gsk GlaxoSmithKline

CONSENSUS ON THE MANAGEMENT

of

PARKINSON'S DISEASE

Malaysia Parkinson Disease Society

CONTENTS

MESSAGE FROM THE PAST PRESIDENT, MALAYSIAN PARKINSON DISEASE SOCIETY

The truth is that **Parkinson's Disease(PD)** is a very much unknown disease in Malaysia. This is unfortunate because it causes long term physical, mental and social disabilities among elderly people. The exact prevalence of PD in Malaysia is unknown, but it could be up to 10 000 patients. As the proportion of elderly people in Malaysia increases over the next decade, PD is certainly going to become a significant health burden to the country.

In view of this, one of the major objectives of the ***Malaysian Parkinson's Disease Association(MPDA)*** is to create awareness of PD among the Malaysian community. We hope that there will be better health care for the Parkinson's community, especially in terms of quality of specific treatment. And this is exactly where the role of the Consensus Statement on PD is: it helps to update the Malaysian doctors on the recent advances in the treatment of PD, particularly the drugs and brain surgery.

I would to thank ***Dr S'ng Kim Hock(the Chairman of the Consensus Statement on PD)*** and ***Dr Samuel Easaw*** for their kind guidance and experience. Without both of them, this Consensus Statementt on PD would not be complete. I would also extend my gratitude to the ***Malaysian Society of Neuroscience*** and ***GlaxoSmithKline*** for their support.

Dr Chew Nee Kong
Past President of MPDA (www.mpda.org.my)
26th May 2006.

MESSAGE FROM THE CO-CHAIRMEN OF MALAYSIAN PARKINSON'S DISEASE CONSENSUS

Dear Doctor,

It is indeed a great privilege and honour for me and ***Dr Samuel Easaw*** to undertake this task of drafting the ***Malaysian Consensus for Parkinson's Disease***. So formidable the task it was, that we both hesitated and were deliberately bradykinetic for several months until the gentle persuasion of the then - ***Malaysian Parkinson's Disease Chairman Dr NK Chew*** moved us on.

Like any other consensus, it would not have been possible without the help and assistance of all parties - particularly the secretaries, the contributing members, participating members, fellow neurologists and neurosurgeons who contributed in comments and suggestions, international expert neurologists and reviewers, the secretariat and the ***Malaysian Parkinson's Disease Association***. We, on behalf of the committee say: "Terima kasih", which means Thank You in the Malay language.

There is no doubt that such a consensus is critically necessary at a time when accountability and responsibility rests on none other than the doctor's shoulders. Patients now know and want the best. The Internet is not only at their doorsteps or their bedroom, it is on their laptop and even pockets. Thus, doctors need to know too.

While this consensus is far from perfect, it hopes to give a reasonably concise and coherent bird's eye view of the whole problem and allow the doctor/practitioner to make a decision on how to proceed, how to treat, whether to treat and to follow-up of patients with PD. I have no doubt that it may well be out of date in a matter of months. Nevertheless, it can still be a useful guideline or aid to good care of patients with **Parkinson's Disease**.

We welcome your views, comments, even critical review of this Consensus, which is written for you, by your neurology colleagues for your neurological patients.

Like any consensus, it is of little use sitting on the shelf. Thank you for reading it!

Dr Sng Kim Hock | Dr Samuel Easaw
Co Chairmen Malaysian Parkinson's Disease Consensus

1.0 INTRODUCTION

Parkinson's Disease (PD) is a chronic, disabling neurodegenerative disease affecting about 1% of the population above the age of 65 years The mean prevalence of PD is approximately 160 per 100,000 and incidence 20 per 100,000, rising by several - fold with age.

This consensus is aimed at all practitioners to assist in arriving at an accurate diagnosis and a guide to the care of patients, especially with the availability of a wider ranger of medication and therapeutic modalities in the management of Parkinson's Disease.

2.0 CLINICAL DIAGNOSIS OF PARKINSON'S DISEASE: UK BRAIN BANK CRITERIA

The criteria for diagnosis are based on clinical grounds with bradykinesia, rigidity, tremor and postural instability as the main cardinal features. PD needs to be differentiated from all other disorders that cause parkinsonism. **Please see Appendix I.**

This consensus adopts the UK Brain Bank Criteria [1992].

UK Parkinson's Disease Society Brain Bank Criteria[1]

Step 1 : Diagnosis of Parkinsonian syndrome

Bradykinesia plus at least one of the following...

- Muscular rigidity
- Rest tremor
- Postural instability

Step 2 : Exclusion criteria including

- History of repeated strokes
- History of repeated head injury
- History of definite encephalitis

Step 3 : Supportive prospective criteria
(at least three required)

- Unilateral onset
- Rest tremor present
- Evidence of progression
- Persistent asymmetry
- Excellent response to L - dopa
- Severe L-dopa-induced chorea
- L - dopa response for 5+ years
- Clinical course of 10+ years

3.0 CLINICAL FEATURES

Early non-specific features include easy fatigability, tiredness, malaise, lethargy and cramp-like sensation in the legs, besides deterioration in handwriting (micrographia), difficulty in concentration, overall tremulousness, sleep disturbances and general slowness in motor activity.

