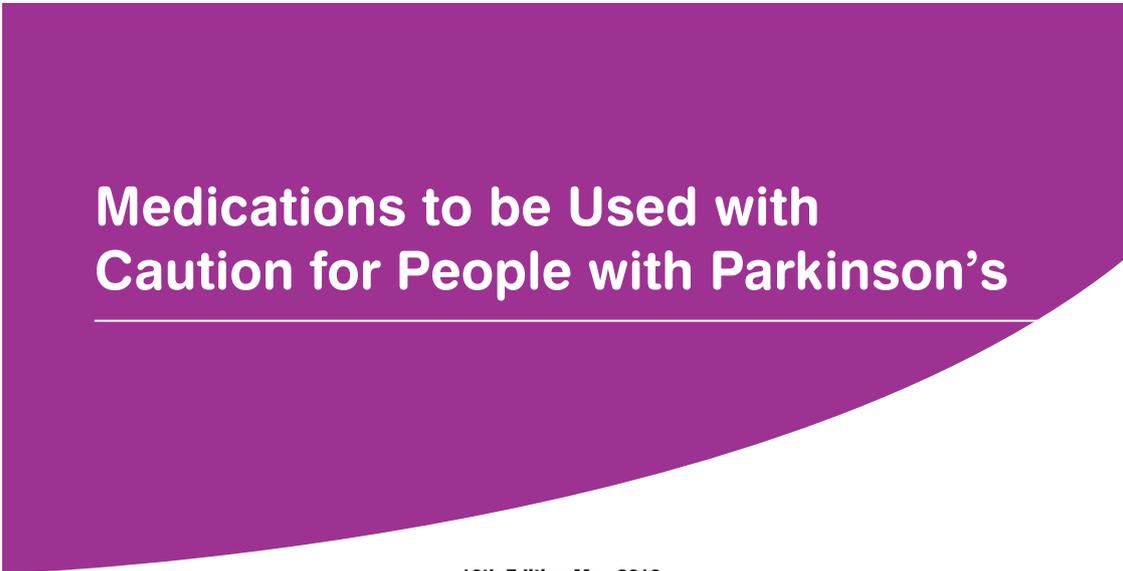
www.wemove.org

Medtronic

www.medtronic.com

14. APPENDICES

Appendix 1 – Medications to be Used with Caution for People with Parkinson's



10th Edition May 2016

Parkinson's is a progressive neurological condition characterised by tremor, stiffness, slowness of movement and postural instability. The symptoms are primarily due to depletion, in the brain, of the neurotransmitter dopamine. This leads to an imbalance with other neurotransmitters. The majority of medications used to treat Parkinson's aim to replace or increase the levels of dopamine within the brain.

Many medications used in the treatment of other medical conditions have the potential to alter or interfere with the brain's dopamine system and may be overlooked as having a detrimental effect on Parkinson's.

It is important to consider the possibility that treatment of other medical conditions may cause or exacerbate existing Parkinson's symptoms.

YOUR DOCTOR MAY DECIDE THE USE OF THESE MEDICATIONS IS JUSTIFIED

This leaflet provides information on those medications that most commonly cause problems for people with Parkinson's. It is not an exhaustive list and therefore a doctor or pharmacist must be consulted before any medications are taken by people with Parkinson's. This includes complementary medicines or medicines available 'over the counter' at pharmacies, health food stores and supermarkets.

This leaflet focuses on medication interactions and medications that are known to worsen the symptoms of Parkinson's. This brochure refers to medications available in Australia. Please note that overseas these medications may be known by different trade names.

Throughout the leaflet, brand names are in ***bold italics***.

Medications Associated with Interactions or Worsening of Parkinson's Symptoms

Antiemetics (Used for nausea and vomiting)

<i>Maxolon, Pramin</i>	Metoclopramide
<i>Stemetil, Stemizine, Nausegil</i>	Prochlorperazine

Antihistamines (Used for colds and hayfever)

<i>Phenergan, Avomine, Fenezal</i>	Promethazine
<i>Vallergan, Vallergan Forte</i>	Trimeprazine

Antidepressants (Used for depression)

Monoamine oxidase inhibitors (MAOIs)

<i>Nardil</i>	Phenelzine
<i>Parnate</i>	Tranylcypromine
<i>Amira, Aurorix, Clobemix</i>	
<i>Mohexal</i>	Moclobemide

