



## GUIDELINE

## Guideline for the treatment of Parkinson's disease

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Parkinson's disease (PD) is a common neurodegenerative disorder that affects the central nervous system. It has a prevalence of about 3% in the age group over 60, and becomes increasingly common with advancing age, particularly affecting men.<sup>1</sup> The epidemiology of the condition is unknown in South Africa and limited in Africa, although it is thought to be commonest in people of Northern European origin.

Although a number of genes have been implicated in the genesis of PD, the cause in the majority of patients remains unclear, especially given that the prevalence is highest in the elderly, whereas a clear genetic predisposition is best defined in those with disease of earlier onset.<sup>2</sup> The illness is progressive and associated with significant disability and there is no proven way of slowing or altering the course, although many of the symptoms are amenable to therapy.

PD has traditionally been viewed predominantly as a disturbance of the motor system, manifesting with tremor and slowness. However, it is increasingly clear that so-called non-motor manifestations are associated with much of the morbidity.

### 1. Course and symptoms

A revision of the neuropathology of PD has allowed for a new approach to the course of the illness.<sup>3</sup> A preclinical phase exists, which may be characterised by loss of the sense of smell and by REM sleep behaviour disorder (RBD). RBD is a condition in which the normal mechanisms of REM sleep are affected, as a result of which patients may act out their dreams, sometimes in a violent fashion. The motor manifestations of PD are typically noted when up to 80% of existing dopaminergic cells have been lost. There has been particular interest in this stage, since early intervention that results in a reduction in cell damage could potentially halt or slow the progression of the disease.

As the disease advances there is progressive loss of dopaminergic cells, but other monoaminergic systems, such as the serotonergic system, may also be affected, as well as other brainstem nuclei. PD is essentially a multisystem disease affecting many areas of the brain, ranging from the medulla to the cerebral cortex.

The early stages of the disease are well known to be highly responsive to treatment. However, with increasing loss of dopaminergic and other cell groups there is a trend towards requirement of increasing amounts of dopamine. The

development of motor fluctuations, while not inevitable, is a common problem. Motor fluctuations describe the situation whereby a patient initially finds that the beneficial effect of dopamine tends to wear off after a few hours and subsequently that obvious fluctuations in the clinical state develop, termed 'on' and 'off' and describing better and worse motor function, respectively. The 'off' state is frequently accompanied by non-motor symptoms such as confusion or depression.

Frequently associated with motor fluctuations are abnormal movements typically related to the use of dopamine and often termed dopamine-induced dyskinesias. These may be very complex in terms of the type of movement seen and the relationship to dopamine levels, and some of the commonest types are directly related to dopamine levels peaking in the brain.

Although dyskinesias are very common, in the majority of patients they do not have a major impact on quality of life and may be improved by adjusting medication. However, in a number of patients, especially those who develop PD at a young age, dyskinesias are markedly disabling.

Changes in the motor state may become increasingly unpredictable, so-called 'yo-yoing', and are often associated with an increasingly short duration of response to dopamine. In addition, dopamine-resistant phenomena such as freezing may develop. Freezing most frequently refers to the sudden onset of loss of mobility, and is commonly encountered when people with PD find themselves in novel environments, or approach a narrow space such as a doorway. Freezing may also affect many other movements, such as bringing the hand to the mouth, or speech.

The non-motor manifestations of PD become increasingly common as the disease progresses. Some of the more distressing include autonomic dysfunction, associated with constipation, bladder disturbance, impotence and postural hypotension. The latter is particularly disturbing because therapy for PD may lower blood pressure further in a group of patients who are already prone to falling. Other features associated with significant morbidity include the development of hallucinations and cognitive impairment, with prominent involvement of planning and working memory.

### 2. Treatment of PD

Treatment of PD should be tailored to the stage of the illness, and is predominantly symptomatic. Unfortunately polypharmacy is often inevitable, and the undesirable situation

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of needing to add additional agents to treat iatrogenic side-effects is not uncommon.

## 2.1 Early PD where severity is mild (Fig. 1)

In this phase the patient has limited signs, typically involving one side of the body, with tremor being the predominant dysfunction. There is ongoing controversy regarding the 'best' agent to treat PD in its early phases. Patients and treating physicians are well aware of the progressive nature of the disease, and seek ways to slow this progression. Similarly, concerns about motor fluctuations and dyskinesias are valid and raise questions about whether starting treatment with dopamine early is potentially a source of problems in the long term. It is currently established that dopamine agonists are associated with a lower incidence of dyskinesias.<sup>4</sup> However, dopamine agonists have less benefit on motor function than dopamine itself, and there are increasing concerns about their side-effect profile.

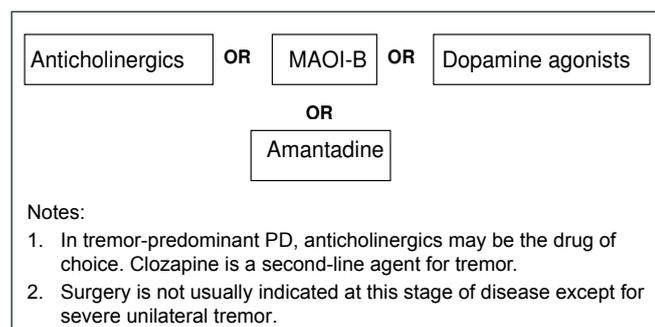


Fig. 1. Treatment of PD where severity is judged to be mild.

