2012 Consensus Guidelines for the Treatment of Parkinson's Disease

MDC
Movement Disorders Council

From the Movement Disorders Council, Malaysian Society of Neurosciences

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Authors' note

This Guideline, written by clinicians experienced in the management of Parkinson's disease (PD), is intended to provide a brief but up-to-date framework for doctors involved in the care of patients with PD (including, but not limited to, general practitioners, hospital medical officers, physicians, geriatricians, rehabilitation medicine specialists, psychiatrists and neurologists).

Since the publication of the original "Consensus on the Management of PD" in 2006, substantial developments have taken place and the optimal management of PD continues to evolve. The current guidelines have been completely rewritten to reflect these changes. For the reader requiring more in-depth information, we have also carefully compiled a selective list of useful references for further reading.

An important development has been the increasing role that evidence-based medicine (EBM) plays in the practice of clinical medicine. The recommendations adopted by these guidelines are in line with this advance. Nevertheless, it needs to be emphasized that therapeutic recommendations should always be tailored to the individual patient, based not only on an accurate understanding of the efficacy and side effect profile of available treatments (the primary focus of guidelines), but also the physician's judgment, patient preference, and economic determinants. For example, some treatments may not be available in low-resource settings, even if their usefulness is well established by now. Even in urban centres, the cost of certain treatments remains a limiting factor and many patients who might otherwise benefit, for example, from deep brain stimulation surgery or infusional treatments, are currently unable to afford these treatments.

Another development has been the establishment of the Movement Disorders Council (MDC), under the auspices of the Malaysian Society of Neurosciences, in February 2010. The MDC represents clinicians (neurologists) with a special interest in PD and other movement disorders and was recognized by the international Movement Disorder Society in 2012 as an official Affiliate Member. Under the able leadership of Prof. Datin Dr. Norlinah Mohd. Ibrahim (the inaugural Chairperson), the MDC has, in a relatively short space of time, staged several successful programs. This Guideline is one such initiative.

There is no doubt that since the introduction of levodopa into clinical use forty-plus years ago, the life expectancy and (just as importantly) the quality of life of patients with PD have improved considerably. It is our sincere hope that the situation for PD patients in Malaysia will continue to see progress in the coming years. As members of the MDC, we undertake to advance this agenda to the best of our ability, so that patients with PD can continue to lead fulfilling and rewarding lives for the longest time possible.

Thank you & best wishes,

Prof. Dr. LIM Shen-Yang
on behalf of all co-authors

Contents

Appendices

1. Introduction - What is Parkinson's disease (PD)?

- PD is a **degenerative disease** of the nervous system, affecting primarily the brain, but also other structures such as the peripheral autonomic nervous system.[1]

- PD is more common in **older** people (affecting about 1% of people over the age of 60), but younger individuals can also be affected. It is slightly more common in men than women.

- The common **motor** problems of PD are rest tremor (although this is not present in all patients), bradykinesia and muscle rigidity. The diagnosis of PD is based on the presence of these motor problems. The bradykinesia of PD is often described by patients as a "weakness" of a hand or leg, but strength testing reveals no abnormalities. Imbalance (postural instability) with falls occurs only in the later stages of the disease. Most patients with early-stage PD experience motor symptoms on only one side of the body. However, it soon spreads to the other side but typically remains **asymmetric** throughout the disease course.

- **Non-motor symptoms** also occur frequently.[2-4] Some examples include fatigue, anxiety, depression, slowness of thinking, difficulty concentrating, visual hallucinations, pain or paraesthesias, constipation, urinary frequency or urgency, postural lightheadedness, excessive sweating, and sleep disturbances (e.g., dream-enacting behaviours with shouting or kicking during sleep, or excessive sleepiness during the day). In some patients, non-motor symptoms such as hyposmia, REM sleep behavior (RBD), constipation and depression have been found to precede motor symptoms of PD.

- A lack of the neurotransmitter **dopamine** in the brain is the cause of the motor (and possibly some non-motor) problems in PD. However, the underlying reason why people develop PD is still not fully understood, hence the term "idiopathic" PD.

- Both genetic factors as well as probable environmental factors contribute to the risk of developing PD. However, only 5-10% of patients have other family members also affected by the disease, which is why PD is usually regarded as a **sporadic** (rather than a familial) condition.

- There is **no test** (during life) currently that can definitely identify PD. Instead, the diagnosis of PD is based on the history and a careful neurologic examination. There are other disorders that can mimic PD and investigations may be needed in some patients (e.g., those with onset of symptoms below the age of 50 years, or if atypical features are present) to exclude some of these conditions (e.g., Wilson's disease).

- There is currently **no cure** (or prevention) for PD, and the disease **worsens gradually** over years. Nevertheless, motor symptoms can often be **well controlled** with treatment, especially in the earlier stages of the disease. At present, these treatments are mainly based on **restoring dopaminergic** stimulation in the brain. There are also effective treatments for some of the non-motor symptoms of PD.

- PD affects everyone differently and treatments need to be **tailored** to the individual. The benefits of treatments need to be balanced against their potential side effects. Referral to a physician (e.g., neurologist) with a special interest in PD is recommended.[5-7]

2. Diagnosis of Parkinson's disease

Diagnosing Parkinson's disease. PD is by far the commonest cause of parkinsonism (i.e., a constellation of clinical manifestations including bradykinesia, rigidity and tremor). The diagnosis of PD is based on the history and a careful neurologic examination.[7-10] To date, no single test has been shown to have sufficient sensitivity and specificity to reliably diagnose PD or distinguish PD from other forms of parkinsonism.

In most patients, the diagnosis is straightforward (e.g., onset of asymmetric parkinsonism including rest tremor in an individual in his 50s or 60s, with a robust response to dopaminergic medication treatment). Certain non-motor features, such as hyposmia, REM sleep behavior (RBD) or constipation are non-specific, but in the appropriate context the presence of these features may lend further support to the diagnosis.[1-3]

In a typical case, further investigations including brain imaging are seldom necessary.[9]

However, PD is a heterogeneous disorder with clinical presentation varying substantially from patient to patient, and occasionally it is difficult to be certain whether a patient has PD, especially early in the disease. Some differential diagnoses that are regularly encountered in clinical practice are described in Table 1.

Table 1. Differential diagnoses of Parkinson's disease. *These MRI abnormalities are quite highly specific for MSA / PSP, but sensitivity is only around 70%.[10]

Disorder	Characteristic features
Essential tremor [11,12]	Predominantly upper limb action tremor, which is typically symmetric. Head and voice may also be affected. There are usually no other neurologic deficits. There may be a positive family history, and tremor may improve with ingestion of alcohol
Dystonic tremor [11]	Dystonic posturing (e.g., of the hands when held in a certain position) may be evident. This diagnosis is often difficult to make