Tricyclic and Tetracyclic anti-depressants

<i>Anafranil, Placil</i>	Clomipramine
<i>Dothep, Prothiaden</i>	Dothiepin
<i>Deptran, Sinequan</i>	Doxepin
<i>Tofranil, Tolerade</i>	Imipramine
<i>Allegron</i>	Nortriptyline
<i>Lumin, Tolvon</i>	Mianserin
<i>Surmontil</i>	Trimipramine

Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs)

<i>Cipramil, Ciazil, Citalobell, Talam, Celapram</i>	Citalopram
<i>Lexapro, Esitalo, Lexam, Esipram, Loxalate</i>	Escitalopram
<i>Luvox, Faverin, Movox, Voxam</i>	Fluvoxamine
<i>Lovan, Prozac, Fluohexal</i>	Fluoxetine
<i>Zactin, Auscap, Fluoxebell</i>	Fluoxetine
<i>Edronax</i>	Reboxetine

THE FOLLOWING MEDICATIONS FROM THE ABOVE GROUP ARE COMMONLY UTILISED UNDER SPECIALIST SUPERVISION IN PARKINSON'S

<i>Aropax, Paxtine, Extine</i>	Paroxetine
<i>Avanza, Axit, Mirtazon, Avanza SolTab</i>	Mirtazapine
<i>Efexor - XR, Efexor</i>	Venlafaxine
<i>Zoloft, Xydep, Eleva, Concorz</i>	Sertraline
<i>Sertra, Setrona</i>	

Antipsychotics (Used for sedation and treatment of hallucinations)

Serenace	Haloperidol
Neulactil	Pericyazine
Largactil	Chlorpromazine
Fluanxol	Flupenthixol
Modecate	Fluphenazine
Orap	Pimozide
Navane	Thiothixene
Stelazine	Trifluoperazine
Clopixol	Zuclopenthixol
Risperdal, Rispa, Ozidal, Rixadone	Risperidone

THE FOLLOWING MEDICATIONS ARE COMMONLY UTILISED UNDER SPECIALIST SUPERVISION IN PARKINSON'S

Clozaril, Clopine	Clozapine
Seroquel	Quetiapine
Zyprexa, Zyprexa Zydys	Olanzapine

Cardiovascular (Used for heart conditions and blood pressure)

THE MEDICATIONS IN THIS GROUP ARE UNDER CONSTANT DEVELOPMENT THEREFORE IT IS VITAL THAT THE PRESCRIBING DOCTOR IS AWARE OF PARKINSON'S AS A DIAGNOSIS AND THAT THERE IS A RISK OF LOW BLOOD PRESSURE DUE TO PARKINSON'S. THE MEDICATIONS USED IN THE TREATMENT OF PARKINSON'S CAN OFTEN CAUSE A LOWERING OF BLOOD PRESSURE UPON STANDING.

AVOID: METHYLDOPA. CAUTION WITH CALCIUM CHANNEL ANTAGONISTS, ACE INHIBITORS, ANGIOTENSION II BLOCKERS AND IMDUR.

Other medications to be used with caution include

Buspar	Buspirone
Dilantin	Phenytoin
Lithicarb, Quilonum SR	Lithium
Tetrabenazine	Tetrabenazine
Clorprax, Prexaton, Zyban SR	Bupropion

Special Considerations if Apomorphine (Apomine, Movapo) is Used to Manage Parkinson's

Nausea and vomiting are side effects of **Apomorphine**. Ondansetron (antiemetic) should not be used with **Apomorphine**.

Special Considerations if Taking Azilect, Eldepryl, Selegiline or Selgene

These medications must not be taken in combination

Medication	Interaction
Pethidine	Risk of serotonin syndrome [#] and other potentially life-threatening reactions
Tramadol	Risk of serotonin syndrome [#] and other potentially life-threatening reactions
SSRIs	Risk of serotonin syndrome [#] and other potentially life-threatening reactions
Dextromethorphan (cough suppressant)	Risk of serotonin syndrome [#]
Moclobemide	Increased risk of raised blood pressure
Tricyclic anti-depressants	Risk of serotonin syndrome [#] and other potentially life-threatening reactions
Clozapine	Risk of serotonin syndrome [#] and other potentially life-threatening reactions
St John's Wort	Risk of serotonin syndrome [#]
Ciprofloxacin (antibiotic)	Risk of increased levels of Azilect
Norfloxacin (antibiotic)	Risk of increased levels of Azilect

[#]Serotonin syndrome is a potentially fatal condition which can present as increased temperature, shivering, changes in mental status, raised blood pressure, restlessness and muscle twitching (myoclonus).