Notes

Bradykinesia

Bradykinesia/Akinesia is an absolute hallmark feature of PD and correlates best with the extent of doparninergic loss in the basal ganglia. It refers to slowness of initiation of voluntary movement with progressive reduction in amplitude and speed of repetitive actions.

Bradykinesia affects speech, initially a loss of normal fluctuations of pitch and volume (hypophonic) and later slowness of initiation and a monotonous speech. There is also reduction or loss of arm swing during walking, often asymmetrical, unlike in normal ageing. Paucity of facial gestures with reduced blinking is classically described as 'mask-like' facies.

mask-like facies

Tremor

Tremor is characteristically described as 'pill-rolling' with a frequency of 3-5Hz and occurs at rest when the limb is fully supported. Seen in 70% of patients, usually unilateral and upper limb initially, it disappears in sleep, is exacerbated with stress.

'Tremor predominant' PD has a relatively better prognosis compared to the akinetic-rigid type of PD.

Involvement of the jaw, tongue or trunk may also occur late in illness. Isolated head tremor is unusual in PD. Postural tremor may be concurrent or be the predominant form of tremor.

pill-rolling

Rigidity

Rigidity in PD is described as resistance to passive movements. The lead-pipe or sustained type of rigidity refers to resistance to passive movements in both directions. Cogwheel (ratchety) type refers to the intermittent jerky type of rigidity due to superimposed tremor. Other features of rigidity in PD are asymmetrical onset, involving extremities initially and may be enhanced by simultaneous repetitive tasks on the contralateral limb.

Axial rigidity leads to the typical stooped posture. It is tested by rotating the patient sideways while standing. Marked axial rigidity early in the disease is atypical and points to Progressive Supranuclear Palsy.

Postural Instability

Postural imbalance can be due to many causes. Axial rigidity and akinesia lead to freezing phenomenon, difficulty turning and falls. In advanced disease, loss of postural reflexes further contributes to the gait instability, demonstrated by a positive pull-test [Gently tugging the upright patient from behind tips the patient backwards]. Finally, medications such as dopamine agonists and anticholinergics contribute to further impairing postural balance in patients.

progressive supranuclear palsy

postural balance

4.0 NON-MOTOR MANIFESTATIONS

Recognition of non-motor manifestations of PD is equally important as the latter contributes significantly to the overall quality of life of patients with PD.

A Dementia and Depression

Dementia due to degeneration of cholinergic pathways in frontal region can be as high as 40%. Impairment in the visuospatial and executive abilities results in apathetic, less attentive and withdrawn patient - mimicking akinesia. Alzheimer's disease may coexist in elderly patients with PD. If dementia occurs within two years, consider Diffuse Lewy Body Disease.

B Autonomic impairment

Autonomic impairment in PD typically leads to orthostatic hypotension, postural imbalance, constipation, urinary symptoms such as frequency, urgency, and hesitancy and sexual dysfunction. In addition, these symptoms may be exacerbated by the use of anticholinergics, which are commonly prescribed in such patients.

C Sleep disturbance

Sleep disturbance in PD is common and includes excessive daytime somnolence, fragmented REM sleep and difficulty sleeping at night and early morning awakening.

Other non-motor manifestations include dysphagia, dysarthria, limb paraesthesia, restless leg syndrome, diplopia and impaired sense of smell (anosmia).

D Gait disorder

Gait disorder in PD deserves a special mention. The combination of rigidity and bradykinesia leads to the typical 'shuffling gait' of PD. A typical PD patient will walk with small, shuffling steps, with a stooped posture as a result of axial rigidity and later on, postural instability may result in imbalance or even falls. There will be difficulty at the initiation of gait with difficulty turning and stopping (festinant). In addition, there may also be asymmetrical or bilateral loss of arm swing during walking.

shuffling gait

5.0 CLINICAL STAGING OF PARKINSON'S DISEASE

Clinical staging is based on the extent of disease involvement using the Hoehn and Yahr classification.

Stage I	Unilateral disease
Stage II	Bilateral disease with no postural instability
Stage III	Worsening bilateral disease with postural imbalance
Stage IV	Worsening of disease; patients are unable to live alone or independently
Stage V	Patients need wheelchair assistance; bed-bound

6.0 AETIOLOGY AND PATHOGENESIS OF PARKINSON'S DISEASE

The etiology of PD remains largely unknown, except for a small group where there is a definite genetic basis. The following factors have been implicated :

Environmental

Epidemiological studies have implicated the following risk factors: pesticides / herbicides, rural environment, consumption of well water and proximity to industrial plants or quarries.

Toxins – MPTP - *induced parkinsonism*

Further evidence for an exogenous toxin was provided by the emergence in 1983 of cases of parkinsonism among drug users. 1-methyl-4-phenyl-1 ,2,3,6-tetrahydropyridine (MPTP), a contaminant in the manufacture of "designer drugs", was shown to result in selective destruction of the substantia nigra. Subsequently, it was demonstrated that the metabolite MPP+ produces parkinsonism in animal models. MPP+ accumulates in mitochondria, where it inhibits complex I. Other chemicals which are inhibitors of complex I may also cause similar toxicity.