Disorder	Characteristic features
Drug-induced parkinsonism[13]	Clinically, this condition may appear identical to PD (e.g., presenting with unilateral rest tremor). A careful drug history to exclude exposure (within the last 1 year) to dopamine receptor blockers (most commonly anti-psychotics or anti-emetics such as metoclopramide or prochlorperazine) is therefore essential
Wilson's disease [14,15]	Onset of neurologic Wilson's disease is usually in childhood or young adulthood. Patients may present with tremor, parkinsonism and/or dystonia. **As a general rule, patients presenting with movement disorders below age 50 should undergo tests to rule out this condition.** Psychiatric manifestations are common, including behavioural changes, anxiety and psychosis. Investigations include brain MRI (abnormal in 90% of cases; a variety of abnormalities may be seen, e.g., T2 hyperintensity of the basal ganglia), slit lamp examination by an ophthalmologist (Kayser-Fleischer rings in almost all cases), serum caeruloplasmin (usually □↓‡), and 24-hour urinary copper (usually□–
Dementia with Lewy bodies[16]	Many experts now view this disorder as being on a spectrum with PD. In PD, dementia and visual hallucinations are typically late features, whereas in DLB these are present early in the disease course (preceding, or occurring within a year of motor symptom onset)
Multiple system atrophy[17,18]	The motor problem may be predominantly parkinsonism (MSA-P) or cerebellar (e.g., gait or limb ataxia) (MSA-C). Significant autonomic dysfunction (e.g., urinary incontinence or severe orthostatic hypotension) is usually present. Patients may have significant dysarthria/dysphagia early in the disease course. Upper motor neuron signs (e.g., hyper-reflexia or extensor plantar responses) may be present. Brain MRI may show cerebellar or brainstem atrophy, "hot-cross bun" sign, putaminal rim T2 hyperintensity, etc. *
Progressive supranuclear palsy[19,20]	Characterized by vertical gaze deficits (restriction or, in earlier stages, slowing of down-saccades). Falls are usually an early feature (within the 1st year of symptom onset). May have axial (neck) > limb rigidity. Patients may have significant dysarthria/dysphagia early in the disease course. Brain MRI may show midbrain atrophy (e.g., "hummingbird" sign on mid-sagittal image)*
Vascular parkinsonism [21-23]	Parkinsonism is usually lower-body predominant. Typical rest tremor is absent. Features of stroke may be present. Patients usually have significant vascular risk factors, and brain MRI usually shows widespread ischaemic changes (less commonly, this form of parkinsonism can be due to a small stroke in a strategic location, e.g., in the substantia nigra)
Normal-pressure hydrocephalus [24]	Parkinsonism is usually lower-body predominant. Brain imaging shows enlarged ventricles, out of proportion to any cerebral sulcal atrophy. A positive "tap test" (improvement of gait after large volume removal of cerebrospinal fluid via lumbar puncture) aids in the diagnosis and in predicting response to a shunting procedure

Investigations should usually be performed if these alternative diagnoses are being considered. Neuroimaging should be obtained in those with onset of parkinsonism below the age of 50 years, or if there are atypical features. **Brain MRI** (which is normal in PD) has substantially greater differential diagnostic potential in parkinsonian disorders compared to CT and is preferred.[10] Functional imaging (positron emission tomography [PET] or single-photon-emission computed tomography [SPECT] scanning) to assess the integrity of the dopaminergic nigrostriatal system is not widely available and is also not specific for PD, as nigrostriatal denervation also occurs in MSA and PSP.[10]

Staging the severity of PD. The most widely used rating scales to stage the severity of PD are the **Hoehn and Yahr (H&Y) stage** (Table 2) and the Unified PD Rating Scale (UPDRS).[25,26] H&Y staging is briefer and can be administered in a few minutes. The motor (part III) section of the UPDRS assesses 27 items and takes approximately 10-15 minutes to administer. In patients with motor fluctuations (see section 5 on Motor response complications below), it is important to consider the patient's **medication status** (whether he is "ON", "OFF" or "semi-ON") when assessing motor function (for example, a patient with severe fluctuations may be H&Y stage 5 when "OFF", but H&Y stage 2 when medication has taken full effect). It is important to consider that sometimes non-motor features (e.g., dementia) may have as much or even more impact than motor function on the PD patient's functional status and quality of life.[27]

Table 2. Hoehn & Yahr staging of Parkinson's disease motor severity.[25]

Hoehn & Yahr stage	Description
1	Unilateral involvement only usually with minimal or no functional disability
2	Bilateral or midline involvement without impairment of balance
3	Bilateral disease; mild to moderate disability with impaired postural reflexes; physically independent
4	Severely disabling disease; still able to walk or stand unassisted
5	Confinement to bed or wheelchair unless aided

3. Initiation of antiparkinsonian medication - When and what to start

General approach. The medications currently used to treat PD provide *symptomatic* benefit. This means that they reduce PD symptoms such as tremor, bradykinesia and rigidity. Traditionally, patients start taking medicines when symptoms become **troublesome** (e.g., at the point where symptoms impact negatively on the performance of daily activities). This is still a popular approach.

Nevertheless, some experts have proposed that earlier initiation of treatment can be associated with better clinical outcomes, and some PD specialists are now recommending that treatment be started **as soon as, or very soon after,** a **diagnosis** PD is made.[7,28,29] However, at present there is insufficient evidence to prove this hypothesis and treatment recommendations should take into account the **patient's preferences**, including issues related to medication side effects, cost, and the inconvenience of having to take medication regularly.[30,31]

Once a decision has been made to initiate treatment, there are multiple options to consider (Figure 1 and Appendix 1).

A **"start low, go slow"** approach can help to minimize the occurrence of certain side effects.

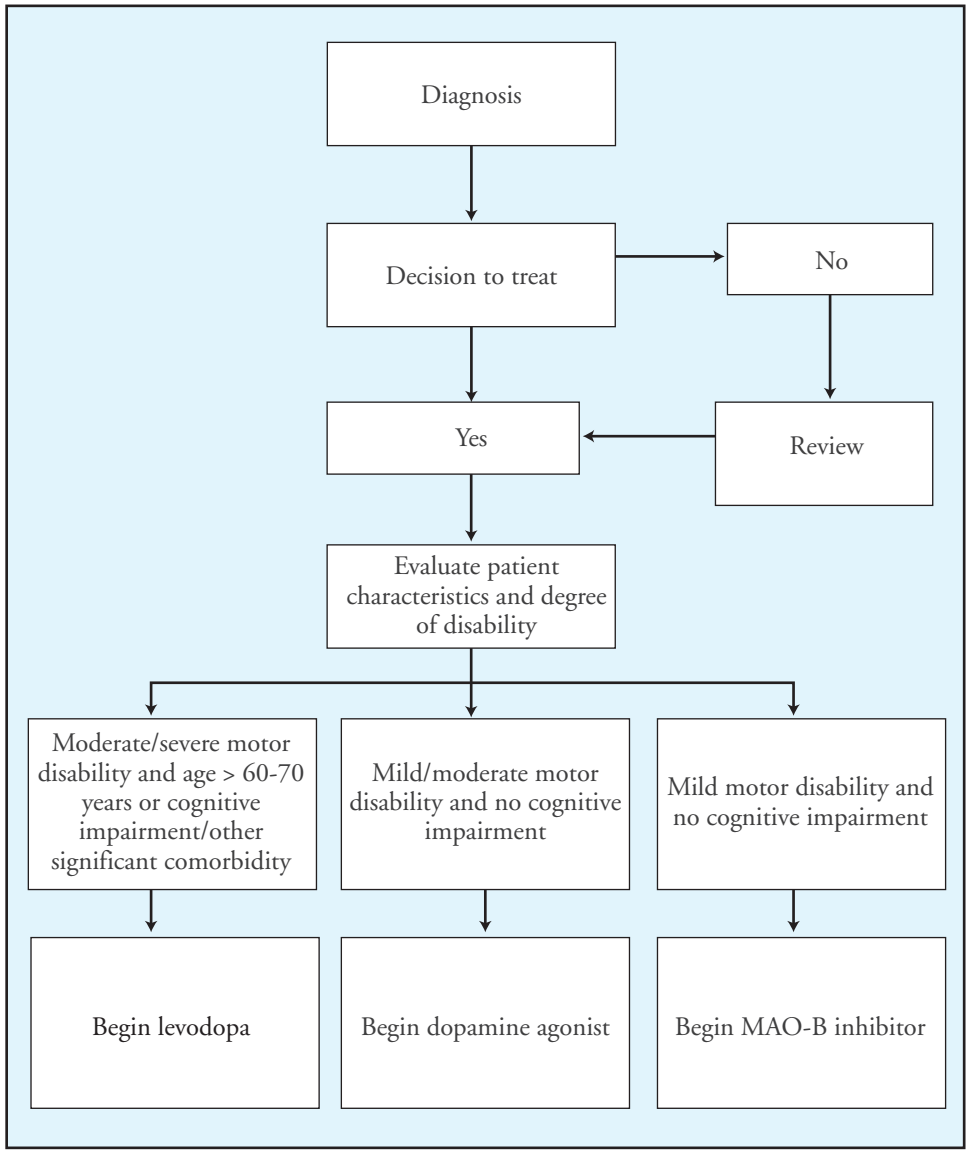


Figure 1. Decision pathway for the initiation of medication treatment for PD (adapted from reference 32).