If you are contemplating surgery

- Talk to your doctor and anaesthetist before surgery and give them a current list of your medications;
- If admitted to hospital give staff a copy of your medication list and this leaflet.

This edition was reviewed by Dr B I Vieira, Consultant Physician and Janet McLeod, Parkinson's Nurse Specialist.

Endorsed by Parkinson's Australia and distributed by Parkinson's W.A.

parkinson's
AUSTRALIA

IN THIS TOGETHER

CONTACT DETAILS
Parkinson's Australia Inc.
FREE CALL 1800 644 189
Web: www.parkinsons.org.au

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Appendix 2 – Health Professionals Medications to be given with Caution to People with Parkinson’s

Health Professionals

Medications to be given with caution to people with Parkinson’s

7th Edition May 2016

Parkinson’s is a complex progressive condition and is often associated with co-morbidities. Many medications used for the treatment of other medical conditions have the potential to alter or interfere with the brain’s dopamine system and their detrimental effect on Parkinson’s is sometimes overlooked, i.e. increased risk of confusion, hallucinations, postural hypotension and motor disturbances such as bradykinesia and dyskinesia.

However, the need to effectively treat other medical conditions and the possibility of causing or worsening existing Parkinson’s has to be considered.

This brochure is designed to provide information on those drugs that most commonly cause problems for people with Parkinson’s. It is not an exhaustive list and therefore a specialist in Parkinson’s, or a pharmacist, should be consulted before any medications are taken by patients with Parkinson’s. This publication covers only medications currently available in Australia.

The stamp below is used in rehabilitation facilities to highlight the most common medications contraindicated in Parkinson’s.

**NO METOCLOPRAMIDE / PROCHLORPERAZINE
NO HALOPERIDOL /
RISPERIDONE / PERICYAZINE**

This edition was prepared by Dr B I Vieira, Consultant Physician, Dr Oksana Burford, Pharmacist and Janet McLeod, Parkinson’s Nurse Specialist. Distributed by Parkinson’s Western Australia and endorsed by Parkinson’s Australia.

LEVODOPA AND COMT INHIBITORS

(Sinemet, Sinemet CR, Madopar, Madopar HBS, Kinson, Duodopa, Stalevo, Comtan)

Medication	Interaction	Action
Baclofen (Lioresal, Clofen, Stelax)	Increased risk of hallucinations, confusion, headache, nausea and symptoms of Parkinson's	Try to avoid combination
Benzodiazepines	Diazepam and nitrazepam may reduce effect of levodopa and increase muscle tone	May be used together but monitor for decline in cognition and symptom control
Antiemetic drugs (See front page)	Will oppose effects of levodopa and will make condition worse	Use alternatives such as domperidone (Motilium) or ondansetron (Zofran)
Antihypertensive and antianginal drugs	May increase hypotensive effect of levodopa	Monitor postural blood pressure
Antipsychotic drugs	May oppose effect of levodopa and may make condition worse	Avoid the combination or use small doses of Quetiapine or Olanzapine (Seroquel and Zyprexa)
Phenytoin	May reduce effect of levodopa	Monitor closely
Isoniazid	May reduce levodopa concentration in plasma and reduce control of Parkinson's	Monitor closely

DOPAMINE AGONISTS

Apomorphine (Apomine, Movapo), Bromocriptine¹ (Parlodel, Kripton), Cabergoline (Cabaser), Pergolide (Permax), Pramipexole (Sifrol, Sifrol ER), Rotigotine (Neupro)

Medication	Interaction	Action
Antipsychotic drugs	May oppose effects of dopamine agonists and may make symptoms worse	Avoid the combination or use small doses of Quetiapine or Olanzapine (Seroquel and Zyprexa)
¹ Erythromycin	Increases the absorption and decreases the metabolism of bromocriptine	Monitor for signs of dopamine agonist toxicity or choose another antibiotic
Sympathomimetic drugs (cough and cold remedies)	Potential to cause hypertension and seizures	Avoid combination
Antihypertensive drugs	Potential to cause postural hypotension and falls	Monitor blood pressure both supine and erect
Ondansetron	Potential to cause postural hypotension	Avoid with Apomorphine

GLUTAMATE ANTAGONIST

Amantadine (Symmetrel)

Medication	Interaction	Action
Anti-cholinergics	Confusion, hallucinations, nightmares, gastrointestinal disturbances	Avoid combination
Bupropion (Zyban)	As above	Avoid combination

MAO-B INHIBITORS

Selegiline, (Eldepryl, Selgene), Rasagiline (Azilect)

