

# CLINICAL PRACTICE GUIDELINES

## Parkinson's Disease



College of Family Physicians,  
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Singapore



MINISTRY OF HEALTH  
SINGAPORE

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**MOH Clinical Practice Guidelines 6/2007**

## Levels of evidence and grades of recommendation

### Levels of Evidence

Level	Type of Evidence
1 <sup>++</sup>	High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 <sup>+</sup>	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1 <sup>-</sup>	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2 <sup>++</sup>	High quality systematic reviews of case-control or cohort studies High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2 <sup>+</sup>	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2 <sup>-</sup>	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

### Grades of recommendation

Grade	Recommendation
<b>A</b> (evidence levels 1 <sup>++</sup> , 1 <sup>+</sup> )	At least one meta analysis, systematic review, or RCT rated as 1 <sup>++</sup> , and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1 <sup>+</sup> , directly applicable to the target population, and demonstrating overall consistency of results
<b>B</b> (evidence levels 2 <sup>++</sup> , 1 <sup>++</sup> , 1 <sup>+</sup> )	A body of evidence including studies rated as 2 <sup>++</sup> , directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1 <sup>++</sup> or 1 <sup>+</sup>
<b>C</b> (evidence levels 2 <sup>++</sup> , 2 <sup>+</sup> )	A body of evidence including studies rated as 2 <sup>+</sup> , directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2 <sup>++</sup>
<b>D</b> (evidence levels 2 <sup>+</sup> , 3, 4)	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2 <sup>+</sup>
<b>GPP</b> (good practice points)	Recommended best practice based on the clinical experience of the guideline development group

# **CLINICAL PRACTICE GUIDELINES**

## **Parkinson's Disease**

**MOH Clinical Practice Guidelines 6/2007**

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## Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

## Foreword

Parkinson's disease is a gradually progressive neuro-degenerative disorder which affects movement or the control of movement, including speech and body language. It poses a significant public health burden, which is likely to increase in the coming years. According to WHO data, worldwide nearly 1.6 million Disability Adjusted Life Years (DALYs) are lost each year due to Parkinson's disease. As the incidence and prevalence of Parkinson's disease increase with age, the DALYs lost due to this disease are expected to increase by 25% by 2040. DALYs loss due to Parkinson's disease as percentage of total DALYs in Western Pacific Region (0.15%) is third highest among WHO sub-regions, next only to European (0.30%) and American region (0.22%).

The Singapore Burden of Disease Study estimated that Parkinson's disease accounted for almost 1700 DALYs lost in the year 2004. In a community-based survey, the prevalence of Parkinson's disease in Singapore was found to be 0.3% for the population aged 50 years and above. This rate is in keeping with those reported in western countries. As Singapore's population is ageing rapidly, the burden of Parkinson's disease is expected to increase. It is timely to develop these first national guidelines on Parkinson's disease to assist our doctors to deal effectively with this disease. A multidisciplinary expert committee has reviewed the latest scientific evidence and combined it with their expertise to develop guidelines appropriate for our population.

I hope this set of guidelines will assist all doctors involved in the care of patients with Parkinson's disease.

A/PROF CHEW SUOK KAI  
Ag DIRECTOR OF MEDICAL SERVICES

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## Executive Summary of Recommendations

Details of recommendations can be found in the main text at the pages indicated.

### Diagnosis of Parkinson's Disease

**D** The schema below shows the factors that should be considered in the diagnostic process of Parkinson's disease (pg 8):

1. Confirm the presence of parkinsonism i.e. the presence of rest tremors, cogwheel rigidity and bradykinesia (See 3.1 and 3.2)
2. Detect atypical features that suggest an alternative diagnosis to Parkinson's disease
3. Assess whether the diagnostic criteria for Parkinson's disease are fulfilled

**Grade D, Level 3**

**D** The following atypical features may be considered when distinguishing atypical parkinsonian syndromes from idiopathic Parkinson's disease (pg 10):

- Frequent falls within 1 year of disease onset
- Poor response to levodopa
- Symmetry at onset
- Rapid progression (to Hoehn and Yahr stage 3 within 3 years)
- Lack of tremor
- Dysautonomia (urinary urge incontinence, fecal incontinence, urinary retention, persistent erectile failure, symptomatic orthostatic hypotension)

**Grade D, Level 3**

**GPP** The diagnosis of Parkinson's disease should be reviewed regularly and reassessed if atypical clinical features develop (pg 11).

**GPP**

### Management of Parkinson's Disease

**A** Although levodopa is the most efficacious drug for the symptomatic management of both early and late Parkinson's disease, the dose of levodopa should be kept to the minimum necessary to achieve good motor function (pg 15).

**Grade A, Level 1+**

**A** Dopamine agonists are efficacious as symptomatic monotherapy. Dopamine agonists may also be used as an adjunct to levodopa in the treatment of Parkinson's disease (pg 17).

**Grade A Level 1+**

**GPP** In younger Parkinson's disease patients, therapy should commence first with dopamine agonists rather than levodopa (pg 17).

**GPP**

**B** Anticholinergic agents may be used as symptomatic monotherapy or as an adjunct to levodopa to treat tremors and stiffness in Parkinson's disease (pg 17).

**Grade B, Level 1+**

- A**
1. Amantadine may be given as symptomatic monotherapy or as an adjunct to levodopa for the treatment of Parkinson's disease.
  2. Amantadine may be considered as therapy to reduce dyskinesia in patients with Parkinson's disease who have motor fluctuations.

(pg 18)

**Grade A, Level 1+**

**A** Entacapone is efficacious and may be used together with levodopa in patients with motor fluctuations (pg 19).

**Grade A, Level 1+**

**B** Selegiline is efficacious as a symptomatic monotherapy and may be used in early stages of Parkinson's disease (pg 19).

**Grade B, Level 1++**

**D** Amitriptyline may be considered to treat depression in Parkinson's disease without dementia (pg 19).

**Grade D, Level 4**

**D** Parkinson's disease patients with psychosis may be treated with clozapine, although leukopaenia is a potential side effect. Quetiapine may also be considered, but not olanzapine (pg 20).

**Grade D, Level 4**

**D** Donepezil or rivastigmine may be considered for Parkinson's disease patients with dementia (pg 20).

**Grade D, Level 4**

**D** Midodrine may be used in the treatment of orthostatic hypotension in Parkinson's disease (pg 20).

**Grade D, Level 4**

**D** Fludrocortisone may also be used to treat orthostatic hypotension in Parkinson's disease, but its use is limited by adverse effects (pg 20).

**Grade D, Level 4**

**D** Constipation and reduced gastric motility are common in Parkinson's disease. Anorexia, nausea and vomiting are common side effects of dopamine agonist therapy. Domperidone, which blocks peripheral dopamine receptors, increases gastric emptying and may reduce drug-induced gastrointestinal side effects (pg 21).