Levodopa (L-dopa). This agent, which has been in clinical use since the 1960s, is still **the most effective** antiparkinsonian medication available. Concerns raised in the past regarding the possibility of a toxic effect on dopamine neurons have largely been discounted.[33] L-dopa therapy extends survival in PD, likely as a result of reduction in parkinsonian disability.[7,8,33]

As an example of the "start low, go slow" approach, L-dopa preparations can be **started at** a dose of **50 mg daily** (e.g., ¼ tablet of Madopar® 200/50 mg or ½ tablet of Sinemet® 100/25 mg), increasing **every 3-7 days** by 50 mg to an initial maintenance dose of 50-100 mg 3x daily, or until a satisfactory clinical response is obtained. If side effects occur, up-titration can be carried out even more gradually.

Individual doses of L-dopa typically range from **50-300 mg**.[34] Daily dosage should rarely exceed 2,000 mg.[8]

With chronic L-dopa therapy, motor response complications including **dyskinesias** (see Section 4 below on Motor response complications) occur frequently and, in a minority of patients, may become severe with pronounced interference with ADLs, especially in **younger** patients.[35] Multiple studies have shown that the risk of developing dyskinesia is higher with L-dopa compared, for example, to dopamine agonist therapy, especially when used at higher doses.[33,36,37] Modified-release L-dopa preparations (controlled-release formulations or preparations containing entacapone) do not delay the development of motor response complications.[7,36]

Many doctors delay the use of L-dopa in **younger patients** (e.g., those under the age of 60-70 years),[9] although recently others are starting L-dopa earlier, using the **lowest effective dose**.[7,8,37] Medications such as dopamine agonists, MAO-B inhibitors, anticholinergics and/or amantadine can be used initially instead. However, these agents are less effective than L-dopa and side effects may limit their use.

Almost every patient with PD will eventually require treatment with L-dopa. The use of L-dopa **should not be inappropriately delayed** if symptoms are not adequately controlled with the less potent medications.

A common **misconception** is that L-dopa should be "**saved for later**" or that "it only works for x number of years". Although it is true that in many patients symptoms become less responsive to medication treatment after having PD for many years, this is primarily due to a change in the nature of the disease (with the development of **non-dopaminergic** lesions),[1] rather than being due to long-term usage of L-dopa. Thus, problems such as slowness of limb movements are due primarily to a deficiency of brain dopamine, which can be addressed by restoring dopamine levels with medications, and which will continue to respond over time. However, symptoms such as imbalance and falls, speech or swallowing difficulties, and dementia that typically occur in the later stages of PD are usually not caused by dopamine deficiency.[1] Therefore, "merely" replacing dopamine with the currently-available medications has limited effectiveness in treating these problems.

Dopamine agonists. These are generally considered the next most potent class of medications after L-dopa, in terms of antiparkinsonian efficacy.[7,9] Ergot dopamine agonists (e.g., bromocriptine) are seldom used now in clinical practice because of the risk of fibrotic complications.[7,36] Non-ergot dopamine agonists available in Malaysia are listed in Table 3. In general, these agents have similar efficacy and side effect profiles.[7,9,38,39] Nevertheless, if one results in side effects, another dopamine agonist could be substituted. A particular dopamine agonist may be preferred in selected circumstances (e.g., the once-daily agonists for added convenience and improved compliance;[40] or rotigotine in situations where transdermal application is desirable).[41]

Table 3. Non-ergot oral dopamine agonists. * denotes dopamine agonists that are usually administered three times daily; ** denotes newer longer-acting agonists that are administered once daily.

Dopamine agonist	Usual starting dose	Maximum recommended dose
Piribedil (Trivastal Retard®)	25-50 mg	300 mg/d*
Ropinirole immediate release (Requip®)	0.25 mg	24 mg/d*
Ropinirole prolonged release (Requip PD®)	2 mg	24 mg/d**
Rotigotine (Neupro®) transdermal patch	2 mg	16 mg/d**
Pramipexole immediate release (Sifrol®)	0.125 mg	4.5 mg/d*
Pramipexole extended release (Sifrol ER®)	0.375 mg	4.5 mg/d**

As examples of the "start low, go slow" approach, ropinirole prolonged release or rotigotine can be started at a dose of 2 mg daily, increasing every week by 2 mg daily (i.e., 2 mg daily for the first week, 4 mg daily for the second week, 6 mg daily for the third week, etc.) until a satisfactory clinical response is obtained. If side effects occur, up-titration can be carried out even more gradually.

Selegiline (e.g., Jumex® and Selegos®). The usual dose is 10 mg in the morning in 1 or 2 divided doses (taking this agent later in the day may cause insomnia). Selegiline has a **mild antiparkinsonian** effect.[36,42] Some clinicians also use selegiline for its **putative neuroprotective** effect, but this is not proven.[43-45] There is also some evidence to suggest that **rasagiline** (Azilect®), another MAO-B inhibitor (not currently available in Malaysia), may have neuroprotective potential, but the results of the recent ADAGIO study were inconclusive.[7,36,46,47]

Anticholinergic agents. These include **trihexyphenidyl** or **benzhexol** (Apo-Trihex® and Benzhexol®) (1 or 2 mg 2-3x daily) and **orphenadrine** (Norflex®) (50 mg 2-3x daily). These agents can be particularly helpful for **tremor** in some patients, but their use is often limited by anticholinergic side effects, particularly in older patients and especially if they have underlying cognitive impairment.[7,36,48] Anticholinergic agents may also have a role for PD-related **dystonia**.[7]

Experimental treatments. Some supplements have been studied for PD. Probably the best known of these is Coenzyme Q10. An initial randomized placebo-controlled double-blind trial showed promise for this agent,[49] but a more recent and larger study conducted in North America by the National Institute of Neurological Disorders and Stroke (NINDS) demonstrated that this treatment was not effective even at high doses (up to 2,400 mg/day); this trial was terminated after an interim analysis.[7] Another antioxidant, Vitamin E, was also found to be ineffective.[7,50]

Other purported treatments have never been subjected to proper scientific scrutiny in human PD subjects. These include ginkgo biloba (e.g., Tanakan®), "stem cell enhancers" (e.g., StemEnhance®), traditional herbal remedies, bovine (cow) colostrum, etc. Unproven treatments that are costly and/or potentially hazardous should be avoided. The placebo effect is well recognized in PD and therefore any treatment should be subjected to rigorous scientific methods to establish efficacy and to ensure that patients are receiving the best value for their time, effort and healthcare expenditure.[7,51,52]

Non-pharmacologic management. Allied health involvement may be particularly valuable in advanced PD, but are often also beneficial for earlier stage patients.[7,36] These include **physiotherapy** (stretching and strengthening exercises, gait and balance training including use of cueing techniques, etc.), **occupational therapy** (rehabilitation techniques that help maximize functional capacity through lifestyle adaptations and possible use of assistive devices; this may include assessment of safety in the home environment, e.g., installation of grab rails, shower seats, etc.), **speech therapy** (rehabilitation techniques to strengthen speech for improved communication, and to improve efficiency of swallowing which may reduce the risk of aspiration),

and advice from a **dietitian** (unintended weight loss is a common feature of PD).[7,36] Primary care physicians can facilitate this by referring patients to the appropriate therapist(s). Many countries have **PD nurse specialists**, who can provide psychological support, practical advice on symptom management, monitoring of medication adherence, wound care, care of devices (e.g., medication infusion pumps, feeding tubes, urinary catheters), home visits (in cases where patients are too disabled to come to the hospital), etc.[7] Many of these services are currently underdeveloped in Malaysia.

