

2014 recommendations for the treatment of Parkinson's disease

Working Group of the Therapy Commission of the Swiss Neurological Society¹

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Introduction

Our last recommendations for the treatment of Parkinson's disease (PD) were published in 2008. Since then, several developments have taken place and therefore an update is necessary.

Most importantly, the role of deep brain stimulation (DBS) has been reassessed and it has been shown in large multicentre trials that DBS can improve quality of life of patients with motor fluctuations, also at an earlier stage of the disease. Second, the role of dopamine agonists has been reassessed due to the growing awareness of potentially serious side effects, particularly concerning the neuropsychiatric side effects and sleepiness.

Due to better treatment options, more patients reach an advanced stage of the disease when quality of life is mostly determined by dopamine-unresponsive motor and non-motor symptoms of the disease. These symptoms are exceedingly difficult to treat, undesired drug interactions are common and the best compromise for each patient has to be found on an individual basis. This challenge makes a close collaboration between the general practitioner and the movement disorders specialist imperative.

For the first time, these recommendations will be published in English, which the Swiss Neurological Society has chosen as the academic language for all written information presented at its yearly meetings.

Treatment of the motor symptoms of Parkinson's disease

Medical therapy

There are three dopaminergic principles of the medical therapy. First, replacement of deficient dopamine levels by application of its precursor levodopa (with inhibitors of peripheral catabolism). Second, activation of dopamine receptors by using dopamine agonists. Third, blocking central dopamine catabolism by MAO-B inhibitors.

Correspondence:
Daniel Waldvogel, MD
Neurologische Praxis Luzern
Hirslanden Klinik St. Anna
CH-6006 Luzern
Switzerland
d.waldvogel[at]bluewin.ch

Anticholinergic or antiglutamatergic treatment may also be indicated. The various pharmacological approaches are discussed according to the stage of the disease.

Early stages

At the present time, there is insufficient scientific evidence for any neuroprotective effect of any kind of treatment. Therefore, treatment is aimed from the start at alleviating symptoms of PD.

The early stage of Parkinson's disease is, in fact, by no means "early". Once a clinical diagnosis of PD can be made, 50–70% of the dopamine producing neurons in the substantia nigra have already been lost.

Patients with Parkinson's disease benefit substantially from dopamine replacement therapy. The quality of life can often be restored almost fully. Treatment should therefore not be withheld when symptoms are present. Motor complications, invariable long-term problems of PD, are not substantially postponed by delaying treatment initiation, and, by doing so, one may lose the option of giving the patient an extended "honeymoon phase" of the disease.

The main choices for treatment are levodopa (always combined with a peripherally acting decarboxylase inhibitor, i.e., benserazide or carbidopa) or dopamine agonists.

Since young or younger patients are particularly prone to develop motor complications, dopamine agonists have been recommended as the treatment of choice for these patients. It has been shown that the development of dyskinesias occurs later in patients treated with agonists compared to levodopa-treated patients. However, dopamine agonists are less effective than levodopa, have to be titrated over a longer period of time, have considerably more side effects (particularly worrisome are the neuropsychiatric side effects) and are far more expensive. Besides, there is no significant difference in the quality of life after several years between patients initiated on levodopa or dopamine agonists, respectively. In addition, young or younger patients who develop motor complications can nowadays be offered an effective treatment in the form of deep brain stimulation (DBS).

1 The members of the Working Group are: Daniel Waldvogel, Lucerne & Zurich; Claudio Bassetti, Berne; Christian Baumann, Zurich; David Benninger, Lausanne; Stefan Bohlhalter, Lucerne; Pierre Burkhard, Geneva; Peter Fuhr, Basel; Alain Kaelin, Lugano; Georg Kägi, St. Gallen; Carsten Möller, Lugano; Pierre Pollak, Geneva; Michael Schüpach, Berne; François Vingerhoets, Lausanne.

If patients do not achieve sufficient benefit from agonists alone, levodopa should not be withheld.

Levodopa is the most effective treatment for the motor symptoms of PD. It is usually well tolerated, cost-effective and can be titrated relatively quickly up to the required dosage. Furthermore, response to levodopa is one of the diagnostic criteria for Parkinson's disease. A patient who does not objectively respond to a daily dosage of 1000 mg standard levodopa for at least three months most likely has a diagnosis other than Parkinson's disease. The main disadvantage of levodopa is its short pharmacokinetic half-life time, the resulting pulsatile dopaminergic stimulation being one of the assumed reasons for the development of motor fluctuations and dyskinesias.