**Grade D, Level 4**

**D** Erectile dysfunction in patients with Parkinson's disease may be treated with sildenafil, although the patient has to be forewarned of side effects like headaches, transient visual effects and flushing, and dangerous side effects like cardiac arrest and hypotension. Priapism is also known to occur (pg 21).

**Grade D, Level 4**

## **Surgical Management of Parkinson's Disease**

**A** Surgery may be efficacious in the treatment of motor complications of Parkinson's disease. Such patients may be referred to a Neurologist for surgical evaluation (pg 22).

**Grade A, Level 1+**

## **Cost-effectiveness**

**GPP** The cost of therapy should be considered in the choice of Parkinson's disease medication (pg 25).

**GPP**

**GPP** Generic formulations usually cost less than non-generic drugs and are acceptable if they meet prescribed standards of quality (pg 25).

**GPP**

## When to Refer to a Specialist

**GPP** The following patients should be referred to the specialist (pg 26):

1. Young-onset Parkinson's disease
2. Atypical Parkinson's disease
3. Patients who do not respond to levodopa or dopamine agonists
4. Patients with cognitive impairment or neuropsychiatric dysfunction
5. Parkinson's disease complicated by dyskinesias
6. Parkinson's disease patients with family history of Parkinson's disease
7. Patients with dystonia, myoclonus or gaze palsies

**GPP**

# 1 Introduction

## 1.1 Background information

These clinical practice guidelines have been produced to familiarize doctors with the key features of Parkinson’s disease, to identify “red flags” that indicate a need to refer the patient to a specialist, and to provide an overview to evidence-based management of Parkinson’s disease. The guidelines are not intended to be a comprehensive review of Parkinson’s disease.

## 1.2 Development of guidelines

These guidelines have been produced by a team comprising neurologists, neurosurgeons and geriatricians subspecialising in movement disorders, as well as general practitioners with an interest in the management of Parkinson’s disease.

## 1.3 Objectives

The main objective of these guidelines is to promote evidence-based management of Parkinson’s disease.

## 1.4 Review of guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supercede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review 4 years after publication, or when new evidence appears that requires updating of the recommendations.

## 2 Definition and Classification

### 2.1 Background

Parkinson's disease is an age-related chronic progressive neurodegenerative disorder. Parkinson's disease invariably manifests with motor symptoms, which are related to loss of dopaminergic neurons in the substantia nigra. In its early stages, Parkinson's disease usually presents with asymmetric tremor, bradykinesia and rigidity. During the later stages of the disease, non-motor features, including autonomic dysfunction, falls, sleep disturbances and cognitive abnormalities appear, as neuronal loss in non-dopaminergic areas become apparent.

In a community-based survey, the prevalence of Parkinson's disease in Singapore was found to be 0.3% for the population aged 50 and above.<sup>1</sup> This rate is in keeping with those reported in western countries.<sup>2-4</sup> There was no significant difference in prevalence rates between the Chinese, Malays and Indians.<sup>1</sup> Worldwide, the incidence and prevalence of Parkinson's disease increase with age, with approximately 1% of the population aged 60 years and older having Parkinson's disease.<sup>2,4,5</sup> The average age of onset is usually in the early to mid-60s. However, Parkinson's disease may occur in the younger population. **Young-onset Parkinson's disease**, which starts between the ages of 21 and 40, affects 5-10% of Parkinson's disease patients.<sup>6</sup> **Juvenile-onset Parkinson's disease** refers to patients with symptoms arising before the age of 20 years.<sup>7</sup> There is a higher frequency of genetically inherited Parkinson's disease amongst patients with a young onset.

### 2.2 Pathogenesis of Parkinson's disease

The main pathologic finding associated with parkinsonism is the loss of pigmented dopaminergic cells in the pars compacta of the substantia nigra, in the midbrain. In addition to this cell loss, many of the remaining cells contain eosinophilic cytoplasmic inclusions called Lewy bodies. Some degeneration also occurs in other areas of the brain, such as the locus ceruleus, mesencephalic reticular formation and sympathetic ganglia.

The pathogenetic mechanism underlying this degeneration is unknown, and may be due to a combination of genes, environmental toxins and free radicles. 10-20% of patients diagnosed with Parkinson's disease show alternate diagnoses at autopsy, such as multiple systems atrophy, progressive supranuclear palsy and cerebrovascular disease.

### 3 Diagnosis of Parkinson's Disease

There is no reliable diagnostic marker for Parkinson's disease. As such, the clinical diagnosis of Parkinson's disease is based on the presence of characteristic features, and the exclusion of alternative diagnoses for parkinsonism. Parkinson's disease is the main cause of parkinsonism.<sup>8,9</sup> However, pathological studies show that 10-25% of patients with parkinsonian syndromes do not have idiopathic Parkinson's disease. Amongst the differential diagnoses to be considered, the commonest causes of parkinsonism are the atypical parkinsonian disorders.<sup>10</sup>

Detailed history, thorough neurological and physical examinations, and a cognitive assessment are essential in differentiating these conditions from idiopathic Parkinson's disease. The greatest challenge lies in distinguishing the early stages of atypical parkinsonian disorders from early Parkinson's disease. To increase the clinical diagnostic accuracy of Parkinson's disease, various diagnostic criteria have been proposed.<sup>10-16</sup> These criteria share a similar clinical diagnostic accuracy of around 75-90%<sup>10-17</sup>, as confirmed on autopsy. Definitive diagnosis however, requires neuropathological confirmation.<sup>18</sup>

**D** The schema below shows the factors that should be considered in the diagnostic process of Parkinson's disease<sup>10-16</sup>:

1. Confirm the presence of parkinsonism i.e. the presence of rest tremors, cogwheel rigidity and bradykinesia (See 3.1 and 3.2)
2. Detect atypical features that suggest an alternative diagnosis to Parkinson's disease
3. Assess whether the diagnostic criteria for Parkinson's disease is fulfilled

Grade D, Level 3

#### 3.1 Parkinsonism

Parkinsonism refers to the presence of *rest tremors*, *cogwheel rigidity* and *bradykinesia*. These constitute the 3 cardinal features of Parkinson's disease.<sup>16</sup>

A distal “pill-rolling” **rest tremor** of 3-5Hz is present in 80-90% of patients with Parkinson’s disease.<sup>9,19</sup> Less commonly, a resting foot tremor may be the presenting sign. Rest tremors are best detected with the limb fully supported against gravity. Apart from the classic rest tremors, patients with Parkinson’s disease may concurrently have postural and action tremors. Tremors are said to be *postural* if they are maximised when the patient assumes and maintains a posture against gravity, whereas action or kinetic tremors only occur during action, and are accentuated with voluntary movements.