Although many patients seek **alternative therapies** such as **acupuncture** and stem cell treatments, there is currently little or no good scientific evidence to recommend these modalities of treatment in PD.[7,36]

The importance of exercise. For all patients, it is useful to encourage attention to a healthy lifestyle, including maintaining an optimistic outlook, a healthy and balanced diet, and **regular exercise** (e.g., walking or swimming). Besides the general health benefits of exercise (improvement of cardiovascular and cerebrovascular health, reduction of osteoporosis/fracture risk, improvement of psychological affect), there is accumulating evidence, albeit indirect, suggesting that vigorous exercise may have a neuroprotective effect in PD.[53]

Being informed & being involved. Provision of education and valid **information** is essential to empower both patients and families in actively participating in disease management.[7] It should be emphasized that with the right treatment and a positive attitude, people living with PD can continue to maintain a rewarding lifestyle for many more years following the diagnosis. The Malaysian PD Association (MPDA) has published accurate and up-to-date **information booklets** for people living with PD, written by senior members of the Movement Disorders Council. These are available in English, Malay and Chinese and can be downloaded for free from the MPDA website (**http://www.mpda.org.my**).

People living with PD can also find purpose and satisfaction in life by being involved in a peer **support group** such as the MPDA.[7] Young patients particularly may benefit from being put in touch with an articulate and positive patient of similar age who is doing well.[8]

4. Potential side effects of antiparkinsonian medications

Medications used to treat PD can cause adverse effects in some patients.

A "**start low, go slow**" approach can help to minimize the occurrence of some side effects (see Section 3 above for examples on how this can be done).

Dopaminergic side effects. The potential side effects of **dopaminergic** medications[3] (L-dopa preparations, dopamine agonists and, to a lesser extent, MAO-B inhibitors) include: **nausea**, **postural hypotension** and daytime **sleepiness**. In predisposed patients, development or worsening of **confusion**, **hallucinations** or **impulse control disorders** (such as hypersexuality, compulsive eating or pathological gambling) can occur, particularly with dopamine agonists.[3,7,33,36,54,55] In many cases, medication adjustment can alleviate these side effects. **Domperidone** 10-20 mg, taken with each dose of dopaminergic medication, can help to counteract nausea and postural hypotension.

MAO-B inhibitors. These agents are generally well tolerated. In a survey of PD specialists, only 2 (0.04%) out of 4,568 patients on a combination of selegiline and an antidepressant experienced serious symptoms possibly consistent with **serotonin syndrome**.[56] In the ADAGIO study of rasagiline (n=1,176) (where concomitant treatment with antidepressants was allowed), there was not a single reported case of serotonin syndrome.[47] Similarly, there was not a single case of tyramine (hypertensive) reactions in this study (where there was no restriction of dietary intake of tyramine).[47] One early report from the United Kingdom of increased mortality with selegiline had important methodologic limitations[57] and has been discounted by subsequent studies.[58,59]

Anticholinergic medications. Side effects include "Anti-SLUD" (salivation, lacrimation, urination, defaecation)" effects: dry mouth, dry eyes, urinary retention, constipation; also confusion and hallucinations.

Amantadine. Side effects include: confusion and hallucinations, leg swelling, livedo reticularis (net-like mottling of the skin - usually harmless), in addition to anticholinergic effects. There is a need to use this medication with caution in patients with renal dysfunction.

Should medications be taken on an empty stomach or with food? Initially (at least during the first several months after initiating treatment), dopaminergic medications should generally be taken with food to reduce **nausea** / vomiting. However, once these medications can be tolerated without food, taking them on an empty stomach (i.e., ½ hour prior to, or 2 hours after, meals) allows for more rapid and reliable absorption.

Rarely, a patient (usually one with long-standing PD and disabling motor fluctuations) can be very sensitive to concurrent intake of dietary **protein**, which may delay L-dopa from reaching the brain. This is because proteins are broken down into amino acids that compete with L-dopa for transport from the gut into the bloodstream, and from the bloodstream into the brain. In such patients, **high-protein foods** (e.g., meat, poultry, fish, milk, cheese and eggs) may be **redistributed,** typically to **dinnertime** (as patients are usually less active in the later part of the day). However, this is not an issue for the vast majority of patients with PD. It should also be remembered that many patients with PD experience unintended weight loss, so maintaining a well-balanced diet (including foods with high protein, e.g., milk shakes or Ensur[e]®) is important

5. Motor response complications (motor fluctuations & dyskinesia) - What are they?

Many patients, after they have been taking dopaminergic medications for some time (usually years) will develop motor fluctuations ("wearing-off" is the commonest type of motor fluctuation) and dyskinesia (involuntary "wriggling" movements).

"Wearing-off". Patients experiencing "wearing-off" improve after taking a dose of PD medication (the "**ON**"-medication state) (typically ½ or 1 hour after medication intake), but start to experience a recurrence or worsening of their PD symptoms before it is time to take the next dose of medication (the "**OFF**"-medication state). For example, a patient may feel that each medication dose lasts for only 3 or 4 hours. Some patients experiencing **motor fluctuations** also experience **non-motor fluctuations** (e.g., pain, mood or panic symptoms, or slowness of thinking that occur or worsen during "OFF" periods). Figure 2 below depicts these fluctuations.

Eventually, some patients may experience more **unpredictable** "on-off" fluctuations as well. These can be much more difficult to manage.

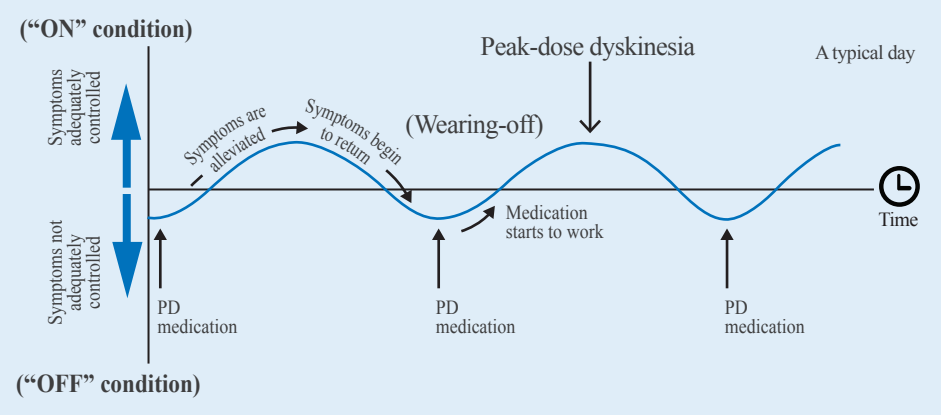


Figure 2. Fluctuations ("ON" and "OFF" periods) and dyskinesia in relation to the timing of PD medication intake. Adapted from reference 60.

Dyskinesia. These are involuntary "**wriggling**" (choreiform) movements that usually occur when patients are "ON" (so called "**peak-dose**" dyskinesia) (Figure 3). This type of dyskinesia is very common, occurring in ≈ 50% of patients after 5 years of treatment with L-dopa. In many patients, it is of little consequence (in fact, patients may not even be aware of the movements in mild cases of dyskinesia). Less commonly, dyskinesia can also occur before a dose of medication takes full effect and/or during the "wearing-off" phase (so called "**biphasic**" dyskinesia).

Figure A. Tremor ("shakes").
These are oscillatory movements. In PD, tremor most commonly affects the hand / arm, but sometimes can also affect the leg or head. It is usually most prominent at rest, but sometimes can also be present when performing actions (e.g., whilst holding a cup or writing).

Figure B. Dyskinesia ("wriggling").
These are involuntary movements that usually occur when a dose of PD medication has taken effect ("**ON**"-medication condition). In the example shown here, the dyskinesia is more severe and generalized, but in most patients the movements are milder.

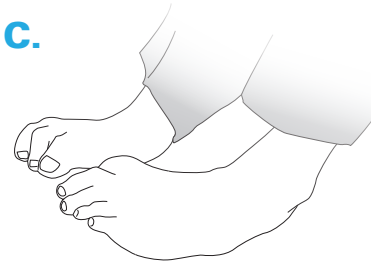


Figure C. Dystonia ("twisting").
This most commonly affects the foot (with the ankle twisting in, or the toes curling up or down). In most patients, it occurs in the "**OFF**"-medication condition, e.g., in the early morning prior to taking the 1st dose of PD medication.

