National Consensus on the Diagnostics and Treatment of Parkinson's disease

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Today, 07.12.2021, we, the undersigned specialists, have reached a consensus on the diagnostics and treatment of Parkinson's disease

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Parkinson's disease affects 0,15% of the general population, with prevalence increasing to 1% in the age group of 55 to 65 years. According to epidemiological data from Bulgaria, the number of people, affected by the disease, should be about 12 000. If treated improperly, patients who are still in active working age rapidly become disabled. If correct treatment is provided, such patients may continue to be capable of working at least over the first 5 years following the onset of the disease and have a mild disability within the first 10 years of onset. Treatment from the very onset with levodopa products leads to faster exhaustion of therapeutic effect and early disability of the patient. After levodopa's effect wears out, the patient enters the phase of the complicated Parkinson's disease (PD) when treatment is difficult, disability is serious and patients become a burden to their families and to society.

Some neuroprotective agents may delay the progression of the disease but their usage should start early in order to be more effective. In order to do so early diagnosis is needed, which may sometimes prove difficult in the first few years following the onset of the disease. Quite often, essential tremor, which is 10 times more common than PD, is misdiagnosed as Parkinson's disease and the patient receives improper treatment for a long time.

Parkinson's disease is a chronic progressive neurodegenerative disorder. It is caused by progressive degeneration of the dopaminergic neurons in the substantia nigra. The cause is unclear; hereditary factors and toxic substance factors from the environment have been suspected. Decrease in number of those neurons leads to a drop of dopamine levels in the nigrostriatal pathways. The dopamine/acetylcholine and dopamine/glutamate balances are disrupted at the level of the dopaminergic striatal receptors. The imbalance of neuromediators is the main reason for Parkinson's disease symptoms. There are no proven prevention options for Parkinson's disease.

Diagnosis

The early diagnosis of Parkinson's disease is difficult because initial symptoms are non-specific. The onset of the disease is gradual and goes an unnoticed; patient usually is not able to specify what the first symptom was. In some patients, symptoms may present only during stress and become permanent later. Only 30% of patients are diagnosed during the first year of the disease. Early diagnosis may be achieved through detailed history, interviewing patients' relatives and neurological examination. Technology-device assessment is rarely needed.

Parkinson's disease is manifested by the classic triad of resting tremor, rigidly increased muscle tone, bradykinesia, with postural disorders added to the triad later.

In order to diagnose the disease, the following **diagnostic categories** have to be fulfilled:

Clinically confirmed: There is Parkinson's disease when 3 of the main symptoms (resting tremor, bradykinesia, rigidity) are present or 2 of them are present, if asymmetric.

Clinically probable: There is Parkinson's disease when 2 of the main symptoms are present, or when 1 of them is present, if asymmetric.

Clinically possible: There is Parkinson's disease when 1 of the main symptoms is present plus postural disorders.

Bradykinesia is one of the earliest symptoms. In early stages, it presents with impairment affecting the gait, the posture, the fine movements of the hands, the facial expression (mask-like face) and the speech (speaking in a quiet voice, with decreased modulation and intonation). Assessment involves various methods:

1. *Observing the gait,* the patient being instructed to walk rapidly with arms relaxed next to the body. A decrease in the physiological synkinesia of the affected arm is detected as well as a gait with short steps.

2. Observing the gait, the patient being instructed to walk barefoot. Decreased movements in one of the arms and contraction of the toes of the affected foot towards the floor upon stepping are more easily detectable. The patient will place the whole foot flat on the floor instead of bending the foot from the heel towards the toes.

3. *Observing the movements* will reveal slow motions when performing daily activities – buttoning and unbuttoning, tie up a shoe, etc.

4. Patients' *gestural capacity* decreases.

5. When the patient *turns around* from a supine position on the examination couch, the movement is initiated with the legs, while healthy individuals' turning around is initiated with the arms.