**Rigidity** occurs in 89-99% of Parkinson’s disease patients.<sup>9,19</sup> It refers to the increased resistance noted uniformly during the range of passive joint movement, and can be enhanced by contralateral motor activity or mental task performance.

Limb **bradykinesia**, referring to slowed movements, is noted in 77-98% of Parkinson’s disease patients.<sup>9,19</sup> It is tested by getting the patient to perform repetitive movements such as finger tapping, alternating pronation and supination of the forearm, foot tapping and opening and closing of the fists.<sup>20</sup>

Other features may also be seen in Parkinson’s disease. Postural instability is often referred to as a parkinsonian sign, but may not be a prominent feature in early Parkinson’s disease.<sup>14,16</sup> It can be assessed by pulling the patient backwards to check for balance recovery (“pull” or retropulsion test). The patient is told to “stand steady”, and informed that the examiner, standing behind him, will “pull” him backwards suddenly, whereupon he should try to recover balance. It is usual to tell the patient that it is acceptable to take one or two steps backward if necessary to maintain the upright posture. Gait disturbances, including a slow shuffling gait, turning *en bloc*, start hesitancy and freezing are noted in later stages of Parkinson’s disease.

The motor features in early Parkinson’s disease are often asymmetric at disease-onset and respond well to levodopa.<sup>21,22</sup> Most diagnostic criteria for Parkinson’s disease incorporate the combined presence of the 3 cardinal features, asymmetry at onset and good response to levodopa, because these features are not specific to Parkinson’s disease if considered separately.

## 3.2 Non-motor manifestations of Parkinson's disease

Non-motor symptoms of Parkinson's disease are increasingly being recognized, and are usually under-treated. These symptoms usually affect three domains: autonomic, neuropsychiatric and sensory, including pain.<sup>23</sup> Non-motor symptoms are thought to be common in Parkinson's disease, as many as 88% of patients having at least one nonmotor symptom and 11% with five nonmotor symptoms.<sup>24</sup> With improved treatment of motor symptoms in Parkinson's disease, the nonmotor symptoms have now emerged as a significant cause of disability.<sup>23</sup> The mechanisms underlying nonmotor symptoms are poorly understood, and may be related to abnormalities within the dopaminergic, serotonergic, adrenergic, cholinergic and other peptidergic pathways.<sup>23</sup> This accounts for the relative resistance of nonmotor symptoms to treatment with dopaminergic agents.

## 3.3 Exclusion of alternative diagnoses

Conditions which may mimic Parkinson's disease include the atypical parkinsonian syndromes (multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration and dementia with Lewy bodies), drug- or toxin-induced parkinsonism, cerebrovascular disease, hydrocephalus and recurrent head trauma. Young-onset parkinsonism may be due to Huntington's disease, Wilson's disease or dopa-responsive dystonia.<sup>25</sup> The tremors in Parkinson's disease may be misdiagnosed as essential tremors or enhanced physiological tremors due to thyrotoxicosis (or vice versa).

It is crucial to distinguish these conditions from idiopathic Parkinson's disease, because early identification and intervention of treatable conditions may halt disease progression and even reverse neurological damage. In the atypical parkinsonian disorders, which generally have a less favourable prognosis than Parkinson's disease, early recognition remains important for doctors to counsel patients as to disease prognosis and to allow anticipation of disease-specific complications. Therefore, in a patient who presents with parkinsonism, it is important to detect atypical features early in the course of the disease.

**D** The following atypical features may be considered when distinguishing atypical parkinsonian syndromes from idiopathic Parkinson's disease<sup>22,26-28</sup>:

- Frequent falls within 1 year of disease onset

- Poor response to levodopa
- Symmetry at onset
- Rapid progression (to Hoehn and Yahr stage 3 within 3 years)
- Lack of tremor
- Dysautonomia (urinary urge incontinence, fecal incontinence, urinary retention, persistent erectile failure, symptomatic orthostatic hypotension)

**Grade D, Level 3**

Other atypical features include<sup>10-16</sup>:

- Signs of pyramidal dysfunction
- Signs of cerebellar dysfunction
- Dysphagia within 1 year of disease onset
- Dementia and hallucination within 1 year of disease onset
- Supranuclear palsy
- Severe apraxia

**GPP** The diagnosis of Parkinson's disease should be reviewed regularly and reassessed if atypical clinical features develop.

**GPP**

### 3.4 Clinical diagnostic criteria

Several clinical diagnostic criteria have been proposed and are shown in Annexes 1 and 2. The criteria shown below have been adapted from those of Calne DB et al.<sup>14</sup>

#### **Clinically possible Parkinson's disease**

The presence of any 1 of the features: tremor, rigidity or bradykinesia. The tremor must of recent onset, but may be postural or resting.

#### **Clinically probable Parkinson's disease**

A combination of any 2 of: resting tremor, rigidity, bradykinesia, or impaired postural reflexes. Alternatively, asymmetrical resting tremor, asymmetrical rigidity or asymmetrical bradykinesia are sufficient.

#### **Clinically definite Parkinson's disease**

A combination of any 3 of the features: resting tremor, rigidity, bradykinesia, or impaired postural reflexes. Alternatively sufficient are 2 of the 3 features, with one of the first 3 displaying asymmetry.

## 4 Course of Disease

Being a progressive disorder, Parkinson's disease results in significant disability 10 to 15 years after its onset. Parkinson's disease exerts a considerable financial and social burden on the patient, their caregivers and society.<sup>29</sup> The rate of disability progression is most marked in the early years of the disease.<sup>9,30,31</sup>

In its later stages, Parkinson's disease patients become increasingly dependent in their activities of daily living. Falls, as a result of postural instability, postural hypotension, dyskinesias, confusion, dementia, suboptimal nutrition, speech and sleep disorders, are common.

In the era predating use of levodopa, the mean survival from disease onset was 9 years, with a mortality ratio of 3.0 compared to the general population. Bronchopneumonia and urinary tract infections were the common causes of death in untreated Parkinson's disease patients.<sup>9</sup>

The introduction of levodopa in the late 1960s represented a major advance in the management of Parkinson's disease.<sup>32</sup> It provides effective treatment for ameliorating the motor symptoms in early stage Parkinson's disease and reduces the mortality ratio to 1.5, compared to the general population.<sup>32,33</sup>

The median disease duration to reach the various Hoehn and Yahr stages for the pre- and post-levodopa periods are shown in Table 1.