Medication	Interaction	Action
Pethidine	Risk of serotonin syndrome** and other potentially life-threatening reactions	Avoid combination
Moclobemide	Increased risk of tyramine-mediated hypertensive episodes	Avoid combination
SSRIs	Risk of serotonin syndrome** and other potentially life-threatening reactions	Avoid combination
Tricyclic antidepressants	Risk of serotonin syndrome** and other potentially life-threatening reactions	Avoid combination
MAOIs	Hypertensive crisis – potentially life-threatening	Do not give selegiline for two to three weeks after ceasing MAOI
Clozapine	Risk of serotonin syndrome** and other potentially life-threatening reactions	Avoid combination
Dextromethorphan, pseudoephedrine (cough suppressant and cold remedies)	Risk of serotonin syndrome**	Avoid combination

**serotonin syndrome may exhibit as signs of sweating, high temperature, restlessness, tremor, confusion, myoclonus, ataxia and hyperreflexia

- Some medications have the potential to prolong the QT interval when combined with Parkinson's medications such as Amantadine and Apomorphine. Caution is advised. Refer to www.azcert.org
- Patients with Parkinson's often have:
 - Severe and difficult to treat constipation: use caution when prescribing narcotic analgesia, e.g. codeine phosphate, morphine.
 - Severe and challenging depression: Tramadol hydrochloride has the potential to interact with SSRI's and lead to increased confusion and delirium.
 - Co morbidities such as cardio vascular conditions and the medications used in the treatment of these are under constant development. The prescriber must be aware that in conjunction with the antihypertensive effect of Parkinson's and the medications used in its treatment, hypotension may occur with an added risk of postural hypotension.

MEDICATIONS ASSOCIATED WITH DRUG INTERACTIONS OR WORSENING OF PARKINSON'S SYMPTOMS

Antidepressants

Monoamine oxidase inhibitors (MAOIs)

Phenelzine
Moclobemide

Tranylcypromine

Tricyclic and Tetracyclic antidepressants

Dothiepin
Imipramine
Mianserin

Clomipramine
Doxepin
Nortriptyline

Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin-Noradrenaline Re-uptake Inhibitors (SNRIs)

Citalopram
Reboxetine

Fluvoxamine
Fluoxetine

The following drugs from the above group are commonly utilised under specialist supervision.

Paroxetine
Mirtazapine

Venlafaxine
Sertraline

Antiemetics

Metoclopramide

Prochlorperazine

Antipsychotics

Amisulpride
Clozapine
Fluphenazine
Pericyazine
Risperidone
Thioridazine
Zuclopenthixol

Chlorpromazine
Flupenthixol
Haloperidol
Pimozide
Thiothixene
Trifluoperazine

Antihistamines

Promethazine
Trimeprazine

Methdilazine

Antihypertensives and Antianginals

Avoid: Methyl dopa.

Caution with Calcium Channel antagonists, ACE Inhibitors, Angiotension II Blockers and Imdur.

Others

Bupropion
Tetrabenzine

Lithium
Phenytoin

Medications are marketed under many names. This page lists only the generic name.

CONTACT DETAILS

Parkinson's Australia Inc.