6. When *sitting down*, the body fails to bend forward, as if the patient falls to a sitting position.

7. When performing the *tilt back chair test*, the doctor stands behind a chair on which the patient has been seated comfortably leaning on the back of the chair and tilts the chair back without warning. The patient tilts together with the chair, while healthy individuals maintain their upright position of the back due to reflexive compensation.

8. *Performing two actions simultaneously* as well as alternating movements (diadochokinesis) are impaired. If the patient lifts up their arm flexed at 90 degrees at the elbow and imitates twisting in a light bulb, the movement gradually slows down and becomes irregular.

9. *Micrography* is manifested when the patient writes down the figures from 1 to 9 on a piece of paper with no lines or checks. The size of the figures decreases from 1 to 3 and then increases from 4 onwards.

10. *Slow eye blink rate* is an early sign.

11. *Meyerson's sign* is positive: when, upon being tapped on the nose or the glabella, the patient blinks with each tap, while in a healthy individual this reflex rapidly wears off.

Muscle rigidity in the early stages is manifested with increased muscle tone, predominantly of the proximal muscle groups of the shoulders and the hip. When tone assessment fails to provide conclusive evidence, early diagnosis tests are used:

1. *Muscle tone* increases while the patient is gripping a heavy item in one hand or clenches one fist while the doctor is examining the tone of the other hand.

2. *In the arms swing test* the doctor stands behind the standing patient and starts to use their arms to move the patient's shoulders, so the patient's arms start to swing as well. If muscle rigidity is present, the affected arm fails to swing freely, unlike the healthy normal arm.

3. *The head dropped test* demonstrates the presence of axillary muscle rigidity. The doctor, using their palm, slightly raises the head of a supine patient and instructs the patient to completely relax the head. After several seconds the doctor pulls away their palm without warning. If rigidly increased muscle tone is present, the head fails to drop down to the bed or drops in a slow, interrupted manner, unlike the head of a healthy person, which rapidly drops down.

4. *The posture* in patients with rigidly increased muscle tone changes, with the body and the head leaning forwards and with flexed, pronated arms, as well as bent knees.

5. *Ache* affecting the joints, the shoulder-arm syndrome (frozen shoulder) and lumbalgia (LBP) occur in patients with long-term increase in muscle tone.

6. *Tendon reflexes* at the affected side are slightly increased due to the increased muscle tone.

Resting tremor is found in 70% of patients but not always clinically manifested from the very onset. It occurs most commonly in the hands while in rest and resolves during movement. When the limb is placed in another position, the tremor starts again (re-emergent tremor) after a latent period of several seconds. It is necessary to distinguish resting tremor

(static) from postural tremor with arms stretched forward, from kinetic tremor, which emerges at the beginning of a movement when performing the finger- to-nose test, and also from intention tremor, which begins when nearing the target. In cases of advanced disease, postural tremor may add up to the static tremor, however the amplitude of the static tremor is greater. In extremely rare cases, the disorder may start with postural tremor. Tests for provoking tremor are used:

1. During *walking*, the tremor of the arms increases.

2. When the patient *is being distracted*, made to count down slowly from 20 to 1, the tremor increases.

3. During *clenching* the fist of the healthy hand, static tremor increases.

Postural disorders are rarely an initial sign and more commonly emerge in the advanced stages of the disease. They are diagnosed by observing the gait. The following methods are used:

1. While walking, the patient is instructed to abruptly turn around and start walking in the opposite direction, at which point the patient loses their balance.

2. The doctor stands behind the patient, who is standing with the legs side by side and places the arms on patient's shoulders. The doctor suddenly tries to put the patient off balance (making sure not to let patient fall) by pushing the patient forward, backward or sideways. A healthy individual keeps their balance, while if postural disorders exist the patient staggers with tiny steps (more than two) on the side of the push and loses balance.

Signs from the autonomous nervous system include excessive sweating, sweating seizures, increased fatty secretion with oily hair, seborrhea, increased salivation, constipation, urinary disorders (need of rapid voiding due to increased detrusor activity), impotency, disrupted blood pressure regulation with a tendency towards arterial and orthostatic hypotension. The latter may be diagnosed using the Schellong test. These signs rarely occur in the early stages of the disease and therefore are not very informative for diagnostic purposes.