Figure 3. Different types of **involuntary movements** that may be associated with different phases of the dopa-cycle.

Table 4 may help to differentiate between peak-dose dyskinesia and biphasic dyskinesia (note, however, that both entities may be present - and one may blend into the other - in the same patient).

Table 4. Types of dyskinesias.

Peak-dose dyskinesia	Biphasic dyskinesia
Much more common	Less common
Occurs at the time of peak "ON" benefit from a dose of dopaminergic medication	Occurs before or after the time of peak "ON" benefit from a dose of dopaminergic medication. End-of-dose dyskinesia usually is more prolonged / disabling than onset-of-dose dyskinesia
Usually choreiform	May be ballistic, dystonic, or involve repetitive pedalling movements
Often upper body is more affected (head, trunk, upper limbs), but may be generalized	Usually affects legs primarily
Usually painless (and patients are often unaware of milder dyskinesia)	Often distressing; may be painful

Patient diary. In some patients, documentation of motor function during waking hours using an hourly (self-completed) diary can be helpful to determine the total daily amount of "OFF" time and dyskinesia, and the relationship of these to the timing of mediation intake[61] (see Appendix 2 for an example; full versions in English, Malay and Chinese can be downloaded from the Malaysian PD Association website [http://www.mpda.org.my]).

6. Treatment of motor fluctuations & dyskinesia

Treatment of motor fluctuations. There are several approaches to reduce "OFF" periods. One option is to increase the **dose and/or frequency** of PD medications (e.g., taking L-dopa 4 or 5x daily, instead of 3x daily; however, this comes at a cost of inconvenience in terms of having to take frequent doses). When the frequency of L-dopa administration is increased, it may be necessary to reduce individual dosages of L-dopa so as not to worsen side effects such as dyskinesia (although this can sometimes result in dose failures because the quantum of L-dopa is insufficient to exceed threshold and turn the patient "ON").

Other approaches to reduce "OFF" periods include **addition** of a **dopamine agonist**, **entacapone** (either by adding Comtan® or by switching from immediate-release L-dopa to Stalevo®, which is a tablet combining L-dopa, carbidopa and entacapone), or a MAO-B inhibitor (selegiline or rasagiline).[36,62-64] Addition of a dopamine agonist is typically more effective than addition of entacapone or MAO-B inhibitor therapy, which have comparable efficacy.[36,65] In patients with overnight wearing-off, dopamine agonist therapy has also been shown to have **beneficial effects on night-time sleep**.[66]

Controlled-release L-dopa (Sinemet CR® or Madopar HBS®) remains useful in addressing overnight wearing-off (e.g., patients experiencing painful early morning foot dystonia). However, these agents may be **erratically absorbed**, resulting in delayed "ON" or no "ON" responses and are therefore not first choice to treat motor fluctuations. It is also important to remember that the amount of L-dopa absorbed is approximately 25% less with controlled-release compared to standard/immediate-release preparations; this should be taken into account when switching between preparations.[7]

In general, medication changes should be undertaken **gradually, especially in a patient who is at higher risk of side effects** (e.g., already experiencing significant dyskinesia, or when cognitive impairment is present). For example, in a patient with significant wearing-off symptoms on immediate-release L-dopa 4x daily, entacapone could initially be added to the first and third doses of L-dopa; if the beneficial response is insufficient but the addition has been well tolerated, after 3-7 days the frequency of entacapone could be increased further to 1 tablet 4x daily.

Treatment of dyskinesia. Troublesome dyskinesia can sometimes be managed by reducing the dose of dopaminergic medications, but this has to be balanced against worsening control of "OFF" periods. However, it is a common **misconception** that patients have dyskinesia due to being "**overdosed**" on medication. While this can certainly happen if a patient's dopaminergic medication has been inappropriately/unnecessarily escalated, the more typical scenario is that of a patient whose medication has been gradually increased to address progressively worsening "OFF" periods. To illustrate this point further: A patient who is taking 1 tablet of immediate-release L-dopa early in the disease course may demonstrate no dyskinesia at all, but **the exact same dose** given years later (when "plastic" changes that underlie the dyskinesia process have occurred in the brain) can precipitate severe dyskinesia.

Amantadine (Pk-Merz®). This agent can suppress dyskinesia in many patients, whilst simultaneously providing mild antiparkinsonian benefit.[36] The dose of amantadine is typically uptitrated gradually to 100 mg 3x daily as tolerated. A recent study showed that patients can experience a sustained anti-dyskinetic effect from amantadine even after more than 4 years of amantadine treatment.[67]

Motor response complications that are refractory to adjustment of oral medications. A minority of patients continue to have disabling motor fluctuations and dyskinesia despite "optimization" of a complex regimen of oral PD medications. To achieve satisfactory control of these problems, these patients may require more invasive / advanced treatments, which are covered in the next section.

7. Advanced therapies for disabling motor response complications

When these treatments are used and why. Patients who experience severe and prolonged "OFF" periods and/or dyskinesia despite optimization of their oral PD medications can be considered for deep brain stimulation **(DBS)** surgery or **pump (infusion) therapy** using apomorphine (APO-go®) or jejunal L-dopa (Duodopa®) (Figures 4-6). Well-selected patients typically experience a **marked reduction of OFF periods** and **dyskinesia** with these treatments.[36] However, these treatments are relatively costly and more complicated and should be carried out in specialized centres managing a large volume of patients with complicated PD.

Deep brain stimulation (DBS) surgery of the subthalamic nucleus (STN) or globus pallidus internus (GPi). DBS has been in clinical use for the treatment of PD since the 1980s.[68,69] In the latest version of the international Movement Disorder Society (MDS) Evidence-Based Medicine (EBM) guidelines for the treatment of PD motor symptoms, DBS of the STN or GPi was designated "efficacious" (the highest level of efficacy designation) and "clinically useful" for the treatment of both motor fluctuations and dyskinesia.[36] DBS results in an average 50-70% improvement in motor fluctuations and dyskinesia, and is superior to best medical therapy in improving quality of life in PD patients.[7,69-71] Studies have also demonstrated the effectiveness of DBS in improving L-dopa-responsive signs and symptoms in the long term.[72-74]

In general, patients undergoing DBS should be under the age of 70 and otherwise medically fit, without major cognitive impairment or severe treatment-refractory psychiatric disorders.[75,76]

A "**L-dopa challenge**" may be required for proper evaluation of the degree of benefit a patient is likely to gain from DBS.[77] This involves overnight withdrawal of PD medications (for 12 hours) so that the patient's "OFF" medication status can be assessed. Following this, a dose of L-dopa (typically

50% more than the patient's usual morning dose) is administered so that the patient's best "ON" condition can be evaluated. When successful, DBS can result in the patient spending much more time in this "ON" condition, and with less dyskinesia.

Other DBS targets. Thalamic DBS is mainly useful to treat drug-resistant tremor and has limited efficacy on other parkinsonian features.[36] The role of pedunculopontine nucleus (PPN) DBS is currently under investigation.[78]

Lesional (ablative) surgery. Although pallidotomy and thalamotomy might still be performed in selected patients, DBS is the surgical treatment of choice, as the latter has reversible effects (and can be adjusted to optimize the individual patient's response), and can be used bilaterally to improve symptoms.[7] Unilateral pallidotomy appears to be inferior to DBS in terms of efficacy, and is limited by significant side effects (which may be permanent) including hypophonia when performed bilaterally.[36,79]

Apomorphine (APO-go®) (subcutaneous infusion or injections). Apomorphine is the most potent dopamine receptor agonist and it can provide symptom relief similar to that of L-dopa.[80] Apomorphine is rapidly absorbed, with onset of effect within 5-15 minutes of subcutaneous injection.[80] In the MDS EBM guidelines, apomorphine (subcutaneous injections) was designated "efficacious" for the treatment of motor fluctuations.[36,81] The efficacy of continuous subcutaneous infusion of apomorphine is supported by case series and extensive clinical experience, but there is a lack of randomized studies.[82-85] The most common side effect is local skin reactions, but this treatment is generally well tolerated.[84,85]

Jejunal L-dopa (Duodopa®). The L-dopa/carbidopa gel is administered into the jejunum via a percutaneous endoscopic gastrostomy (PEG) tube. In the MDS EBM guidelines, jejunal infusion of L-dopa was designated "likely efficacious" for the treatment of both motor fluctuations and dyskinesia.[36] With this treatment, most patients are able to come off all their oral PD medications.[80] Technical (tube-related) complications however appear to be quite common.[36,86]

Figure 4. Typical deep brain stimulation (DBS) setup.