Genetic factors

Twin studies indicate that genetic factors are important when onset of PD is before the age of 50. Familial clusters of PD have long been recognised. These genetic discoveries have provided invaluable insights into the pathogenesis of the disease.

To date, mutations in 5 genes have been identified: a-synuclein, parkin, DJ-1, PINK1, and LRRK2. Mutations in 2 of these genes turned out to be frequent enough to have relevance in clinical practice: parkin mutations are common in early-onset familial and sporadic PD; moreover emerging

data delineate mutations in the LRRK2 gene (encoding the dardarin protein) as a frequent cause of the familial late onset PD forms, and even of few late-onset sporadic cases.

The PD-1 mutation has been shown to alter the configuration of alpha -synuclein into a structure that could aggregate into sheets. All PD may be associated with abnormal folding of alpha-synuclein, leading to excessive aggregation and neuronal death.

Although sporadic PD is not caused by a mutation in the alpha-synuclein gene, active investigation is underway into proteins that interact with alpha-synuclein, including those that guide, promote, or prevent aggregation of the protein.

Lewy bodies, the pathological hallmark of PD, consists of aggregates of synuclein. PD, together with dementia with Lewy bodies (DLB) and multiple system atrophy (MSA), all conditions which exhibit Lewy bodies, have been designated alpha-synucleinopathies.

Homozygous deletions in the Parkin gene on chromosome 6, have been found to cause autosomal-recessive juvenile parkinsonism (AR-JP) in Japan. This form of parkinsonism differs pathologically from PD in that no Lewy bodies are found in the substantia nigra.

Biological factors

- **Apoptosis (Programmed Cell Death)**
  This process is believed to be altered in PD.

- **Genetic studies have identified the proteins involved in PD to be alpha-synuclein, parkin and ubiquitin.**

- **Impaired removal of toxic protein aggregates.**

This may be caused by abnormal configuration of neuronal proteins or impaired degradation.

Alpha-synuclein is a major component of Lewy bodies in all cases of PD. Other than genetic mechanism in PD-1, other factors may alter the structure of alpha-synuclein causing abnormal folding and aggregation.

Parkin is a ligase enzyme that ubiquitinates for proteasomal degradation, proteins which are due for removal. Among these is alpha-synuclein. Failure of the ubiquitin-proteasome system is implicated in PD.

- **The oxidation Hypothesis**

Free radical damage results from the oxidative metabolism of dopamine.

7.0 INVESTIGATIONS

The cause of Parkinson's Disease is not known. There are no laboratory biomarkers for PD. Investigations are done mainly to exclude other causes that may mimic PD and for evaluation of atypical parkinsonism patients. Evaluation of patient's medical, surgical, drug and family history is vital, followed by complete neurological examination.

Blood tests include:

1	Thyroid function tests to exclude hypothyroidism.
2	Toxic screening if exposure or in younger onset PD, especially Manganese, mercury.
3	Copper metabolism studies (Wilson's disease) - Serum ceruloplasmin, serum/urinary copper excretion and slit-lamp examination for Kayser-Fleischer rings.
4	Genetic studies for Huntington's Disease.
5	CT brain scan - to rule out, cerebral infarcts, tumour, hydrocephalus, subdural hematomas, all of which can mimic parkinson's disease.
6	MRI brain not considered helpful for diagnosis of PD. MRI brain is considered for patients with uncertainties, eg when tremor is absent, acute or stepwise progression in illness and young patients.

MRI Brain may pick up abnormalities in Multi System Atrophy [putaminal abnormalities due to loss of neurons and gliosis with iron accumulation, pontine and cerebellar atrophy may occur. In Progressive Supranuclear Palsy, midbrain atrophy may be seen. In Cortico Basal Degeneration, mild to moderate cerebral atrophy with posterior frontal and parietal regions of contralateral side affected mainly.

Functional imaging with PET [^{18}F-L-Dopa] and SPECT [^{123}I-βCIT] is for clinical research, though it can confirm loss of nigrostriatal dopamine neurons and distinguishes idiopathic PD from atypical patients.

multi system atrophy

8.0 PRINCIPLES IN THERAPY OF PARKINSON'S DISEASE

Medical therapy is the mainstay in managing Parkinson's Disease. Surgery is an option to be considered in patients with moderately severe disease when quality of life is impaired despite optimal medical therapy.

Issues that confront the clinician are:

Decision to start medications

Patients with early or mild disease and have minimal functional disability may not need to be commenced on treatment. Several factors need to be considered in deciding when to begin especially age and occupation.

Choice of Medication

Dopamine agonists are currently considered as first line option especially in the early stage of the disease and in the younger PD patients. Current guidelines recommend that treatment with levodopa should be delayed as long as possible provided alternative drugs such as DA can achieve adequate symptom control.

Medication is satisfyingly effective in controlling the symptoms in the early stages of PD. The objective is to balance efficacy against potential long term side effects.

The choice of medication depends on the 'functional' age of the patient and whether tremor or the other symptoms are predominant. Older patients, above the age of 60 can be started on levodopa, while younger ones should be started on dopamine agonists. Other alternatives may be added on as the disease progresses. The use of dopamine agonists before inclusion of levodopa has been shown to delay the onset of dyskinesias.