Psychological signs include depression, anxiety, bradyphrenia and mild memory disturbances. Depression is present in 50-80% of patients due to dopamine deficiency and noradrenergic deficiency. Depression causes a significant deterioration of patients' quality of life and should be diagnosed and treated.

To diagnose Parkinson's disease, a general practitioner should detect one or more of the symptoms below, using already described methods:

- Resting tremor
- Bradykinesia
- Rigidly increased muscle tone
- Postural disturbances

Should this signs being detected, it is necessary to refer the patient to a neurologist without any further diagnostic methods.

The neurologist should confirm the diagnosis using the diagnostic criteria and with the mandatory use of the diagnostic methods under No1 and, where indicated, the diagnostic methods listed under No 2 to No 6.

Diagnostic methods

1. Using **pharmacological diagnostic tests** results in the improvement of signs and symptoms, if they are due to Parkinson's disease.

- **The dispersible levodopa test is performed with** 1 tablet containing 125 mg of dispersible levodopa formulation with benserazide, dissolved in about 100 ml of water. The effect is rapid (15 minutes) and distinct due to the fast absorption of the medication. Therefore, it is preferred to the test with ordinary formulation.
- **The standard levodopa test** is performed with 1 tablet containing 250 mg of levodopa. Due to slow absorption and slow reaching of therapeutic serum levels, the onset of effects is in about 1 hour and is not distinct. This is a serious shortcoming of this test.
- The dopamine agonist test with **apomorphine** 3 mg administered subcutaneously has a rapid and distinct effect but is associated with side effects such as vomiting and is therefore not recommended.
- **The amantadine sulfate** half infusion 200 mg/500 ml administered intravenously over 1 hour has an easily detectable effect. The problem with this test is that it is time-consuming and requires a specified place for the administration of the infusion.
- **The lack of effect** from the pharmacological diagnostic test does not fully rejects the diagnosis. In such cases at least two weeks of high dose levodopa (1000 – 1500 mg daily) treatment is administered and its effectiveness is clinically assessed.

2. The electromyography test (EMG) may be used for the early diagnosis of Parkinson's tremor and for distinguishing essential tremor from other types of tremor.

Tremor gives a typical EMG pattern with a frequency of 5-7 Hz and alternating activity of antagonistic muscles. The patient may be referred by a neurologist for this test if the neurological examination and the use of the pharmacological tests were not sufficient for the diagnosis.

3. Functional Neuroimaging methods give information on the dopaminergic terminals, serotonin cells, noradrenergic and cholinergic function. They include positron emission tomography (PET) and single photon emission computer tomography (SPECT).

SPECT has a lower resolution as compared to PET but provides a more precise assessment of the neurodegenerative process and is performed using a standard gamma-chamber with a high-resolution collimator. The radioligand [^{123}I]-FP-CIT (Datscan) contains an analogue of cocaine, ioflupane (^{123}I), which binds selectively to striatal dopamine transport protein (DAT) in presynaptic membranes of the nigrostriatal dopaminergic terminals. DAT levels correlate with the striatal dopamine, i.e. with the presynaptic dopaminergic system and the functioning nigrostriatal dopaminergic neurons. The method is routinely used for early diagnosing of Parkinson's disease and for distinguishing essential tremor. This method is not suitable for distinguishing Parkinson's disease from multiple systemic atrophy, progressive supranuclear paralysis and cortical-basal degeneration. Findings of a normal image may not reliably reject the presence of Parkinson's syndrome and those cases require re-examination at a later point.

This method should be used for patients with unclear tremor without accompanying bardykinesia or rigidity in order to distinguish between Parkinson's syndrome and essential tremor.

4. Consultation with a psychiatrist should be performed if depression fails to respond to the antidepressant treatment administered.