FREE CALL 1800 644 189

Web: www.parkinsons.org.au

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Appendix 3 – Glossary

Action tremor	A tremor that happens when a person moves, or begins a movement.
Akinesia	Absence of movement (Greek; <i>a</i> -without, <i>kinesis</i> -motion). In clinical use refers to difficulty initiating movement or interchangeably with bradykinesia and hypokinesia.
Alpha synuclein	Protein present in normal brain whose function is unknown. Found in large clumps within intracellular neuronal inclusions known as Lewy Bodies in brains of people with Parkinson’s disease, Lewy Body Dementia and Multiple System Atrophy (MSA).
Bradykinesia	Slow movement (Greek; <i>brady</i> -slow, <i>kinesis</i> -motion). In clinical use refers to slowness of movement or interchangeably with akinesia and hypokinesia.
Cog-wheeling	A jerky or ratchet-like sensation felt by a physician when a patient’s limb is moved around a joint.
Dopamine	A neurotransmitter produced by the substantia nigra in the basal ganglia. It is responsible for transmission of signals between nerve cells that control movement. A lack of dopamine is a primary factor in Parkinson’s. The reason for the depletion of dopamine remains unknown.
Dopaminergic	Having the effect of dopamine.
Dyskinesia	Involuntary, uncontrollable and often excessive movements, commonly seen in advanced Parkinson’s disease where they are called ‘levodopa-induced dyskinesias’.
Dysphagia	Difficulty swallowing.
Dystonia	Involuntary contraction of muscle groups resulting in abnormal movements and postures of the trunk or limbs.
Hypokinesia	Decreased movement (Greek; <i>hypo</i> -decreased, <i>kinesis</i> -motion). In clinical use refers to reduced amplitude of movement or interchangeably with akinesia and hypokinesia.
Hypomimia	Reduced facial expression.
Hypophonia	A weak or soft voice.
Hyposmia	Reduced smell.
Levodopa	A chemical precursor of dopamine which can be taken orally. It is converted to dopamine and crosses the blood brain barrier.
Lewy Bodies	Abnormal, round pink-staining bodies found in the cytoplasm of the dopamine cells of the substantia nigra, the noradrenaline cells of the locus ceruleus and the cerebral cortex.
Lewy body disease	Refers to the group of neurological conditions of which the presence of Lewy Bodies (at post mortem) is the definitive diagnostic marker. Dementia with Lewy Bodies presents as fluctuating cognitive impairment and early visual hallucinations with extra pyramidal signs occurring within one year of onset.
MAO inhibitors	Monoamine Oxidase Inhibitors are medications which block the breakdown of dopamine in the brain by inhibiting monoamine oxidase which has been shown to deplete dopamine in mice. This group of medications include Selegiline®, Elderpryl® and more recently Azilect®.
Micrographia	Small handwriting, a common early presentation of PD.

Monoamine	Refers to chemicals which play an integral role in neurotransmission. They include catecholamines dopamine, norepinephrine and 5-hydroxytryptamine.
Multiple System Atrophy	Included in the conditions known as Parkinson's Plus. The motor symptoms while similar to Parkinson's do not demonstrate a positive response to levodopa. Early presentation of autonomic changes such as bladder involvement, balance and blood pressure regulation are suggestive of MSA. The progression of the condition is much more rapid than idiopathic Parkinson's disease.
Neuroprotection	A therapeutic strategy intended to slow or halt the progression of neuronal loss and thereby alter the natural history of the disease. Neuroprotective therapies act on the pathogenic mechanisms underlying cell death.
Nigrostriatal system	Is part of the basal ganglia and degeneration of this area is associated with Multiple System Atrophy.
Off period	Refers to a fluctuation in efficacy of levodopa therapy when the medication is not having a visible effect. This can be related to end of dose failure and is often associated with anxiety.
On period	Refers to the positive effect of levodopa therapy which results in alleviation of Parkinsonian symptoms (usually motor symptoms).
'On-off' phenomenon	Refers to the often sudden reduction in mobility in a person with PD as a result of falling dopamine levels in the brain. Not seen in early PD where there is enough endogenous dopamine production to prevent its occurrence.
Parkinsonism	Term used to refer to symptom complex which includes tremor, bradykinesia, rigidity and postural instability. Most commonly due to Idiopathic Parkinson's Disease (PD) but seen in other diseases. Can be reversible when caused by implicated medications.
Pill-rolling tremor	Is a term first used by Dr James Parkinson to describe the typical movement of the fingers occurring usually four to five Hz per second. Is exacerbated by stress and occurs mostly at rest.
Postural instability	In PD, refers to the lack of normal postural reflexes in response to external changes as well as poor balance in general.
Progressive Supranuclear Palsy	Included in the conditions known as Parkinson's Plus. Presents with impaired downward gaze, rigidity and bradykinesia. Poor response to levodopa with a more rapid progression than idiopathic Parkinson's disease. Associated with tau protein positive neurofibrillary tangles.
Rigidity	Abnormal stiffness of body part on passive movement. Often referred to as 'lead pipe rigidity'.
Striatum	Refers to the collection of basal ganglia structures above the midbrain, including the caudate nucleus and lentiform nucleus (globus pallidus and putamen), to which the substantia nigra sends dopaminergic connections.
Substantia nigra	One of the basal ganglia nuclei located in the midbrain. Contains dopamine producing cells which project up to the striatum.
Wearing Off	A variance in response to levodopa therapy which may develop after a few years of treatment. This can be 'wearing off' or 'on/off' phenomena. This is also known as motor fluctuations – in addition to motor symptoms sensory and autonomic symptoms may appear as 'wearing off' occurs. These include sweating, anxiety and pain.

Appendix 4 – References and Further Reading

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[Note: Other similar evidence-based guidelines exist, and are updated periodically]

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