Once medication is commenced, there is a need for monitoring side effects and clinical response. As the disease progresses, the efficacy of medications also diminish over the years, requiring the clinician to make adjustments and additions to maintain clinical benefit.

medical therapy

Neuroprotection

Efforts to discover neuroprotective therapy have produced limited success. To date, there has not been any major RCT evidence to support the routine use of any medications in the neuroprotective role.

Selegiline has been shown to delay the need to initiate patients on Levodopa by ten months while newer dopamine agonists, such as ropirinole and pramipexole may have neuroprotective benefits.

Are Certain Medications Potentially Neurotoxic?

At present, there is no clinical evidence to show that levodopa is toxic to the nigrostriatal neurons at the usual therapeutic dosages, although it has been in use for more than three decades.

5 main classes of drugs are available

A	Levodopa (+ peripheral dopa decarboxylase inhibitors)
B	Dopamine agonists
C	Anticholinergics
D	Amantadine
E	Enzyme Inhibitors such as Monoamine Oxidase Type B (MAO –B) Inhibitors, Catechol-O-Methyl Transferase (COMT) - Inhibitors

neuroprotective benefits

A. LEVODOPA

Levodopa remains the gold standard and is the most effective drug therapy for PD. Failure to respond to levodopa raises doubts to the diagnosis of PD. The long term use of levodopa however, has several inherent problems as listed below.

1. Motor fluctuations which include end of dose or "wearing off" effect, unpredictable motor fluctuations or "on-off" phenomenon, dose failures and freezing episodes.
2. Occurrence of disabling dyskinesias, as early as three years.
3. Poor response of non-motor symptoms to levodopa.

on-off phenomenon

a Patients above the age of 60 can be commenced on levodopa, using the lowest possible effective dose.

b Sinemet [levodopa+carbidopa] or Madopar [levodopa+ benzerazide] are both equally effective. Controlled release formulations Sinemet CR or Madopar HBS can also be used as first-line, or in combination with regular levodopa. Most patients can be maintained on a dosage of 300-400mg of levodopa reaching 600-800mg daily, as the disease progresses. Frequency of dosing can vary from twice to as frequent as 3 hourly, though slow release preparations and COMT inhibitors should be considered.

c Slow release preparations and addition of a COMT inhibitor produces a smoother drug level, with less fluctuation. The fluctuations between peak and trough levels or pulsatility of the drug levels in levodopa therapy appear to be a factor in development of dyskinesias.

COMT inhibitors are indicated when motor fluctuations, especially "wearing off" problems set in. They allow a longer duration of action when used with each dose of levodopa. STALEVO, a 3-in-one preparation with levodopa, carbidopa and entacapone is now available.

B. DOPAMINE AGONISTS

Dopamine agonists are indicated in early symptomatic disease in younger patients and as add-on therapy in more advanced disease.

Initiating therapy with a dopamine agonist has been shown to delay the onset of levodopa-induced dyskinesias. *There is early evidence that the newer non-ergot dopamine agonists may have a neuroprotective effect on the striatonigral neurons. (REF)*

Always begin with a low dose, gradually increasing to minimize side effects, the most common of which are nausea, vomiting, orthostatic hypotension, hallucinations and somnolence. Nausea can be reduced by taking it after meals, temporary dose reduction, and by concomitant use of domperidone, a peripheral dopamine antagonist (10 –20 mg tds).

Dopamine agonists have been shown to delay the need to start levodopa and to allow for lower doses of the latter when it is required

Dopamine agonists can be divided into ergot and non-ergot derivatives, the former include bromocriptine, pergolide, piribedil, and cabergoline. The latter include ropinirole and pramipexole.

ERGOT DOPAMINE AGONISTS

a. BROMOCRIPTINE	Begin with 1.25 mg once daily, gradually increasing to 40 mg per day in 3 – 5 divided doses. Some patients do not respond and others only modestly so.
b. PERGOLIDE (withdrawn from Malaysian market)	Begin with 0.05 mg once daily, gradually increasing by 0.05mg every 4-7 days up to 2-4mg a day, in 3 divided doses.
c. PIRIBEDIL	Dose - 50mg once daily gradually increasing to 50mg 5 times a day.
d. CABERGOLINE	Has a long duration of action, with a half-life of 65 hours. Can be used once daily or once every 2 days. Requires monitoring with ultrasonography for retroperitoneal fibrosis

e. PRAMIPEXOLE	Standard initial dose is 0.125 mg tds, increased weekly by 0.125mg tds till effective dose obtained or side effects occur. Average maintenance dose is 3 – 4.5 mg daily. The dose should be reduced in renal failure.
f. ROPINIROLE	Starting dose is 0.25 mg tds, increasing by the 0.25 mg tds weekly. Most clinicians agree that 3mg tds is the usual effective dose (up to as high as 9 mg tds may be required). Side effects include hallucinations, psychosis and other alterations in behaviour particularly in the elderly. A rare but serious side effect is retroperitoneal fibrosis in the case of longer acting ergot dopamine agonists. Sleepiness is a noted side effect of the non-ergot agonists.