5. Neuro-psychological tests are used for a screening evaluation of cognitive functions and depression assessments.

6. Neuro-imaging methods - computer tomography (CT) and magnetic resonance imaging (MRI) are not used in diagnosing Parkinson's disease. They are indicated when suspecting brain tumour, stroke or Parkinson-plus syndromes. Referral to such tests may be done only by a neurologist provided that sufficient clinical evidence is present to suspect any of the above-mentioned conditions.

7. Transcranial neurosonography is used to distinguish from vascular parkinsonism. The vascular ethiology of Parkinson's syndrome is likely in about 3% of the patients.

8. Laboratory methods for serum and urine testing are not useful for diagnosing the disease. In patients with suspected Wilson's disease, the neurologist should test copper levels in serum and urine, as well as serum ceruloplasmin levels.

9. Ophthalmological examination is of no diagnostic value, except in cases of suspected tumor or Wilson's disease. In such cases, the neurologist should consult with an ophthalmologist to perform funduscopic examination or to look for the presence of a Kayser-Fleischer ring.

10. Autonomous tests are of no diagnostic value in Parkinson's disease. They are used to distinguish certain forms of Parkinson-plus syndromes such as multiple systemic atrophy.

11. Electroencephalography is not among the methods used for diagnosing Parkinson's disease.

Differential Diagnosis

1. **Early non-specific** Parkinson symptoms are frequently misinterpreted as exhaustion, depression, dementia, hemiparesis, shoulder-arm syndromes, coxarthrosis or Becheterew's disease.

2. **Essential tremor** represents the most serious challenge in the differential diagnosis. It may be inherited, it may occur without any family history (sporadic) or it may develop after the 60th year of life (senile). However, it is the same type of tremor which presents in the family for the first time due to a gene mutation or develops later in life due to altered gene expression. The most important issue in its diagnosis is carefully mapping disease history to clarify if there is evidence of family history of tremor, regardless of the age of onset. The second important fact in the disease history is whether the tremor is briefly suppressed by drinking small amounts (of up to 100 g) of strong alcoholic drinks, which is typical in 50% of patients with essential tremor. Clinical examination findings include a tremor which prevails when stretching the arms forward, in front of the body (postural tremor), which may continue when moving the arms towards the nose (finger-to-nose test) and intensify when the hand reaches the nose (intentional tremor). Resting tremor of the hands may be observed in advanced stages of the disease when the other types of tremor are markedly presented. In general, resting tremor is of lower amplitude than the other types of tremor.

The cogwheel phenomenon, as a finding during muscle tone testing, does not constitute a pathognomonic sign of Parkinson's disease tremor, but may occur in patients with essential tremor because some of them involuntarily contract the muscles of a limb to

suppress the tremor amplitude. The cogwheel phenomenon is due to a combination of a tremor and increased muscle tone.

When the clinical examination and the disease history are insufficient, pharmacological tests for the diagnosis of Parkinson's disease are used. In case of negative results, treatment with primidone 250 mg in the evenings is started and the clinical effect is assessed about 1 week later. If these diagnostic methods fail, the patient may be referred by the neurologist for an EMG examination to assess the tremor and for SPECT.

3. **Severe physiological tremor**, that occurs when the arms are stretched forward, is associated with depression, anxiety, withdrawal syndromes, certain types of poisoning or hyperthyroidism. The tremor is clinically distinct, having a high frequency rate (10-12 Hz), low amplitude, affects both arms and results in a specific posture when presenting (with the arms stretched forward). If the diagnosis is uncertain, the neurologist should refer the patient for an EMG examination to assess the tremor.

4. **Tremor in cerebellar or rubral injury** associated with trauma, poisoning or multiple sclerosis is characterized by a prevalent intentional tremor, but also with tremor during motions of the limbs, while the arms are stretched forward and at rest; however, these are of lesser amplitude. Other clinical signs of rubral or cerebellar structural damage are present, most commonly presenting with coordination disorders or alternating brain stem syndromes. If the diagnosis is uncertain, the neurologist should refer the patient for an EMG examination to assess the tremor.