**Table 1            Median disease duration to reach the various  
Hoehn and Yahr stages**

<b>Hoehn and Yahr stage</b>	<b>Clinical severity</b>	<b>Median disease duration (years) for untreated patients<sup>9</sup></b>	<b>Median disease duration (years) for levodopa-treated patients<sup>33</sup></b>
<b>I</b>	Unilateral parkinsonism	3	Not available
<b>II</b>	Bilateral parkinsonism	6	9
<b>III</b>	Mild to moderate disability with postural impairment	7	12
<b>IV</b>	Severe disabling disease, able to walk unassisted but markedly incapacitated	9	12
<b>V</b>	Confined to bed or wheelchair unless aided	14	18

## 5 Investigations

No clinical test has been identified as a “gold standard” to diagnose Parkinson’s disease. As such, clinical criteria are used instead. In patients who present with typical features of Parkinson’s disease in the correct age group, no further investigations are required for diagnosis. However, patients with young-onset parkinsonism, and patients with unusual or “atypical” features require further investigations to exclude alternative diagnoses.

## 6 Management of Parkinson's Disease

Management of Parkinson's disease can broadly be divided into pharmacotherapeutic, surgical and ancillary management strategies.

### 6.1 Pharmacotherapeutic management: Motor symptoms in Parkinson's disease

#### Levodopa

Parkinson's disease is characterized by the loss of dopaminergic neurons, the resulting dopamine deficiency accounting for the motor dysfunction seen in the disease. Levodopa, the precursor of dopamine, is readily converted to dopamine by dopa decarboxylase. Levodopa is usually administered with a peripheral dopa decarboxylase inhibitor, carbidopa (Sinemet) or benserazide (Madopar), in order to reduce the peripheral metabolism of levodopa. This enables more of it to cross the blood-brain barrier and reach the brain. Levodopa has been used for more than 3 decades in the treatment of Parkinson's disease. The elimination half-life of levodopa from plasma (in combination with a decarboxylase inhibitor) is approximately 1.5 hours. The benefits of levodopa may diminish after a few years of treatment. Sustained-release formulations of levodopa may provide more stable plasma concentrations. Many studies have shown that levodopa is effective in both early and late Parkinson's disease.<sup>34-38</sup> Evidence-based reviews have shown that both standard and controlled-release formulation are efficacious as monotherapy in Parkinson's disease.<sup>39</sup>

Between 50-70% of patients with Parkinson's disease may develop involuntary movements (dyskinesias) within 5-6 years of starting levodopa therapy, a phenomenon believed to arise from pulsatile stimulation of the striatal dopamine receptors.<sup>40</sup>

**A** Although levodopa is the most efficacious drug for the symptomatic management of both early and late Parkinson's disease, the dose of levodopa should be kept to the minimum necessary to achieve good motor function.<sup>39</sup>

**Grade A, Level 1+**

## **Dopamine Agonists**

Dopamine agonists directly activate dopamine receptors, bypassing the presynaptic synthesis of dopamine.<sup>41,42</sup> There are two main classes of dopamine receptors: D1 (comprising subtypes D1 and D5), linked to the enzyme adenylate cyclase, and the D2 class (comprising subtypes D2, D3, and D4), coupled to G proteins that inhibit adenylate cyclase.<sup>43</sup> The dopamine agonists modulate motor function, as well as other non-motor activities such as cognition, emotion, and neuro-endocrine secretion. Clinical trials comparing dopamine agonists against levodopa showed that agonists can delay the onset of levodopa-induced dyskinesias, albeit with worse motor function, disability and other dopaminergic adverse events.<sup>43</sup> To reduce the risk of dyskinesias, young patients should preferably be prescribed monotherapy with a long-acting dopamine agonist. Despite the many ergot and non-ergot agonists available in the market, there is a paucity of data to guide the selection of the most appropriate agonist for the individual Parkinson's disease patient.<sup>43</sup> As more agonists become available, claims are usually made that the new products are superior to pre-existing agonists. At present, there is no clear evidence to indicate that any one dopamine agonist is superior to any other for the treatment of Parkinson's disease. As such, selecting a particular dopamine agonist should be influenced not only by the available pharmacologic and clinical information, but also by the clinician's familiarity with dosage, titration (if requires) and side effect profile.

Although dopamine agonists have similar side-effect profiles, retroperitoneal and pulmonary fibrosis appear to be more frequent in patients treated with the older ergot agonists (e.g. bromocriptine, pergolide, cabergoline). This is presumably caused by ergot-related vasoconstriction.<sup>39</sup> Of particular concern is the association of ergot agonists with valvular heart disease.<sup>39</sup> More studies need to be carried out to determine if this is a class effect for all ergot dopamine agonists.

**Ergot agonists should be used with caution in patients with renal and heart problems.** Non-ergot dopamine agonists are not without side effects, however. Edema of the distal leg and ankle is frequently seen with non-ergot agonists.<sup>43</sup> Recently, sleep-related automobile accidents have been reported with the non-ergot agonists, pramipexole and ropinirole. Initially thought to be restricted to non-ergot agonist, more recent published reports suggest that this is likely a class effect and common to all dopamine agonists.<sup>44,45</sup>

**A** Dopamine agonists are efficacious as symptomatic monotherapy. Dopamine agonists may also be used as an adjunct to levodopa in the treatment of Parkinson's disease.<sup>34,45a,45b</sup>

**Grade A Level 1+**

**GPP** In younger Parkinson's disease patients, therapy should commence first with dopamine agonists rather than levodopa.

**GPP**

### **Anticholinergic agents**

Drugs with anticholinergic properties have been used to treat Parkinson's disease long before dopamine was discovered as a neurotransmitter.<sup>46</sup> Although efficacious for control of symptoms, the antiparkinsonian effects are usually minimal. In Singapore, the most common anticholinergic agent used is Benzhexol (Artane). Side effects include xerophthalmia (dry eyes), xerostomia (dry mouth), urinary retention, constipation, confusion, hallucinations and blurred vision. Other side effects include tachycardia, impaired sweating, gastrointestinal obstruction, and megacolon. Anticholinergic agents may also precipitate acute angle glaucoma.<sup>47</sup> Although anticholinergic agents are commonly used as initial therapy for Parkinson's disease, especially in cases where tremor is predominant, there is little evidence that anticholinergic agents are better than levodopa for ameliorating tremors.<sup>48,49</sup> Anticholinergic agents should be used with caution in elderly patients in view of their central and peripheral anticholinergic side effects.

**B** Anticholinergic agents may be used as symptomatic monotherapy or as an adjunct to levodopa to treat tremors and stiffness in Parkinson's disease.