Other therapies include amantadine and anticholinergic agents, although there are concerns about cognitive impairment in patients on the latter, albeit limited to a single study that has not been replicated.<sup>5</sup> Monoamine oxidase (MAO) inhibitors have a part to play in the treatment of early PD. Rasagiline, an MAO inhibitor, improves parkinsonian symptoms, and its potential role in slowing the progression of the degenerative process is being investigated. One published study supports this notion and other studies are awaited (Parkinson's Study Group, 2004).<sup>6</sup>

## 2.2 PD where severity is moderate or there is functional impairment (Fig. 2)

In this phase a patient has more obvious disease that is impairing function. At this stage many neurologists would consider that addition of levodopa to the treatment regimen is an appropriate step. Domperidone is a useful agent that limits side-effects arising from the peripheral action of levodopa. COMT (catechol-O-methyl transferase) inhibitors retard the breakdown of levodopa, resulting in more sustained dopamine levels. The claim that this may prevent later motor

complications needs to be further substantiated, but there may be a role for early introduction of COMT inhibitors with levodopa.

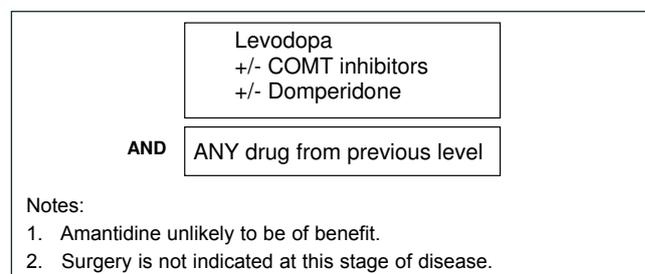


Fig. 2. Treatment of PD where severity is judged to be moderate with functional impairment.

## 2.3 PD where severity is moderate to severe (Fig. 3)

A patient in this phase has more advanced disease, frequently associated with motor fluctuations and an increasing burden of non-motor manifestations. Critical problems may include the short half-life and the narrow therapeutic window of levodopa. Agents such as the dopamine agonists, COMT inhibitors and MAO-B inhibitors can assist in addressing these.

Treatment of some of the non-motor manifestations of PD is dealt with in section 2.3 below. Neurosurgical intervention has its major role at this stage, and issues related to this are discussed in section 2.4.

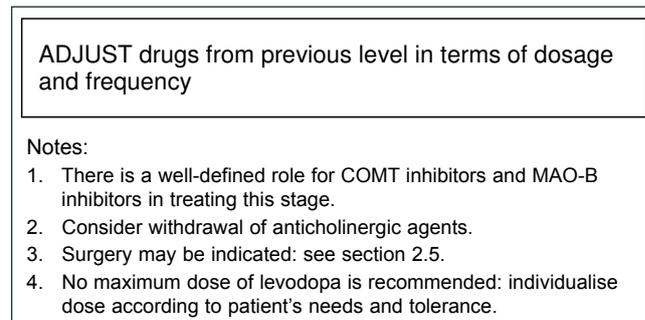


Fig. 3. Treatment of PD where severity is judged to be moderate to severe.

## 2.4 Specific categories of disability requiring intervention

- Dyskinesias: amantadine, botulinum toxin, surgery (see section 2.5)
- Autonomic dysfunction: fludrocortisone, pyridostigmine, treatment of bladder dysfunction (urinary antispasmodics), treatment of constipation (bulk laxatives, osmotic laxatives)
- Psychosis: modify regimen, atypical antipsychotics (quetiapine, clozapine)
- Depression: selective serotonin reuptake inhibitors (SSRIs),



mirtazapine, tricyclics, tetracyclic agents

- Anxiety: SSRIs, benzodiazepines (include sublingual forms)
- REM sleep behaviour disorder: benzodiazepines
- Hypersalivation: botulinum toxin, atropine drops.

## 2.5 Surgical intervention for PD

Patients require assessment by a neurologist prior to surgery. The response to levodopa should be established.

### 2.5.1 Suggested indications for surgical intervention

- Severe fluctuations, with preservation of responsiveness to levodopa
- Tremor resistant to medical treatment
- Moderate to severe dyskinesias.

### 2.5.2 Exclusion criteria for surgical intervention

- Severe non-motor symptoms
- Severe gait disorder unresponsive to levodopa
- Ongoing poorly controlled neuropsychiatric disturbance
- Dementia
- Psychosis.

Guidelines for the treatment of Parkinson's disease were drawn up by those attending the inaugural meeting of the Movement Disorders Group of South Africa (MGSA) in Johannesburg on 27 September 2008. Professors J Carr and B Kies and Dr J Fine formed

the writing committee. The meeting was sponsored by Novartis, and attendance was arranged by invitation to all neurologists in South Africa, as arranged by the Parkinson's Disease and Related Movement Disorders Association of South Africa. Attendees included Dr D Anderson, Dr B Cheyip, Professor J Carr, Dr J Fine, Dr D Giampolo, Dr J Green, Dr M Isaacs, Professor B Kies, Dr M Moagi, Dr N Shah, Dr J Smuts, Dr C Wolpe. Ms K Willems and Ms Gisela Stanek of the Parkinson's Disease and Related Movement Disorders Association of South Africa. No member of the group declared any financial interest in a pharmaceutical company.

The guidelines are endorsed by the Neurological Society of South Africa.

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