For most patients, particularly elderly patients, levodopa is the treatment of choice.

Occasionally, in a young patient with tremor-dominant PD, anticholinergics may be given, however, in elderly patients, their side-effect profile makes them a particularly undesirable choice.

In a patient with mild symptoms, rasagiline, a MAO-B inhibitor with a weak symptomatic effect, may be given as initial therapy.

Advanced stages

In more advanced stages, when the storage capacity of dopamine neurons is reduced, fluctuations and consecutive dyskinesias develop. At this stage, the therapeutic window between too high levels of dopaminergic stimulation with dyskinesias and too low levels of dopaminergic stimulation resulting in an "off" state becomes more and more narrow.

There are several strategies that may be considered. Once a so-called "wearing-off" develops, i.e., the patient experiences the recurrence of symptoms before the next dosage of dopaminergic medication is due, controlled release forms of levodopa may be tried, COMT (Catechol-O-Methyl-Transferase) inhibitors can be used in levodopa-treated patients (entacapone or, if entacapone fails, the more potent tolcapone, which requires monitoring of liver enzymes). A combination of agonists and levodopa may be chosen, a MAO-B inhibitor (selegiline, rasagiline) may be added or levodopa may be given more frequently. Sometimes several of these approaches may be combined.

Dyskinesias usually respond to reducing dopaminergic stimulation, which however is not always tolerated because of the resulting worsening of motor symptoms. In some cases the administration of amantadine can provide benefit, which often wears off within a year. In exceptional cases clozapine may be tried. If dyskinesias remain troublesome, DBS or continuous dopaminergic stimulation need to be considered (see below).

Levodopa is actively taken up by a specific transporter system in the small intestine. Levodopa competes with proteins from food sources for these transporters, in the gut as well as at the level of the blood brain barrier. In addition, due to the denervation of the stomach that invariably occurs in advanced PD, gastric emptying becomes erratic. As a result of these pharmacokinetic difficulties, drug levels may fluctuate remarkably despite regular intake, causing almost

intractable fluctuations and dyskinesias. Patients should be made aware of these potential food and drug interactions. Patients may benefit from keeping the interval between doses at or below four hours, taking the levodopa-containing tablets on an empty stomach and shifting the main dietary protein intake towards the end of the day.

For patients with advanced and fluctuating disease who are not candidates for DBS, for example because of their age, other treatment options based on the use of an external pump can be offered. These options include the subcutaneous infusion of apomorphine or the intrajejunal application of levodopa through a PEG tube. These systems produce a more stable delivery of the pharmacological agent by continuous application and bypassing the irregular gastric emptying. These treatments require a specialised team for initiation and follow-up.

In general, assessment and management of advanced Parkinson's disease in many cases warrants an interdisciplinary approach including a neurologist, family care physicians or internists, a rehabilitation physician and/or physiotherapist, a specialised nurse, a psychiatrist and a neuropsychologist as well as a specialised neurosurgeon.

Special circumstances

Patients who had surgery and cannot swallow may be treated with levodopa through a nasogastric tube, with repeated apomorphine subcutaneous injections, with a rotigotine patch or with amantadine infusions for a short period of time.

Surgical therapy

At present, deep brain stimulation (DBS) is the best surgical approach for Parkinson's disease, as opposed to lesioning surgery which is nowadays nearly abandoned. Patients who qualify for surgery are those who either suffer from tremor that does not respond sufficiently to medication or patients who suffer from insufficiently controlled motor fluctuations and dyskinesias. There is a trend towards earlier DBS, substantiated by a large multicentre study published last year. The most frequently chosen target is the subthalamic nucleus, however, some patients may benefit from stimulation of the globus pallidus internus (GPI) or occasionally, when the tremor is predominant, from the thalamic nucleus ventralis intermedius (VIM). Patients selected for surgery should not have severe non-levodopa responsive symptoms (including dementia) and should usually not be older than about 75 years, however, general health being a more decisive factor than chronological age. Except for tremor, the best possible result of DBS corresponds to the best possible "on" state achieved with levodopa but without fluctuations and without dyskinesias. Tremor responds to DBS even if it does not sufficiently respond to levodopa.