**Grade B, Level 1+**

### **Amantadine**

Initially marketed as treatment for influenza, amantadine was serendipitously discovered to have beneficial effects in Parkinson's disease.<sup>50</sup> It has been proposed that it produces benefit in Parkinson's disease via anti-glutamatergic effects, and blockade of N-methyl-D-aspartate (NMDA) receptors.<sup>51,52</sup> Interest in amantadine has resurfaced recently with reports of its anti-dyskinetic properties, possibly related to glutamate antagonism. However, the antidyskinetic effects of amantadine seldom last for more than a year.<sup>53</sup>

Adverse effects include livedo reticularis, leg edema, confusion, and hallucinations. In addition, abrupt withdrawal or dose reduction can precipitate a rebound psychosis or the neuroleptic malignant syndrome.<sup>54</sup> Amantadine has been shown to be effective in Parkinson's disease treatment.<sup>55-59</sup> Amantadine should be used with caution in patients with renal impairment, urinary tract infection and dehydration.

- A**
1. Amantadine may be given as symptomatic monotherapy or as an adjunct to levodopa for the treatment of Parkinson's disease.
  2. Amantadine may be considered as therapy to reduce dyskinesia in patients with Parkinson's disease who have motor fluctuations.

**Grade A, Level 1+**

### **Catechol-O-methyltransferase (COMT) inhibitors**

In addition to being metabolized by dopa decarboxylase, levodopa is also metabolised by peripheral catechol-O-methyltransferase (COMT) to 3-O-methyldopa. Inhibition of COMT prolongs the plasma elimination half-life of levodopa, thereby prolonging the clinical levodopa response.

Tolcapone was the first COMT inhibitor introduced in 1998, but was subsequently discovered to induce hepatotoxicity.<sup>60,61</sup> It has since been withdrawn in most countries, including Singapore. Entacapone, the other COMT inhibitor, is effective in reducing off time in Parkinson's disease patients.<sup>62-65</sup>

Side effects of entacapone are attributable to enhanced dopaminergic effects, i.e. dyskinesia, nausea, orthostatic hypotension, and hallucinations. Other side effects include diarrhoea and discoloration of urine. To date, there have been three possible cases of entacapone-induced hepatic dysfunction<sup>66</sup>, but no fatalities. Patients taking entacapone may need to reduce their daily levodopa intake if dyskinesia appears or is exacerbated. Although there is no requirement to monitor hepatic enzymes during entacapone treatment, it should be used with caution in patients with hepatic impairment.

Stalevo is a '3-in-1' tablet that contains levodopa, carbidopa (a peripheral decarboxylase inhibitor), and entacapone. Essentially, taking one tablet of stalevo is the same as taking a 200 mg tablet of entacapone and a standard dose of Sinemet (with a

levodopa/carbidopa ratio of 4:1). The preparations available in Singapore include Stalevo 50 (with 50 mg of levodopa) and Stalevo 100 (with 100 mg of levodopa).

It is believed that continuous dopaminergic stimulation may reduce onset of dyskinesias and motor fluctuations.<sup>67</sup> However, whether early administration of entacapone together with levodopa can delay dyskinesias or motor fluctuations is not known. There are on-going clinical studies to address this issue.<sup>68</sup> There is no significant difference between taking Stalevo and taking entacapone plus Madopar or SINemet with regard to efficacy and the safety profile.<sup>69</sup>

**A** Entacapone is efficacious and may be used together with levodopa in patients with motor fluctuations.

**Grade A, Level 1+**

### **Monoamine oxidase-B Inhibitors**

Selegiline is, currently, the most widely used monoamine oxidase-B inhibitor for Parkinson's disease. Meta-analyses have shown that MAO-B inhibitors do not appear to delay disease progression but may have a beneficial effect on motor fluctuations. There is presently no conclusive evidence that selegiline is associated with increased mortality<sup>39,70</sup> despite early fears to the effect.

**B** Selegiline is efficacious as a symptomatic monotherapy and may be used in early stages of Parkinson's disease.

**Grade B, Level 1++**

## **6.2 Pharmacotherapeutic management: Nonmotor symptoms in Parkinson's disease**

### **6.2.1 Neuropsychiatric symptoms in Parkinson's disease**

#### **Depression**

**D** Amitriptyline may be considered to treat depression in Parkinson's disease without dementia.<sup>71</sup>

**Grade D, Level 4**

### **Psychosis**

**D** Parkinson's disease patients with psychosis may be treated with clozapine, although leukopaenia is a potential side effect.<sup>71</sup> Quetiapine may also be considered, but not olanzapine.<sup>71</sup>

**Grade D, Level 4**

### **Dementia**

**D** Donepezil or rivastigminie may be considered for Parkinson's disease patients with dementia.<sup>71</sup>

**Grade D, Level 4**

## **6.2.2 Autonomic dysfunction in Parkinson's disease**

Autonomic dysfunction is a common side effect in Parkinson's disease, though it may be a side effect of standard pharmacotherapy. A significant minority of Parkinson's disease patients experience disabling autonomic impairment.

### **Orthostatic hypotension**

#### **Midodrine**

Midodrine is a peripheral alpha adrenergic agonist without cardiac effect. It may be used to treat orthostatic hypotension, although it can cause supine and even standing hypertension.<sup>72</sup>

#### **Fludrocortisone**

Fludrocortisone enhances sodium reabsorption and potassium excretion in the kidney, and causes a rise in blood pressure by causing an increase in blood volume and cardiac output.<sup>72</sup> Hypertension, hypokalaemia and ankle oedema are known adverse effects.

**D** Midodrine may be used in the treatment of orthostatic hypotension in Parkinson's disease.<sup>72</sup>

**Grade D, Level 4**

**D** Fludrocortisone may also be used to treat orthostatic hypotension in Parkinson's disease, but its use is limited by adverse effects.

**Grade D, Level 4**

### **Gastrointestinal side effects**

**D** Constipation and reduced gastric motility are common in Parkinson's disease. Anorexia, nausea and vomiting are common side effects of dopamine agonist therapy. Domperidone, which blocks peripheral dopamine receptors, increases gastric emptying and may reduce drug-induced gastrointestinal side effects.<sup>72</sup>

**Grade D, Level 4**

### **Erectile dysfunction**

**D** Erectile dysfunction in patients with parkinson's disease may be treated with sildanefil, although the patient has to be forewarned of side effects like headaches, transient visual effects and flushing, and dangerous side effects like cardiac arrest and hypotension. Priapism is also known to occur.<sup>72</sup>

**Grade D, Level 4**

## 7 Surgical Management of Parkinson's Disease

Surgery for Parkinson's disease has long been recognized as a valuable addition to medical therapy in the management of severe advanced Parkinson's disease. Surgery is directed towards one of 2 hyperactive nuclei in the basal ganglia: the subthalamic nucleus or the globus pallidus pars internus. The subthalamic nucleus is the preferred target in the majority of cases. Surgery involves the placement of stimulating electrodes (Deep Brain Stimulation) into the relevant nucleus to depolarize it.<sup>73</sup> The electrodes (usually placed bilaterally) are then connected to a battery implanted subcutaneously in the pectoral region, much like a cardiac pacemaker.