C. ANTICHOLINERGIC AGENTS

The commonly used anticholinergic agent is benzhexol. Begin low with 1mg twice a day, increasing as the patient tolerates. It is useful in tremors and early motor symptoms. Side effects include blurring of vision, dry mouth and confusion in the elderly. Orphenadrine is an alternative.

- **PARENTERAL PREPARATIONS OF DOPAMINE AGONISTS**

- **APOMORPHINE** *(Currently not available in Malaysia)*
  Apomorphine is a useful parenteral dopamine agonist in patients with advanced disease with intractable "off" periods and incapacitating motor fluctuations. It has a rapid onset of action, usually within 10 minutes, and a short duration of action, 45 to 120 minutes. Domperidone, 10 – 20 mg tds, prior to injections, can prevent or reduce nausea and vomiting associated with its use.

- **LISURIDE** *(Currently Not Available In Malaysia)*
  Parenteral DA similar to apomorphine.

D. AMANTADINE

Amantadine is a tricyclic amine and is an old drug, having been used for decades as an antiviral agent. Its antiparkinsonian mechanism of action is not well understood. Putative effects include enhanced dopamine release, inhibition of dopamine reuptake, antimuscarinic activity and more recently its antagonism at the glutamate receptor level. It is useful in levodopa induced dyskinesias and motor fluctuations. Response is maintained for at least a year after treatment initiation. Typical maintenance dosage is 300 – 400mg a day in 3 – 4 divided doses.

Putative effects

E. ENZYME INHIBITORS

Monoamine Oxidase Type B Inhibitors (MAO B)

Selegiline 5-10mg daily given in the morning before noon has a potential symptomatic effect in early stage of PD and has been shown to delay the onset of need for levodopa for up to several months.

Catechol-O-Methyl Transferase (COMT)- Inhibitors

COMTAN used concomitantly with each dose of levodopa enables a lower dose as well as a more prolonged effect of levodopa. It allows a smoother drug delivery and reduces the 'pulsatility' of levodopa, which may be a contributory factor in the long term side effects of levodopa.

COMTAN is now included in a 3-in-1 preparation (STALEVO) comprising levodopa and benzerazide.

pulsatility of levodopa

NON-MOTOR COMPLICATIONS OF PARKINSON'S DISEASE

Non-motor complications associated with Advanced Parkinson's Disease (PD) may be classified as follows :

Autonomic Dysfunction

- **I** Constipation
- **II** Orthostatic hypotension
- **III** Seborrhea
- **IV** Pain / dysesthesias
- **V** Dysphagia
- **VI** Thermoregulation /sweating
- **VII** Sexual problems
- **VIII** Urinary problems

Falls

- **I** Postural instability
- **II** Symptomatic orthostatic hypotension
- **III** Freezing & festination
- **IV** Drug-induced dyskinesias
- **V** Others

Sleep Disorders

- **I** Restless legs syndrome (RLS) / periodic limb movements of sleep (PLMS)
- **II** Insomnia & sleep fragmentation
- **III** Nightmares & parasomnias
- **IV** REM sleep behaviour disorders
- **V** Excessive daytime sleepiness

Neuropsychiatric issues

- **I** Depression
- **II** Hallucinations / delirium
- **III** Cognitive impairment
- **IV** Behavioural impairment

CONSTIPATION

A commonly encountered problem as a results of the following mechanisms :

- Delayed colonic transit affecting all segments of the colon - thought to be from both central as well as peripheral causes
- Decreased basal anal sphincter pressures
- Hyper-contractile external sphincter response

The aim is to increase stool bulk by :

- adding more fibre to diet
  - eat more fruits & raw vegetables
  - eat products with bran
- increasing daily liquid intake
- exercise
- discontinue anticholinergics that inhibit gastric motility and result in gastrointestinal dryness
- stool softeners *e.g. lactulose preparations*

ORTHOSTATIC HYPOTENSION

Defined as a drop of 20 mm Hg in mean blood pressure when assessed in a supine position followed by a standing position.

Patients may be asymptomatic, have vague complaints of fatigue, headache, light-headedness and show cognitive slowing or be severe enough to have syncope.

The following measures may be tried :

- **I** discontinue any unnecessary medications - diuretics or antihypertensives
- **II** elevate head of bed and avoid lying flat
- **III** encourage consumption of 8 or more glasses of water / fluid a day
- **IV** be more liberal with salt in diet (upto 150 – 250 mEq)
- **V** increase intravascular volume with mineralocorticoids such as Fludrocortisone (0.1 – 0.6mg a day)
- **VI** Increase vascular resistance by stimulating alpha receptors.

A word of caution here and that is care must be taken to avoid congestive heart failure.