Physiotherapy and speech therapy

Physiotherapy is indicated at every stage of the disease. Most neurorehabilitative efforts focus on strategy training, teaching patients to switch from the more impaired habitual mo-

tor control to a less impaired goal-directed mode of action. Different forms of active training have been shown to be helpful, also improving well-being. In more advanced stages, patients typically benefit from sensory cueing, which can be applied to overcome freezing episodes. Physiotherapy may help to prevent secondary complications. In patients with pronounced speech impairment, voice treatment is considered helpful. A speech therapist may also help a patient who has difficulties swallowing.

Ergotherapy

An ergotherapeutic assessment of the home environment of patients may be helpful for optimising appliances and preventing falls from “stumbling blocks”.

Treatment of the non-motor symptoms of Parkinson's disease

Psychiatric and cognitive symptoms

Depression

Depression affects as many as 30–50% of patients with PD. It may often be the first symptom of the disease, apart from RBD (REM Sleep Behaviour Disorder) or hyposmia. The diagnosis and treatment of depression is challenging, due to the overlap of symptoms and a paucity of randomised controlled trials.

Depression may improve with dopaminergic treatment. There is evidence for an antidepressive effect of pramipexole, a dopamine agonist. If depression persists after the successful treatment of motor symptoms, antidepressants may be necessary. Tricyclic antidepressants may be effective, however, their anticholinergic effect makes them a problematic choice in many patients, particularly with a more advanced condition. Nortriptyline is less anticholinergic than other tricyclic antidepressants. A recent double-blind, randomised, placebo-controlled parallel group design study, the largest so far, showed that a SSRI and a SNRI were effective in reducing depressive symptoms without worsening motor

symptoms. Insufficient data are available for any other treatment modality.

Hallucinations and psychosis

Psychotic symptoms may develop over time in PD. They range from non-disturbing visual hallucinations or vivid dreams and mild illusions (often illusions of presence) to a psychotic state with disturbing hallucinations and frightening delusions. The occurrence of visual hallucinations may predict the development of dementia.

Despite limited available data from controlled trials, there is agreement among most experts to first adjust medication, i.e., to stop all medication with anticholinergic properties and, if possible, switch from dopamine agonists to levodopa. Like in non-PD patients developing delirium, concurrent infections, endocrine or metabolic disturbances must be ruled out. In PD patients with cognitive impairment and hallucinations, the introduction of rivastigmine may be helpful, yet daily dosage should be increased slowly. If necessary, low doses of quetiapine or clozapine may be used as the only permitted antipsychotics in PD. The latter is more effective but requires regular monitoring for agranulocytosis and is contraindicated in the presence of heart disease. Both drugs should be started at the lowest possible dose, as severe sedation or orthostatic hypotension may occur.

Apathy

Apathy frequently overlaps with depression or dementia, but, in a substantial number of patients, apathy may develop in isolation.

Apathy, almost by definition, is a more troublesome symptom for the caregiver than for the patient him-/herself. To discuss its existence, its pathology and its acceptance as one of the difficult non-motor symptoms of PD may help the caregiver to cope with it and is therefore encouraged.

Apathy is commonly seen after DBS and, in this case, likely results from the massive postoperative reduction of dopaminergic agents. Re-initiation of dopaminergic treatment usually solves this particular problem.

Dementia

Dementia is a particularly serious problem in the evolution of Parkinson's disease. The longest follow-up study so far estimated the risk of dementia at roughly 40% after 10 years, increasing to 80% after 20 years. However, age above 70 years seemed to be a more relevant risk factor than disease duration per se. Dementia poses a substantial burden on the caregiver and is the leading cause for nursing home placement.

Parkinson's disease dementia (PDD) may affect any core cognitive domain, however, executive dysfunction is more prevalent at the early stages of the neurocognitive decline. PDD is frequently associated with behavioural and neuropsychiatric symptoms, including depression, as well as sleep problems. There is still an ongoing debate about the best screening tools for PDD, however due to the pronounced frontal executive dysfunction, it is mostly agreed

Table 1

This table shows the estimated equivalent dosages of different dopaminergic agents. These estimates can be used to calculate corresponding dosages if one needs to switch from one agent to another agent (•••ref: Tomlinson et al, Mov Dis 2010).