An alternative to Deep Brain Stimulation is lesioning surgery, where the target nucleus is destroyed by coagulating it. Deep Brain Stimulation is preferable to lesioning because it is non-destructive, reversible, adjustable and associated with less side effects.<sup>73-79</sup> It is, however, more costly.<sup>80</sup> In appropriately selected cases, lesioning has a clear role.<sup>81</sup>

There is a body of published evidence supporting the efficacy of Deep Brain Stimulation in Parkinson's disease, in terms of significantly reduced "off" time, dyskinesias and medication dose, in addition to significantly improving motor function, reducing disability and improving quality of life.

Parkinson's surgery (Deep Brain Stimulation or lesioning) can now be performed dependably, with minimal morbidity. It is, however, a complex undertaking. For optimal results, it is best performed in a tertiary center with an experienced, well-trained and well-equipped surgical team. Such a team, working within a multidisciplinary setting, will evaluate patients as to suitability for surgery, provide pre- and post-operative evaluation, perform intra-operative neural recording and stimulation, and manage stimulation parameters and medication adjustments post-operatively.

**A** Surgery may be efficacious in the treatment of motor complications of Parkinson's disease. Such patients may be referred to a Neurologist for surgical evaluation.<sup>73</sup>

**Grade A, Level 1+**

## 8 Ancillary Management of Parkinson's Disease

Although pharmacotherapy and surgery can improve the quality of life of the patient with Parkinson's disease, ancillary management cannot be overlooked. Intuitively, rehabilitation services comprising physical, occupational and speech therapy, can do much to help patients who have gait difficulties, dysphonia or dysphagia.<sup>82</sup>

<b>Problem</b>	<b>Support service</b>	<b>Management</b>
General fatigue	Physical therapy <sup>83-85</sup>	Exercise therapy
Gait difficulties/ start hesitation/ falls	Physical therapy <sup>85,86</sup>	Gait training Strengthening exercises Visual and auditory cues
Difficulty with activities of daily living (work, leisure and self-care activities)	Occupational therapy <sup>86</sup>	1. Group occupational therapy 2. Occupational aids
Dysphonia	Speech therapy <sup>87</sup>	1. Lee Silverman Voice Treatment (LSVT) 2. Pitch Limited Voice Treatment (PLVT)
Stuttering	Speech therapy <sup>88</sup>	1. Prosody exercises 2. Chorus speech 3. Smooth speech 4. Delayed auditory feedback
Tachyphemia and problems with prosody (intonation, rhythm, and lexical stress in speech)	Speech therapy <sup>86</sup>	1. Prosody exercises 2. Smooth speech
Dysarthria	Speech therapy <sup>86</sup>	1. Lee Silverman Voice Treatment (LSVT)
Dysphagia	Speech therapy	Investigation and intervention (thickeners) May require feeding via nasogastric tube or percutaneous endoscopic gastrostomy

Other services which may be useful include education, support services, professional, legal and financial counseling, management of the emotional needs of the patient and caregiver, exercise, diet/nutrition, home help and respite care.

## 9 Special Considerations

Three main groups of Parkinson's disease patients need special consideration:

- Young-onset Parkinson's disease
- Pregnant
- Elderly

The patient with *young-onset Parkinson's disease* has a long treatment horizon, and is more likely to develop motor complications. In addition, a genetic cause of Parkinson's disease has to be considered in the young-onset Parkinson's disease patient with a positive family.<sup>89</sup>

Although there have been no reports of teratogenicity in *pregnant* patients with Parkinson's disease, the British National Formulary states that all antiparkinsonian medications are contraindicated in pregnancy.<sup>90</sup> In animal models, high doses of levodopa can lead to stillbirth. Concerns have been voiced about the use of dopamine agonists, especially ergot derived dopamine agonists, in pregnancy.<sup>90</sup> The pregnant state is also thought to cause the symptoms of Parkinson's disease to deteriorate.

The main consideration in the *elderly* patient with Parkinson's disease is that of neuropsychiatric symptoms. Elderly patients are prone to developing confusion, sedation and psychosis with Parkinson's disease medications (especially selegiline, anticholinergics and dopamine agonists). A number of them are already on other medications for various conditions, and drug interactions may result in potentiation of these adverse effects. As such, it is wise to forewarn the patients and their carers of the possibility of these side effects, and to consider levodopa monotherapy.<sup>89</sup> In addition, elderly Parkinson's disease patients are more susceptible to falls, and may recover less quickly from such falls.

**Cost-effectiveness of Parkinson's disease drugs**

**GPP** The cost of therapy should be considered in the choice of Parkinson's disease medication.

**GPP**

**GPP** Generic formulations usually cost less than non-generic drugs and are acceptable if they meet prescribed standards of quality.

**GPP**

Examples of generic drugs for the treatment of Parkinson's disease include levodopa, benzhexol, bromocriptine and selegiline. Some combination preparations may cost less than the total cost of their separate components or when social costs are considered. A recent study concluded that levodopa/carbidopa/entacapone (Stalevo) in the treatment of Parkinson's disease patients with wearing-off was more likely to offer savings to society as a whole compared to standard therapy of levodopa/copa decarboxylase inhibitor with other anti-parkinsonian medications added as needed.<sup>91</sup> Another study also found that slow-release preparations (i.e. Sinemet CR vs Sinemet) which are more costly, may be more cost-effective in patients with motor fluctuations.<sup>92</sup> However, for initial treatment of Parkinson's disease, a study found no added benefit pramipexole over levodopa treatment.<sup>93</sup>

To date, there has been no vigorous study to support the use of generic Parkinson's disease formulations over non-generic ones. The choice of Parkinson's disease drug should be tailored to the individual patient, taking into account risk profile, cost, side effects, drug interactions and patient preference.

Ideally, patients with Parkinson's disease should be co-managed with the specialist, unless the disease is stable. Parkinson's disease patients should be referred to the specialist at the time of diagnosis for an initial consultation.