SEBORRHEA

Patients may not uncommonly complain of excessive oiliness, flaking & redness of skin. Clinicians may try :

- **I** Hydrocortisone cream 1%
- **II** Dandruff shampoos that contain salicylic acid and coal tars or selenium base
- **III** Ketoconazole as prescribed cream or shampoo
- **IV** Referral to a Dermatologist

Notes

PAIN / DYSESTHESIAS

This may be related to Parkinson's disease in which case, may be treated by adjusting and optimizing medication. Quite often, patients will find that these symptoms are more severe on the side in which parkinsonian symptoms are worse. It can also be due to arthritis or neuropathy.

optimizing
medication

DYSPHAGIA

Clinicians may come across patients complaining of a "choking' sensation when eating or difficulty in swallowing. These symptoms may be the result of esophageal dysfunction or abnormalities in the oropharyngeal phase of swallowing. Such patients should be advised to :

I Eliminate hard foods from their diet
II Increase dopaminergic therapy (levodopa) to tolerance level
III Eat only during "on" times
IV Have an expert assess the swallowing mechanism to define the nature of dysphagia
V As a last resort, invasive interventions e.g. feeding gastrostomy may be considered

Approximately two-thirds of PD patients will experience problems with 'drooling'. This is caused by saliva pooling in the oral cavity secondary to swallowing difficulties. Aspiration or chemical dermatitis may be serious consequences of this problem if not addressed. Measures worth considering are as follows :

I Increase dopaminergic therapy to improve swallowing and drooling
II Anticholinergic medication that can reduce saliva production BUT has considerable side effects to watch out for especially in the elderly
III Botulinum toxin injection in to the salivary glands

THERMOREGULATION / SWEATING

This may occur during "off" periods and respond to increased dopaminergic therapy. Alternatively, when associated with peak-dose chorea, dose reduction may be tried. Medical evaluation may be worthwhile to uncover any endocrine dysfunction or medical cause of impaired thermoregulation.

SEXUAL PROBLEMS

Loss of sexual interest has been commonly reported in PD patients in addition to lack of mobility and difficulty in achieving & maintaining erection as reasons for sexual dysfunction. Depression and the use of medication e.g. beta-blockers may also be 'culprits'.

Consider the following steps :

I Discontinue potentially offending drugs
II Treat depression
III Consultation with an urologist to exclude other causes and advise on management
IV Sildenafil citrate (Viagra®), a phosphodiesterase type V inhibitor for erectile dysfunction where indicated

peak-dose chorea

beta-blockers

URINARY PROBLEMS

Urinary frequency, urgency and nocturia may result from detrusor hyperreflexia with synergia or incomplete pelvic floor relaxation while instability of detrusor muscles causes urinary incontinence.

Consider :

I Cystometric studies and urological evaluation to rule out other causes
II Treating urinary tract infection, if present
III Reduce fluid intake in the evening and especially, after dinner
IV Add on anticholinergic medication : Propantheline (15 – 30 mg ON), Oxybutynine (5- 10 mg ON) or Hyoscamine
V Intermittent catheterization

Falls remain the leading cause of morbidity and mortality in elderly population and are pivotal in determining nursing home placement. Older age, longer duration of disease, advanced stage of disease, increased disability, inability to rise from chair postural instability and gait impairment are all predisposing factors. Other contributory factors may be associated medical conditions, environmental causes and dementia.

POSTURAL INSTABILITY

At present, there is no known therapy that is effective to treat postural instability and once present, this symptom is likely to progress with time. There is however, non-Parkinson's signs e.g. sensory dysfunction or weakness that should be considered as possibly contributory.

A clinician may want to consider the following :

I Poor mobility and shortened gait that may improve with increase levodopa therapy
II Aim to keep the patient active but safe
III Physiotherapy
IV Use of walking aids such as three-wheeled walker with hand brakes

FREEZING AND FESTINATION

Often, this occurs on initiating gait or when passing through a narrow spaces e.g. doorway. This incapacitating motor block may reflect inadequate or excessive dopaminergic effect though in the majority of cases, it remains independent of medication and refractory to treatment.

Close questioning and determination of the timing of the freezing may offer some clues as to the strategy to be adapted. Some of the non-pharmacological strategies (sensory cues) that may be tried are as follows :

- counting out a rhythm and trying to walk in time
- stepping over a stick / cane laid out in front, on the floor
- stepping towards a target on the floor
- walking in a 'military' style – slow march
- utilizing assistive devices such as canes with laser prompting

If anxiety is the underlying factor then measures should be directed at treating such a state as it may exacerbate freezing and motor blocks.

DRUG-INDUCED DYSKINESIAS – Kindly refer to chapter on motor complications.

SLEEP DISORDERS

Nearly 75% of PD patients will complain of sleep disturbances and reversal of sleep. Good sleep habits are worth emphasizing and sleep 'hygiene' should be looked into. Regular sleep schedules, reduction of daytime naps with reduced intake of stimulants e.g. caffeine at nighttime are simple measures to implement. Primary sleep disorders or medical conditions such as hypothyroidism should be addressed and treated if appropriate. Physicians should also review all current medications as these may affect sleep. If related to medications, then adjustments are to be made accordingly.

sleep hygiene

INSOMNIA & SLEEP FRAGMENTATION

If idiopathic insomnia detected, then use of short-acting sedating agents is permissible. Longer-acting hypnotics are to be considered only if patients have difficulty in staying asleep but resultant hangovers and potential falls in the morning are potential, undesirable consequences.