Equivalent dosage		Dose corresponding to 100 mg levodopa standard release
Levodopa	Standard	100 mg
	Controlled release	130 mg
	+ Entacapone	75 mg
	+ Tolcapone	65 mg
Pramipexole		1 mg
Ropinirole		5 mg
Rotigotine		3.5 mg
Apomorphine		10 mg

that for example the Montreal Cognitive Assessment (MoCA) is a more effective and sensitive screening instrument than the MMSE (Folstein).

After having excluded treatable causes of cognitive decline, cholinesterase inhibitors can be recommended as they have been shown to have a positive impact on global assessment, cognitive function, behavioural disturbance and activities of daily living rating scales. In Switzerland, so far only rivastigmine is approved by the Federal Social Insurance Office.

Dopamine-induced behavioural disorders

Dopaminergic treatment may cause several behavioural disorders, which are broadly categorised as impulse control disorders (i.e., hypersexuality, pathological gambling, compulsive shopping, and binge eating), punding (i.e., intense fascination with excessive, repeated, non-goal-oriented, unproductive repetitive behaviours or complex hobbyism like hoarding) and compulsive medication use. While dopamine agonist treatment is more associated with impulse control disorders, compulsive medication use is more associated with levodopa overuse, particularly fast acting formulations. Early intervention is imperative and physicians must be vigilant not to miss the first signs of these serious iatrogenic complications.

Autonomic nervous system symptoms

Constipation

Constipation may be one of the presenting symptoms of the disease, occurring years before the motor symptoms of PD. The prevalence of constipation is very high, estimates ranging from 30% to 60% of patients. The first step in treatment is to assure that there are no anticholinergic medications used which invariably worsen constipation. Dopamine agonists also worsen obstipation. Adequate fluid and fiber intake and regular exercise seem important. If medication is needed, the best evidence is available for the use of macrogol.

Disorders of micturition

Lower urinary tract symptoms (LUTS) occur in a substantial number of patients over the course of the disease. If incontinence is already present early in the disease course, it is considered a „red flag“ and should raise the suspicion that the patient may suffer from Multiple System Atrophy.

Patients mostly complain about nocturia, urgency and frequency and, at a late stage of the disease, urge incontinence. Detrusor hyperactivity seems to be the underlying cause, since basal ganglia output is assumed to have an overall inhibitory effect on the micturition reflex. If patients have no significant residual volume, a mainly peripherally acting anticholinergic can be tried, however, one has to be aware of the potential side effects (cognitive worsening, worsening of other autonomic dysfunctions like constipation and orthostatic hypotension). There are insufficient data to recommend either a particular anticholinergic drug or an alternative treatment approach like intravesical botulinum toxin or sacral stimulation. However, some drugs may have lower central side effects due to their lower penetrability through

the blood-brain-barrier (e.g., trospium chloride). Overall, there are also insufficient data to recommend night-time desmopressin for the treatment of nocturia.

Orthostatic hypotension

Orthostatic hypotension (OH) is defined as a decrease of at least 20 mm Hg in systolic blood pressure (SBP) and/or 10 mm Hg in diastolic blood pressure (DBP) within 3 minutes of standing up or passive tilting, with or without postural symptoms. OH is associated with cardiac and extra-cardiac sympathetic denervation and baroreflex failure, the latter causing marked blood pressure variability. Orthostatic hypotension in PD is frequently accompanied by supine hypertension, with sometimes exceedingly high values at night or early in the morning. Any treatment of OH that increases intravascular volume or sympathetic tone is likely to worsen supine hypertension.

Presently, there is insufficient evidence for any particular kind of treatment.

Most experts recommend a three-step approach, the first being a thorough evaluation of concomitant drugs that may worsen OH, like anticholinergics, antihypertensive medication or alpha-blocking agents due to prostate problems, the second step being non-pharmacological measures and the third being drugs.

Non-pharmacological measures include compressive stockings, elevation of the bed head, avoidance of large meals in favour of several smaller ones, physical counter-maneuvres such as crossing the legs, squatting, tensing the muscles of the legs, abdomen or buttocks, increasing the water intake to 1.5–2.5 l/day and increasing salt intake.

The most frequently used drugs are the α_1 -adrenoceptor agonist midrodrene and the mineralocorticoid fludrocortisone, which invariably worsen supine hypertension. Pyridostigmine, which is hypothesised to improve baroreceptor function, may be tried as well as domperidone, both of which do not worsen supine hypertension.