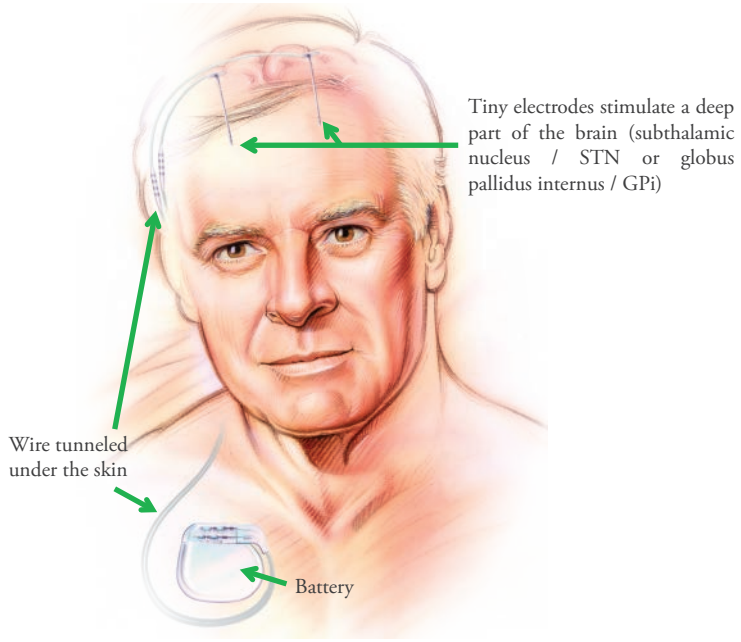


Figure 5. Typical apomorphine infusion setup.

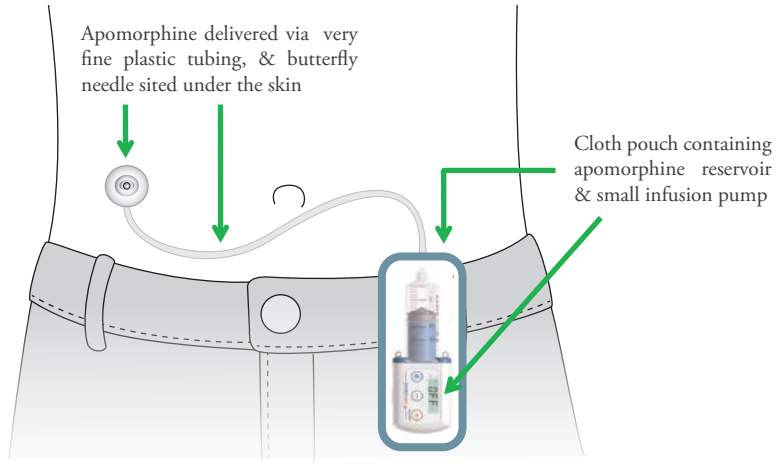
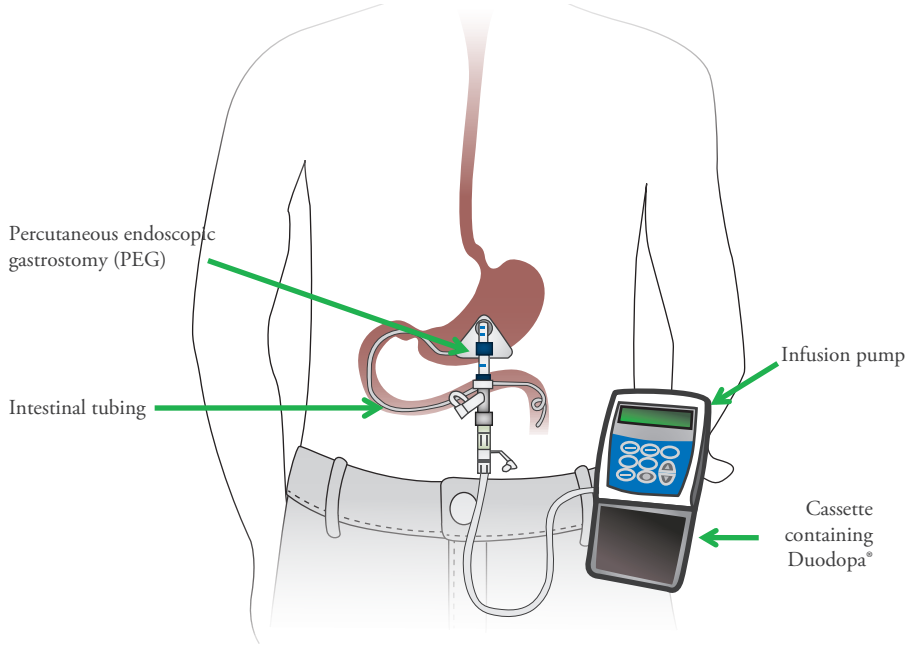


Figure 6. Typical jejunal L-dopa infusion setup.



8. The non-motor symptoms of Parkinson's disease

Patients with PD can experience a variety of non-motor symptoms (NMS).[1-4] Studies in the local Malaysian setting confirm a high frequency of these symptoms in our population of PD patients.[4,55] NMS can have a **large negative impact** on patients' quality of life, sometimes to an even greater extent than the motor symptoms of PD.[3,27] These therefore deserve greater attention in the routine management of PD. Some of these problems will only come to light if they are **specifically asked about**; in some cases, this is because patients are unaware of the link with PD or its treatments (e.g., constipation); in other cases, patients may be too embarrassed to bring up these issues (e.g., sexual dysfunction).

Some symptoms are due primarily to the disease process itself (e.g., dementia); some are thought to be due primarily to PD treatment (e.g., impulse control disorders); and others are due to a combination of both the disease and its treatment (e.g., orthostatic hypotension, visual hallucinations, excessive daytime somnolence) (Figure 7).

Table 5 lists common NMS and a suggested approach to the management of these symptoms.