**GPP** The following patients should be referred to the specialist:

1. Young-onset Parkinson's disease
2. Atypical Parkinson's disease
3. Patients who do not respond to levodopa or dopamine agonists
4. Patients with cognitive impairment or neuropsychiatric dysfunction
5. Parkinson's disease complicated by dyskinesias
6. Parkinson's disease patients with family history of Parkinson's disease
7. Patients with dystonia, myoclonus or gaze palsies

**GPP**

Parkinson's disease Diagnostic criteria proposed by Gelb DJ et al.<sup>16</sup>

**Table A Grouping of clinical features according to diagnostic utility**

<p><b><i>Group A features: characteristic of Parkinson's disease</i></b></p> <ol style="list-style-type: none"><li>1. Resting tremor</li><li>2. Bradykinesia</li><li>3. Rigidity</li><li>4. Asymmetric onset</li></ol>
<p><b><i>Group B features: suggestive of alternative diagnoses</i></b></p> <ol style="list-style-type: none"><li>1. Features unusual early in the clinical course<ul style="list-style-type: none"><li>• Prominent postural instability in the first 3 years after symptom onset</li><li>• Freezing phenomenon in the first 3 years</li><li>• Hallucinations unrelated to medications in the first 3 years</li><li>• Dementia preceding motor symptoms or in the first year</li></ul></li><li>2. Supranuclear gaze palsy or slowing of vertical saccades</li><li>3. Severe, symptomatic dysautonomia unrelated to medications</li><li>4. Documentation of a condition known to produce parkinsonism and plausibly connected to the patient's syndrome (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)</li></ol>

**Table B Proposed diagnostic criteria for Parkinson’s disease**

<p><b>1. Criteria for POSSIBLE diagnosis of Parkinson’s disease</b>          At least 2 of 4 features in Group A are present, at least 1 of these is tremor or bradykinesia.</p> <p style="text-align: center;"><b>And</b></p> <p><b>Either</b>      None of the features in Group B is present  <b>Or</b>              Symptoms have been present for less than 3 years, and none of the features in group B is present to date</p> <p style="text-align: center;"><b>And</b></p> <p><b>Either</b>      Substantial and sustained response to levodopa or a dopamine agonist has been documented  <b>Or</b>              Patient has not had an adequate trial of levodopa or dopamine agonists.</p>
<p><b>2. Criteria for PROBABLE diagnosis of Parkinson’s disease</b>          At least 3 of 4 features in Group A are present</p> <p style="text-align: center;"><b>And</b></p> <p>None of the features in Group B is present (note: symptoms duration of at least 3 years is necessary to meet this requirement)</p> <p style="text-align: center;"><b>And</b></p> <p>Substantial and sustained response to levodopa or a dopamine agonist has been documented.</p>
<p><b>3. Criteria for DEFINITE diagnosis of Parkinson’s disease</b>          All criteria for POSSIBLE Parkinson’s disease are met</p> <p style="text-align: center;"><b>And</b></p> <p>Histopathological confirmation of the diagnosis is obtained at autopsy.</p>

### **The UK Parkinson's Disease Society Brain Bank criteria<sup>10</sup>**

#### **1. Diagnosis of Parkinsonian Symptom:**

BRADYKINESIA (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions).

And at least one of the following:

- a. muscular rigidity
- b. 4-6 Hz rest tremor
- c. postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.

#### **2 Exclusion criteria for Parkinson's disease:**

- a. history of repeated strokes with stepwise progression of Parkinsonian features
- b. history of repeated head injury
- c. history of definite encephalitis
- d. oculogyric crises
- e. neuroleptic treatment at onset of symptoms
- f. more than one affected relative
- g. sustained remission
- h. strictly unilateral features after three years
- i. supranuclear gaze palsy
- j. cerebellar signs
- k. early severe autonomic involvement
- l. early severe dementia with disturbances of memory, language and praxis
- m. Babinski sign
- n. presence of a cerebral tumor or communicating hydrocephalus on CT scan
- o. negative response to large doses of levodopa (if malabsorption excluded)
- p. MPTP exposure

- 3. Supportive prospective criteria for Parkinson's disease.** Three or more required for diagnosis of definite Parkinson's disease.
- a. unilateral onset
  - b. rest tremor present
  - c. progressive disorder
  - d. persistent asymmetry affecting the site of onset most
  - e. excellent response (70-100%) to levodopa
  - f. severe levodopa-induced chorea
  - g. levodopa response for 5 years or more
  - h. clinical course of 10 years or more

## Clinical Quality Improvement

The following clinical quality improvement parameters, based on recommendations in these guidelines, are proposed:

1. Every new drug that is prescribed to the Parkinson's disease patient should have a documentation of the response to the therapy and occurrence of the drug's side effects.
2. All patients with Parkinson's disease should have documentation that they were asked about the occurrence of recent falls.
3. All patients with Parkinson's disease should have documentation that they were asked about the occurrence of depression.
4. All patients with Parkinson's disease should have documentation that they were asked about the occurrence of recent orthostatic hypertension
5. If a Parkinson's disease patient is receiving clozapine for psychosis, then blood monitoring should be performed to monitor for leucopenia.
6. All Parkinson's disease patients who are not bed-bound should receive an assessment of their activity level and be provided with counselling to promote physical activity

## Useful Links

1. Parkinson's Disease Society of Singapore: [www.parkinsonsingapore.com](http://www.parkinsonsingapore.com)
2. WE MOVE™ (Worldwide Education and Awareness Movement Disorders): [www.wemove.org](http://www.wemove.org)
3. U.S.National Parkinson Foundation: [www.parkinson.org](http://www.parkinson.org)

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## Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category III (Self-Study) of the SMC Online CME System. Before you login to claim the CME point, we encourage you to evaluate whether you have mastered the key points in the Guidelines by completing this set of MCQs. This is an extension of the learning process and is not intended to “judge” your knowledge and is not compulsory. The answers can be found at the end of the questionnaire.

*Instruction: Choose the right answer.*

1. Which of the following is NOT a clinical feature of Parkinson’s disease?
  - A) Cogwheel rigidity
  - B) Postural instability
  - C) Bradykinesia
  - D) Ataxia
  - E) Masked facies
2. Which of the following features is NOT a feature of idiopathic Parkinson’s disease?
  - A) Extensor plantar response
  - B) Limb bradykinesia
  - C) Cogwheel rigidity
  - D) Limb tremors at rest
  - E) Shuffling gait
3. Which ONE of the following clinical features EXCLUDES a diagnosis of idiopathic Parkinson’s disease?
  - A) Rest tremors
  - B) Asymmetric cogwheel rigidity
  - C) Kayser-Fleischer ring
  - D) Constipation
  - E) Retropulsion
4. A 50 year-old man is diagnosed to have idiopathic tremor-predominant Parkinson’s disease. Which of the following drugs would you prescribe FIRST?