Erectile dysfunction

Erectile dysfunction is one of the non-motor symptoms of PD that is not well studied. If needed, most experts recommend the use phosphodiesterase inhibitors like sildenafil, vardenafil or tadalafil. Patients should be cautioned about worsening orthostatic hypotension after the use of this class of drugs. Before prescribing any of these drugs, the physician must evaluate the possibility of a pathologically increased libido due to dopaminergic treatment.

Hyperhidrosis

Sweating dysfunction frequently occurs together with other autonomic disturbances. Bouts of hyperhidrosis may be particularly severe during “off” periods or during dyskinetic states. Improving the motor fluctuations may improve these episodes of hyperhidrosis. There are no well-documented treatment options for night sweats or hyperhidrosis not correlated to motor complications.

Saliva

Swallowing is an automated motor function that is affected by PD. Therefore, saliva frequently accumulates, may drip

and handicap the patient socially. If the problem persists after optimal control of motor function, chewing gum to increase swallowing frequency may help. If a patient is severely disturbed by drooling, botulinum toxin can be injected into the salivary glands to reduce saliva production. Botulinum toxin may not be covered by health insurance.

Sleep-associated symptoms

Sleep problems are a frequent complaint in patients with PD and may even herald PD long before the motor symptoms become apparent.

Conceptually, sleep can be disturbed due to the neurodegenerative process per se, which affects the sleep/wake regulatory centres in the brainstem, or due to ensuing autonomic dysfunction with urgency and nocturia or due to nightly decrease of dopaminergic stimulation resulting in restlessness, pain and akinesia. The latter can be treated by adjusting dopaminergic medications or by DBS; the treatment of autonomic dysfunction has been discussed above. There are no evidence-based recommendations for the treatment of the sleep/wake disturbance associated with PD except for low-level recommendations for the treatment of RBD.

REM sleep behaviour disorder

RBD results from a loss of muscle atonia during REM sleep, which is clinically expressed in a wide variety of symptoms ranging from uttering words to violent attacks against the bed partner. RBD may precede the motor symptoms of PD for many years. If a patient shows violent behaviour or injuries from falling out of bed during sleep, medical treatment may be warranted. The most commonly used drug is clonazepam, more recently low-dose melatonin has also been suggested.

Excessive daytime sleepiness

A substantial number of patients complain about excessive daytime sleepiness (EDS). EDS is considered multifactorial, resulting from the degeneration of the brainstem sleep/wake regulatory centres, the poor night sleep and the dopaminergic medications. No evidence-based treatment recommendations can be given. According to expert opinion, power naps may be tried as well as switching from dopamine agonists to levodopa. Wake-promoting agents like modafinil are not generally recommended.

Sensory symptoms

Pain and restlessness

The basal ganglia are involved in the network that processes pain, however, the exact role of the basal ganglia in pain perception remains to be elucidated.

Pain can affect patients long before the diagnosis of PD is made. Particularly common in that regard seems to be shoulder and lower back pain, which then may improve with dopaminergic treatment resulting in reduction in rigor and immobility.

Many different suggestions have been made to classify pain in PD, however, a thorough discussion of this topic is beyond the scope of this article. For everyday practice, a reasonable approach to pain in PD is to differentiate whether the pain responds to dopaminergic stimulation or not, or whether a mechanical, inflammatory or visceral cause is more likely. The most frequent pain responding to dopaminergic treatment is the pain associated with early morning "off"-dystonia. Most experts recommend either levodopa in liquid form or apomorphine for this particular pain. Patients with severe fluctuations and pain during the "off" state may be candidates for DBS.

Restlessness can occur as part of a manic state when a patient suffers from dopamine dysregulation syndrome or in the form of akathisia or restless legs syndrome, the latter usually when the levels of dopaminergic medications decrease towards the end of the dosing interval, particularly at night. In that case, low levels of long-acting dopamine agonists may be helpful.

Hyposmia

Together with constipation and RBD, hyposmia is now considered one of the earliest symptoms of PD and may occur years before the motor signs become evident.

There is no treatment for this particular symptom.

Conclusions

In this review, a working group of the Swiss Neurological Society proposes updated recommendations for the medical and surgical treatment of motor and non-motor symptoms of Parkinson's disease. These recommendations are either evidence-based whenever data are available or commonly supported by movement disorders experts and they correspond to what may be referred to as the therapeutic state of the art for this condition in 2014. By no means can they be taken as rigid guidelines and they should be adapted for the needs of each individual patient suffering from Parkinson's disease.