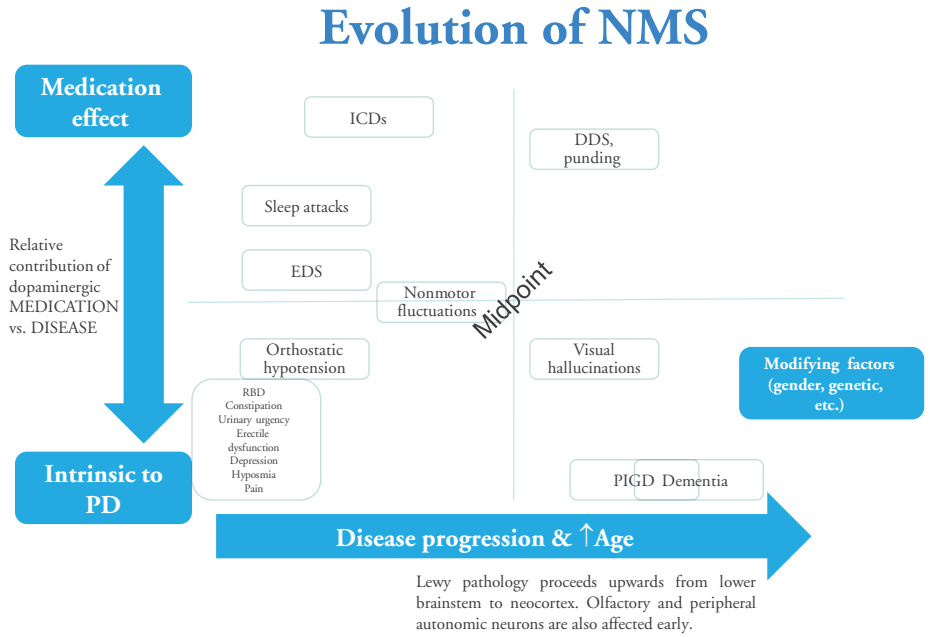


Figure 7. Evolution of the nonmotor symptoms (NMS) of PD (adapted from reference 3). Schematic representation of the development of NMS in relation to disease course (horizontal axis) and relative contribution of disease vs. dopaminergic medication (vertical axis). Both axes are divided by a Midpoint to denote the half-way mark in the disease course (horizontal axis), and equal contribution of disease and medication effect in the pathogenesis of the symptom (vertical axis). For example, according to this figure, there is a greater role for disease in the development of visual hallucinations, and patients have generally passed the half-way mark in their disease course when this symptom develops. The overlapping boxes for PIGD and dementia indicate that dementia more often occurs in patients who have developed axial-predominant parkinsonism. Abbreviations: DDS, dopamine dysregulation syndrome; EDS, excessive daytime somnolence; ICDs, impulse control disorders; PIGD, postural instability and gait difficulty; RBD, rapid-eye-movement sleep behaviour disorder.

Table 5. Commonly used treatments for NMS.[7,87-92] Abbreviations: BTX, botulinum toxin injections; CBT, cognitive-behavioural therapy; CPAP, continuous positive airway pressure; DAs, dopamine agonists; DBP, diastolic blood pressure; DRT, dopamine replacement therapy; ECT, electroconvulsive therapy; EDS, excessive daytime somnolence; ESS, Epworth sleepiness scale; LID, L-dopa-induced dyskinesia; MAO-B, monoamine oxidase B; MMSE, Mini-Mental State Examination; OH, orthostatic hypotension; OSA, obstructive sleep apnoea; PDD, Parkinson's disease dementia; RBD, rapid-eye-movement sleep behaviour disorder; RCTs, randomized controlled trials; R/o, rule out; Rx, treatment; SAs, sleep attacks; SEs, side effects; SBP; systolic blood pressure; SL, sublingual; SSRIs, selective serotonin-reuptake inhibitors; TURP, transurethral resection of the prostate; WCC, white cell count (peripheral blood).

Non-motor symptoms	Treatment Options	Comments
Depression	1. Consider emotional fluctuations associated with "OFF" periods → Reduce "OFF" time 2. Involvement of geriatric or neuro-psychiatrist; role for CBT 3. SSRIs, e.g., escitalopram(Lexapro®) 5-20 mg/d, fluoxetine (Prozac®) 20-60 mg/d, fluvoxamine (Luvox®) 50-300 mg/d, paroxetine (Seroxat®) 20-50 mg/d, sertraline (Zoloft®) 25-200 mg/d 4. Others: agomelatine(Valdoxan®) 25-50 mg nocte, amitriptyline 25-150 mg/d, desvenlafaxine (Pristiq®) 50 mg/d, duloxetine (Cymbalta®) 30-60 mg/d, mirtazapine (Remeron®) 15-45 mg nocte, venlafaxine (Effexor® 37.5-187.5 mg bd or Effexor XR® 75-375 mg/d) 5. Pramipexole (Sifrol®) may have antidepressant effects over and above its antiparkinsonian effects 6. ECT in severe refractory cases	• SSRIs have a favorable SE profile and are typically 1st choice; they do not, in general, worsen the motor signs of PD • Consider targeting antidepressant to accompanying symptoms, e.g., mirtazapine or amitriptyline if associated insomnia; anticholinergic SEs of amitriptyline may be advantageous in patients with drooling or overactive bladder
Anxiety / Panic attacks	1. Consider emotional fluctuations associated with "OFF" periods → Reduce "OFF" time 2. Involvement of geriatric or neuro-psychiatrist; role for CBT 3. SSRIs (also to Rx depression, which is highly comorbid with anxiety) 4. Benzodiazepines, e.g., alprazolam (Xanax®) 0.25-0.5 mg PRN, lorazepam (Ativan®) 0.5-1 mg PRN	• There is no clinical trial data concerning Rx choice for anxiety in PD. Treatment is similar to patients without PD • Benzodiazepines should be used cautiously (may result in dependence and cognitive impairment)
Psychosis	1. R/o secondary (e.g., metabolic) causes; PD medications should be eliminated in the following order: anticholinergics → amantadine → DAs → MAO-B inhibitors. L-dopa has the greatest motor effect with the least mental SEs; the lowest dose that satisfactorily controls PD symptoms should be used 2. Atypical antipsychotics for problematic psychosis: quetiapine (Seroquel®) immediate release (12.5-200 mg nocte) or extended release (50-200 mg nocte); clozapine (Clozaril®) (6.25-50 mg nocte) 3. Cholinesterase inhibitors may have anti-psychotic effects in PD 4. ECT in severe refractory cases	• Not all hallucinations require Rx (if mild and well tolerated by patient and family) • High-potency typical neuroleptics (e.g., haloperidol) should NOT be used. Atypical antipsychotics such as olanzapine and risperidone also worsen motor function and generally should not be used in PD • Quetiapine is typically 1st-line, even though the evidence base for this is relatively weak. It may be associated with worsening parkinsonism, although typically mild and usually does not warrant discontinuation • Clozapine is the most effective and best-tolerated agent, but requires long-term blood monitoring (weekly WCC for 18 weeks, then fortnightly or monthly; < 1% risk of agranulocytosis, which may occur even on small doses as an idiosyncratic SE and can be fatal if not discovered early). Clozapine may also suppress tremor and LID very effectively • There is a high rate of relapse even with careful tapering of antipsychotic
Cognitive impairment	1. Compensatory strategies (e.g., cueing, simplifying complex tasks) 2. Less potent PD medications should be eliminated (see above under Psychosis) 3. Cholinesterase inhibitors: rivastigmine (Exelon®) 1.5 mg PO bid, ↑ by 3 mg/d every 4 weeks to 6 mg bd according to tolerance; rivastigmine patch 4.6 mg/d, increase after 4 weeks to 9.5 mg/d; donepezil (Aricept®) 5 mg/d, ↑ after 4 weeks to 10 mg/d 4. Memantine (Ebixa®) has conflicting data for efficacy in PDD	• Cholinesterase inhibitors generally well-tolerated • Tremor may ↑ (e.g., in 10% of patients taking rivastigmine and may be severe enough to cause drug withdrawal in < 2%) • Modest cognitive benefit overall
Fatigue	1. DRT may be effective in some patients (fatigue may be less likely to worsen in patients treated with L-dopa, and apathy scores are improved in L-dopa-induced "ON"-states) 2. Selegiline (Jumex®/Selegos®) 10 mg morning, amantadine (PK-Merz®) 100 mg tds, methylphenidate (Ritalin®) 10 mg tds or modafinil (Provigil®) 200-400 mg/d may be tried	• Often refractory to treatment • Exclude / treat co-morbid depression, EDS, anaemia or hypothyroidism • Methylphenidate and modafinil are well-tolerated
Insomnia / Nocturnal sleep disturbance	1. Attention to sleep hygiene (e.g., establish a regular pattern of sleep, restrict daytime naps, exercise, avoid caffeine and fluids in evening, comfortable bedding and darkness during the night) 2. Effects of DRT on sleep is variable; it may help to avoid nighttime dosing; on the other hand DRT (e.g., controlled-release L-dopa) may benefit nocturnal motor symptoms (parkinsonism or dystonia) 3. Identify and treat underlying cause, e.g., CPAP for OSA; look for depression and ICDs (may be associated with sleep disturbance) 4. Sedating antidepressant, e.g., amitriptyline 12.5-25 mg nocte or mirtazapine (Remeron®) 15-45 mg nocte; non-benzodiazepine hypnotic, e.g., zolpidem (Stilnox®) 5-10 mg nocte; benzodiazepine, e.g., lorazepam (Ativan®) 0.5-1 mg nocte; atypical antipsychotic, e.g., quetiapine (Seroquel®) immediate release 12.5-50 mg nocte	• Polysomnography required in some cases, e.g., to diagnose OSA • Benzodiazepines should be used cautiously (may result in dependence and cognitive impairment) • Sedating medications may increase risk of falls
Rapid-eye-movement sleep behavior disorder (RBD)	1. Mild RBD may not need medication Rx; safety of the sleeping environment may be sufficient (e.g., removing potentially dangerous objects, placing cushions around the bed or mattress on the floor) 2. In moderate or severe cases (e.g., sleep disruption or injury to self or partner) medication Rx is warranted, e.g., clonazepam (Rivotril®) (0.25 mg nocte, ↑ according to response and tolerability up to 4 mg/d) 3. Consider melatonin (3 mg nocte, ↑ by 3 mg every week as necessary and tolerated up to 12 mg)	
Excessive daytime somnolence (EDS) and Sleep Attacks (SAs) SAs (falling asleep suddenly and irresistibly without warning signs such as yawning) generally represent a sudden exacerbation of antecedent EDS	1. Improving nighttime sleep may (or may not) improve EDS 2. DRT (especially DAs) should be used at the lowest dose that satisfactorily controls PD symptoms 3. Consider modafinil (Provigil®) 200-400 mg/d (well-tolerated, but conflicting evidence for efficacy from placebo-controlled RCTs) 4. If EDS or SAs persist despite medication changes, driving should preferably be curtailed	