If a patient should awaken at night and find it difficult to go back to bed as he is in an "off" state, then a standard levodopa dose can be dissolved or chewed and swallowed to provide relief. Should the nighttime awakening be a result of dystonia, tremors or reduce movement, an extended-release levodopa, COMT inhibitor or Stalevo® may be utilized.

RESTLESS LEGS SYNDROME / PERIODIC LIMB MOVEMENTS

This is an uncomfortable sensation in the legs with paresthesias, 'crampy' aches and an overwhelming need to move or walk. Symptoms appear to worsen in the evening or at night and only improve when the patient walks or stretches. In over half of these patients there is also periodic limb movements of sleep (PLMS) which can last 5 to 6 seconds and occur every 20 to 40 seconds thereby disrupting sleep architecture. Dopa agonists e.g. Ropinirole® have been found to be effective in these situations with other treatment options to be considered being low-dose Clonazepam and extended-release formulations of levodopa. TCAs may exacerbate RLS and PLMS and should be avoided.

extended-release levodopa

extended-release formulations of levodopa

NIGHTMARES & PARASOMNIAS

Dopaminergic medications frequently induce vivid dreams. Eliminating or reducing TCA medications may be beneficial. Adding on Quetiapine (Seroquel®) at 25 – 100 m g ON) may also be helpful.

REM SLEEP BEHAVIOUR DISORDERS

More commonly, these are seen in elderly male patients with partners reporting unusual behaviour in the form of semi-purposeful actions, aggression and wandering. These patients may benefit from the use of clonazepam (0.5 – 2 mg ON)

Notes

NIGHTMARES & PARASOMNIAS

Potentially, this symptom may be caused by the disease itself, sleep disorders insomnia or medications. Measures to consider are as follows :

I Review medications that may be the cause of sleepiness e.g. dopa agonists. If possible, reduce or discontinue such medication
II If no obvious cause, then overnight sleep test (polysomnogram / PSG) should be arranged to detect possible sleep apnea or other sleep disorders
III Modafinil (Provigil®), a wake-promoting agent may be considered in the right setting

EXCESSIVE DAYTIME
SLEEPINESS

DEPRESSION IN PARKINSON'S DISEASE

- **Prevalence of depression in PD**

Anxiety and depression may be part of Parkinson's disease.
Depression occurs in about 40-50% of those with Parkinson's disease. Despite its high prevalence it is vastly unrecognised and untreated. Depression is usually mild to moderate and at times, occurs prior to onset of motor symptoms. Depression is more of an integrant part of Parkinson's disease indicating that mood disturbances might be more closely related to brain pathology. Interestingly enough, bipolar mood disorder seems to be rare in this population.

Prevalence of depression

- **Clinical features of depression in PD**

- Early loss of initiative
- Loss of self esteem
- Co-morbid panic attacks and other symptoms of anxiety
- Presence of depressive symptoms has been associated with more rapid deterioration of motor and cognitive functions.
- Those with depression have more physical disability as well.
- The impact of depression in PD is significant as it leads to a poorer quality of life.

- **Types of depression**

About one half of PD patients suffers from depression that fulfills DSM criteria for major depression while the other half had minor depression or dysthymia.

There are some clinical difference between depression suffered by patients with Parkinson's disease and primary depressive disorder

	Primary depressive disorder	Depression in Parkinson's disease
1	Excessive guilt	High levels of dysphoria
2	Self blaming	Anxiety
3	Psychotic features	Pessimism
4	Completed suicide	Irritability and suicidal ideation but no completed suicide

- **Risk factors for depression in patients with PD include:**

- Female gender
- previous history of depression
- bradykinesia
- greater functional disability
- earlier age of onset of PD
- greater degree of left brain involvement

- **Treatment of depression in Parkinson's disease**

- Antidepressant used in treating depression in PD include
- Tricyclic antidepressant (TCA's)
- Specific seratonin reuptake inhibitor (SSRI's)
- MonoamineOxidase Inhibitor (MAOi)

TCA's can worsen autonomic disturbances such as postural hypotension.

SSRIs have shown some worsening of motor symptoms in PD such as 'off' time and tremor.

MAOI type B inhibitor (Selegiline) has been shown to have some antidepressant effects as well as improvement in the parkinsonism symptoms. But it has only modest antidepressant effects.

- **Non pharmacological Treatment of depression in PD**

Electroconvulsive therapy

Unilateral ECT twice weekly is recommended for Parkinson's disease patients who are refractory to antidepressant treatment. Bilateral ECT ,3 times a week has been associated with a higher risk of developing delirium.

If delirium develops post ECT, reducing dopaminergic therapies just prior to subsequent ECT's maybe required.

DEMENTIA /COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

The development of dementia in Parkinson's disease (PD) is associated with increased mortality and morbidity. The prevalence of Parkinson's disease dementia (PDD) among those who suffer from PD is about 30 percent to 40 percent

The risk of dementia in PD patients increases in the following clinical situation:

- **I** Parkinson's disease developing late in life i.e., after the age of 60 years among those having akinetic-rigid syndrome as opposed to PD patients with the tremor-dominant forms.
- **II** those who have postural instability and gait disturbances.
- **III** symmetrical disease presentation.
- **IV** poor to moderate response to dopaminergic treatment.
- **V** also increases as PD progresses.
- **VI** presence of a major depressive disorder..