- A) Levodopa/carbidopa
  - B) Bromocriptine
  - C) Benzhexol
  - D) Entacapone
  - E) Amantadine
5. A 64 year-old woman with idiopathic tremor-predominant Parkinson's disease diagnosed 10 years ago has motor fluctuations in the form of "wearing off" and levodopa-induced dyskinesias, which are bothersome. What drug may be prescribed to ameliorate her dyskinesias?
- A) Selegiline
  - B) Benzhexol
  - C) Bromocriptine
  - D) Levodopa/Carbidopa/Entacapone
  - E) Amantadine
6. The following are known adverse effects of ergot dopamine agonists EXCEPT
- A) Sedation
  - B) Confusion
  - C) Retroperitoneal fibrosis
  - D) Myocardial infarction
  - E) Pulmonary fibrosis
7. Which of the following is NOT a non-motor symptom of Parkinson's disease?
- A) Dementia
  - B) Decreased visual acuity
  - C) Depression
  - D) Erectile dysfunction
8. Which of the following patients need NOT be referred to a specialist?
- A) 23 year-old man with slowed movements, rigidity and rest tremors
  - B) 39 year-old female patient with Parkinson's disease who has a sister and uncle with Parkinson's disease
  - C) 54 year-old man with rest tremors, left sided bradykinesia, cogwheel rigidity and good response to dopamine agonists.
  - D) 61 year-old woman with slowed movements, constipation, orthostasis and minimal response to levodopa.
  - E) 49 year-old man with ataxia, left extensor plantar response, bradykinesia, erectile dysfunction and symptomatic orthostasis.

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**Answer:**

1. D ( Pgs 8,9 )
2. A ( Pgs 8,9 )
3. C ( Pg 8 )
4. B ( Pg 17 )
5. E ( Pg 18 )
6. D ( Pg 16 )
7. B ( Pgs 19-21 )
8. C ( Pg 26 )

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# MOH CLINICAL PRACTICE GUIDELINES 6/2007

## Parkinson's Disease



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Academy of Medicine,  
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MINISTRY OF HEALTH  
SINGAPORE

## Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

### Diagnosis of Parkinson's Disease

**D** The schema below shows the factors that should be considered in the diagnostic process of Parkinson's disease (pg 8):

1. Confirm the presence of parkinsonism i.e. the presence of rest tremors, cogwheel rigidity and bradykinesia (See 3.1 and 3.2)
2. Detect atypical features that suggest an alternative diagnosis to Parkinson's disease
3. Assess whether the diagnostic criteria for Parkinson's disease are fulfilled

**Grade D, Level 3**

**D** The following atypical features may be considered when distinguishing atypical parkinsonian syndromes from idiopathic Parkinson's disease (pg 10):

- Frequent falls within 1 year of disease onset
- Poor response to levodopa
- Symmetry at onset
- Rapid progression (to Hoehn and Yahr stage 3 within 3 years)
- Lack of tremor
- Dysautonomia (urinary urge incontinence, fecal incontinence, urinary retention, persistent erectile failure, symptomatic orthostatic hypotension)

**Grade D, Level 3**

**GPP** The diagnosis of Parkinson's disease should be reviewed regularly and reassessed if atypical clinical features develop (pg 11).

**GPP**

## Management of Parkinson's Disease

**A** Although levodopa is the most efficacious drug for the symptomatic management of both early and late Parkinson's disease, the dose of levodopa should be kept to the minimum necessary to achieve good motor function (pg 15).

**Grade A, Level 1+**

**A** Dopamine agonists are efficacious as symptomatic monotherapy. Dopamine agonists may also be used as an adjunct to levodopa in the treatment of Parkinson's disease (pg 17).

**Grade A, Level 1+**

**GPP** In younger Parkinson's disease patients, therapy should commence first with dopamine agonists rather than levodopa (pg 17).

**GPP**

**B** Anticholinergic agents may be used as symptomatic monotherapy or as an adjunct to levodopa to treat tremors and stiffness in Parkinson's disease (pg 17).

**Grade B, Level 1+**

**A**

1. Amantadine may be given as symptomatic monotherapy or as an adjunct to levodopa for the treatment of Parkinson's disease.
2. Amantadine may be considered as therapy to reduce dyskinesia in patients with Parkinson's disease who have motor fluctuations.

(pg 18)

**Grade A, Level 1+**

**A** Entacapone is efficacious and may be used together with levodopa in patients with motor fluctuations (pg 19).

**Grade A, Level 1+**

**B** Selegiline is efficacious as a symptomatic monotherapy and may be used in early stages of Parkinson's disease (pg 19).

**Grade B, Level 1++**

**D** Amitriptyline may be considered to treat depression in Parkinson's disease without dementia (pg 19).

**Grade D, Level 4**

**D** Parkinson's disease patients with psychosis may be treated with clozapine, although leukopaenia is a potential side effect. Quetiapine may also be considered, but not olanzapine (pg 20).

**Grade D, Level 4**

**D** Donepezil or rivastigmine may be considered for Parkinson's disease patients with dementia (pg 20).

**Grade D, Level 4**

**D** Midodrine may be used in the treatment of orthostatic hypotension in Parkinson's disease (pg 20).

**Grade D, Level 4**

**D** Fludrocortisone may also be used to treat orthostatic hypotension in Parkinson's disease, but its use is limited by adverse effects (pg 20).

**Grade D, Level 4**

**D** Constipation and reduced gastric motility are common in Parkinson's disease. Anorexia, nausea and vomiting are common side effects of dopamine agonist therapy. Domperidone, which blocks peripheral dopamine receptors, increases gastric emptying and may reduce drug-induced gastrointestinal side effects (pg 21).

**Grade D, Level 4**

**D** Erectile dysfunction in patients with Parkinson's disease may be treated with sildenafil, although the patient has to be forewarned of side effects like headaches, transient visual effects and flushing, and dangerous side effects like cardiac arrest and hypotension. Priapism is also known to occur (pg 21).

**Grade D, Level 4**

### **Surgical Management of Parkinson's Disease**

**A** Surgery may be efficacious in the treatment of motor complications of Parkinson's disease. Such patients may be referred to a Neurologist for surgical evaluation (pg 22).

**Grade A, Level 1+**

### **Cost-effectiveness**

**GPP** The cost of therapy should be considered in the choice of Parkinson's disease medication (pg 25).

**GPP**

**GPP** Generic formulations usually cost less than non-generic drugs and are acceptable if they meet prescribed standards of quality (pg 25).

**GPP**

### **When to Refer to a Specialist**

**GPP** The following patients should be referred to the specialist (pg 26):

1. Young-onset Parkinson's disease
2. Atypical Parkinson's disease
3. Patients who do not respond to levodopa or dopamine agonists
4. Patients with cognitive impairment or neuropsychiatric dysfunction
5. Parkinson's disease complicated by dyskinesias
6. Parkinson's disease patients with family history of Parkinson's disease
7. Patients with dystonia, myoclonus or gaze palsies

**GPP**