Non-motor symptoms	Treatment Options	Comments
Orthostatic hypotension (OH) Defined as ↓ SBP ≥ 20 mm Hg and/or DBP ≥ 10 mm Hg during upright posture, with or without postural symptoms	1. Non-pharmacological: ↑ fluid intake, ↑ dietary salt, avoid alcohol / large meals (frequent small meals instead) / excessive warmth, elevate head of bed. Patients should be advised to rise slowly, especially in morning or after sitting/lying for a period of time 2. Discontinue unnecessary medications, e.g., antihypertensives 3. Fludrocortisone (Florinef®) 0.1-0.6 mg/d 4. Domperidone (Motilium®/Motidone®) 10-20 mg tds (particularly effective for DA-induced OH - give 30-60 minutes prior to DRT doses) 5. Midodrine (Amatine®/ProAmatine®/Gutron®) 5 or 10 mg tds 6. Consider pyridostigmine (Mestinon®) 30-60 mg tds	• Supine HTN a potential SE of fludrocortisone and midodrine • Observe for possible hypokalaemia when using higher doses of fludrocortisone
Constipation	1. Consider stopping anticholinergics 2. ↑ dietary fibre and fluid intake (e.g., 6-8 glasses of water/d - although this may worsen urinary symptoms) 3. Psyllium (e.g., Metamucil®) 4. Laxatives, e.g., lactulose 15-30 mL daily or bd, macrogols (e.g., Forlax® 1-2 sachets/d), stimulant laxatives such as bisacodyl (Dulcolax®) 5-15 mg PO nocte or 10 mg suppository PRN	
Urinary frequency and urgency, nocturia (overactive bladder)	1. Avoid fluid intake after dinner (for nocturia); regular visits to the bathroom to avoid urgency; bedside urinal may help to avoid incontinence 2. ↓ intake of caffeine, alcohol 3. Anticholinergic agents: oxybutynin (Voxytane®) 5 mg 1-3x/d, amitriptyline, tolterodine (Detrol LA®) 4 mg/d, trospium (Spasmolyt®) 20 mg bd 4. Referral for urological evaluation - may require Rx for BPH	• Trospium does not significantly cross the blood-brain barrier and thus may be preferred in patients with cognitive impairment • Avoid surgery (e.g., TURP) unless clearly indicated
Erectile dysfunction	1. Treat depression and discontinue potentially offending drugs, e.g., beta blockers 2. Sildenafil (Viagra®) 50-100 mg taken 1-2 hours before sex	• OH may be unmasked by sildenafil
Drooling	1. Chewing gum or sucking on hard candy may serve as a cue to swallowing more frequently 2. Anticholinergic agents such as oral benzhexol (Apo-Trihex®/Benzhexol®), SL atropine (1% ophthalmic drops) 1 drop (0.5 mg) bd, ipratropium bromide (Atrovent®) 0.03% (21 µg) 1-2 sprays into the mouth (SL), up to qid 3. BTX of salivary (parotid ± submandibular) glands 4. Rarely, radiotherapy or surgery required	• Systemic anticholinergic SEs with oral anticholinergics • Atrovent® spray well-tolerated, but effect mild • BTX generally well-tolerated
PD-related pain	1. Pain in untreated and fluctuating PD patients (e.g., frozen shoulder and "OFF"-period dystonic pain, respectively) can often be improved by effective Rx of underlying PD 2. BTX for painful foot dystonia 3. TCAs (e.g., amitriptyline), antiepileptics (e.g., gabapentin [Neurontin®]), duloxetine (Cymbalta®), opioids 4. Deep brain stimulation of the subthalamic nucleus/ globus pallidus internus	

Appendix 1: Parkinson's Disease Drug Identification Chart

Levodopa-Based Medications		
Levodopa/Benserazide	Madopar 100/25mg cap®	
	Madopar 200/50mg tab®	
	Madopar HBS 100/25mg cap®	
Levodopa/Carbidopa	Sinemet 25/100mg tab®	
	Sinemet 25/250mg tab®	
	Sinemet CR 50/200mg tab®	
Entacapone	Comtan 200mg tab®	
Levodopa/Carbidopa/ Entacapone	Stalevo 50(50/12.5/200mg) tab®	
	Stalevo 100(100/25/200mg) tab®	
	Stalevo 150(150/37.5/200mg) tab®	
	Stalevo 200(200/50/200mg) tab®	
Direct Dopamine Agonists (Ergot)		
Bromocriptine	Parlodel 2.5mg tab®	

*Parkinson's disease affects everyone differently and treatments need to be tailored to the individual.

Direct Dopamine Agonists (Non-Ergot)		
Piribedil	Trivastal Retard 50mg SR tab®	
Pramipexole	Sifrol 0.125mg tab®	
	Sifrol 1mg tab®	
Pramipexole extended release	Sifrol ER 0.375mg tab®	
	Sifrol ER 1.5 mg tab®	
Ropinirole	Requip 0.25mg tab®	
	Requip 1mg tab®	
	Requip 2mg tab®	
Ropinirole prolonged release	Requip PD 2mg tab®	
	Requip PD 4mg tab®	
Rotigotine transdermal patch	Neupro®	 2mg 4mg 6mg 8mg
Others		
Selegiline	Jumex 5mg tab®	
	Selegos 5mg tab®	
Trihexyphenidyl hydrochloride	Benzhexol 2mg tab®	
Orphenadrine	Norflex 100mg tab®	
Amantadine	PK-Merz 100mg tab®	

*Parkinson's disease affects everyone differently and treatments need to be tailored to the individual.

Appendix 2 - Patient diary (for motor fluctuations and dyskinesia)

DAY ONE			DATE:			
Time	**ON without dyskinesia**	**ON with minor dyskinesia**	**ON with troublesome dyskinesia**	**OFF**	**Asleep**	**L-dopa intake (please state exact time)**
0600-0700						
0700-0800						
0800-0900						
0900-1000						
1000-1100						
1100-1200						
1200-1300						
1300-1400						
1400-1500						
1500-1600						
1600-1700						
1700-1800						
1800-1900						
1900-2000						
2000-2100						
2100-2200						
2200-2300						
2300-0000						
0000-0100						
0100-0200						
0200-0300						
0300-0400						
0400-0500						
0500-0600						

Each row represents hourly intervals in a day, while each column represents different motor states that can be experienced by PD patients with motor fluctuations. Minor dyskinesia is when the abnormal movements do not bother the patient, while troublesome dyskinesia is when the movements interfere with daily activities. For each row, the patient is instructed to tick the box (ONLY ONE) that best represents his/her motor status for that hour. Patients are also asked to record the exact time of L-dopa intake.

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