Electroconvulsive therapy

mortality & morbidity

Neurochemical deficits associated with PDD

There is degeneration of nigral dopaminergic neurons resulting in striatal dopaminergic deficit that results in intellectual impairment.

Severe cortical cholinergic deficits and neuronal loss in the Nucleus Basalis of Meynert is also noted in PDD patients.

There are also serotogenic deficits, which cause depressive disorder while noradrenergic deficits may cause impaired attention.

intellectual impairment

Clinical features of PDD

When dementia sets in there is confused thinking, severe memory dysfunction and profound behavioral changes.

Other features of PDD:

- Fluctuation in cognition and alertness
- memory impairment - deficits in new information learning
- impairment in executive functions - disability in organizing visuospatial dysfunction
- personality changes and visual hallucinations - about 70 percent of patients
- depression

Diagnosis and management

When PDD is the provisional diagnosis, go through the patient's history to exclude Dementia of Lewy Body (DLB). DLB and PDD share clinical phenomenology but differ in spatial and temporal evolution of the disease process.

Fluctuations in cognition and alertness are present in PDD but it is important to differentiate them from delirium due to drug toxicity and other co-morbidities, which can co-exist in patients with PD. Exclude a diagnosis of delirium before Parkinson's Disease dementia patients are treated with medications.

Drug treatment of Parkinson's disease dementia

Cholinesterase inhibitor is recommended once PDD is diagnosed. Rivastigmine can be initiated as 1.5mg bd and titrated up to 3 mg after 4 weeks.

DRUG INDUCED PSYCHOSIS

Drug induced psychosis is seen in managing Parkinson's disease and it posses as a major therapeutic challenge.

- Drug induced psychosis can be seen in monotherapy with Levodopa and it becomes a challenging task trying to balance between achieving adequate motor symptoms as well as reducing the emerging psychotic symptoms.
- The frequency of drug induced psychosis increase as the disease progresses as well as if there is cognitive impairment.
- The frequency if higher with dopamine agonist therapy compared with levodopa monotherapy.
- Psychotics symptoms can occur in patients with parkinson's disease in the following:

Anything to cause delirium, i.e. correct dehydration and any infection, review Polypharmacy, and drugs that are glutamate antagonist and MAOI-A drugs like Amantadine and Selegiline.

Treatment

Antipsychotics drugs like Clozapine and Quetiapine drugs should be added.

Clozapine

12.5 mg and titated up to a dose of 50 mg daily. The increase can be done after a week. The Parkinson's disease motor symptoms is not known to become worse while on this medication
Weekly total white monitoring should be done for 18 weeks and then monthly.
Anticholinergic effects in this medication can cause worsening of the cognitive function

Quetiapine

Fairly safe with its low Extrapyramidal side effects.
Start with a low dose of 12.5 mg nocte and can be titrated up to 600mg daily.

Surgical treatment for PD

Currently, functional surgery is accepted as an essential part of the management of PD.

At present the procedures available are ablative surgery (or lesioning), chiefly pallidotomy and thalamotomy, and neuro-modulation (Deep Brain Stimulation/ DBS).

Benefits of brain surgery

- improvement in motor score of Unified Parkinson's Disease Rating Scale (UPDRS) during "on" and "off"period.
- reduction in dyskinesia, improvement in activities of daily living (ADL).

Selection of patients for brain surgery

The patients should have confirmed PD and must be levodopa-responsive. They should be demonstrated, after adequate trial of therapy, to be medically refractory, i.e. have "on-off" fluctuations, severe immobility, and/or levodopa-induced dyskinesia.
The following are exclusion criteria: Parkinsonism-plus syndromes, secondary parkinsonism, dementia, concomitant serious medical conditions, cardiac pacemakers, MR imaging evidence of other intracranial disease, severe depression and psychosis that are not caused by drug treatment.

What are the predictors of good response to brain surgery?

- younger age of onset of PD, presence of dyskinesia marked levodopa-responsiveness (> 33% reduction in the motor score of UPDRS).

Notes

When should brain surgery be considered?

- advanced stage of PD (Hoehn & Yahr Stage III) with disabling motor complications (especially dyskinesia) causing impaired ADL, despite optimal medical management.
- however, there is no minimum duration of disease that precludes surgery because degree of disability is rather subjective as it depends on an individual's circumstances.

The final decision should be jointly made by after assessment by Neurologists and Neurosurgeons who have experience in brain surgery for PD.

Notes

What are the complicationrates of brain surgery?

- About 2-5% (stroke, stimulation-induced symptoms e.g.dysarthria, dysaesthesia), electrode fracture and infection). Risk of haemorrhage is somewhat higher in lesioning.

Notes

Which is the preferred type of brain surgery?

- DBS is the brain surgery of choice because it can be carried out on bilaterally with minimal risk and the side effects (dysaesthesia, dysarthria) are reversible. In contrast, the side effects of pallidotomy are irreversible. In terms of cost, DBS is more expensive and requires periodic replacement of the implanted pulse generator (IPG). Hence, the lower risk of complications has to be balanced against its higher maintenance cost. These issues are particularly compelling for poorer and older patients.

Notes

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