5. **Dystonic tremor** may have a clinical course that may be indistinguishable from that of Parkinson's one. It affects the arms and has additional symptoms of dystonia, such as mild dystonia of the arms, tremor during thumb extension, tremor dependent on limb position, head tremor, voice dystonia and lack of bradykinesia. No Parkinson's symptoms develop with the disease progression.

6. **Psychogenic tremor** is characterized by irregular frequency and amplitude and onset at diverse positions of the limbs. The clinical diagnosis may be difficult. The neurologist needs to refer the patient for an EMG examination and SPECT.

7. **Brain tumor or cerebral infarction (stroke)** may rarely cause Parkinson's signs. These conditions should be suspected when, in addition to Parkinson's signs, there are also signs of unilateral pyramidal impairment. Unilaterally enhanced deep tendon reflexes without other signs of pyramidal system damage are associated with the rigidly increased muscle tone and should not be confused for pyramidal signs. When clear signs of pyramidal damage are present, neurologists should refer the patient to cerebral CT examination and, if it is negative, MRI examination should be performed.

8. **Parkinson-Plus syndromes** should be suspected when Parkinson's signs and symptoms of bilateral pyramidal impairment are present along with coordination disorders and insufficient vertical movement of the eyes. These are characterized by rapid progression of the disease and lack of response of the Parkinson's signs to levodopa. The levodopa pharmacological test needs to be performed. If diagnostic difficulties arise, the neurologist should refer the patient for a cerebral MRI examination.

9. In **elderly patients** (>65 years of age), gait disorders (lower limbs Parkinsonism) resembling bradykinesia and postural disturbances in Parkinson's disease develop, but these are rather associated with the process of ageing. They do not respond to levodopa and that should be confirmed by the levodopa pharmacological test.

10. **Wilson's disease** and **hepato-cerebral degeneration** need to be eliminated where signs of pyramidal and extrapyramidal injury are present (dyskinesia, dystonia, and chorea-like hyperkinesia). To this end, the neurologist should refer the patient for laboratory tests on blood and urine and for an ophthalmology consultation.

11. **Neuroleptic-induced Parkinsonism** should also be excluded by detailed medication history.

12. **Patients with no evidence of dopaminergic deficits** at the DATSCAN images of the presynaptic nigrostriatal dopaminergic transporters account for 20% of patients with a potential diagnosis of Parkinson's disease. This pooled group consists of misdiagnosed patients, patients with dystonic tremor and with Parkinson's disease with prevalent tremor who had a negative DATSCAN in the early stages of the disease.

Management

I. Early (non-complicated) Parkinson's disease

Treatment for Parkinson's disease should be prescribed by a neurologist after the diagnosis has been **clinically confirmed** based on diagnostic criteria and when the patient's activities of daily living are impaired. In all other cases, the patient should be monitored by a neurologist at 3-month intervals with no medical treatment.

After the diagnosis being confirmed, it is not mandatory to immediately initiate treatment if the patient's activities of daily living are not affected. The evaluation is based on patient's interview. The activities are impacted more severely when dominant limbs are affected, where bradykinesia is present and in cases of actively working patients. The activities are less severely impaired when tremor and muscle rigidity are present and where sub-dominant limbs are affected and the patient is not actively working.

Levodopa products supply the brain with dopamine and thus restore the striatal dopamine/acetylcholine balance. Modern therapy is stipulates DOPA-sparing therapy in view of the evidence that levodopa agents might speed up disease progression. Treatment with other agents, acting on Parkinson's symptoms, is initiated and only after the potential of such agents has been exhausted, adding low-dose levodopa agents may start. Evidence is present suggesting that some of these agents (MAO-B inhibitors and dopamine agonists) have a neuroprotective activity and slow down the disease's progression.

I. MAO-B inhibitors increase dopamine levels by suppressing monoamine oxidase (MAO) which is responsible for its disintegration. Treatment with agents of this group may be initiated provided that the symptoms are mild and in view of the potential slowing down of the disease's progression. They block the formation of free radicals, which are formed during the oxidative metabolism of dopamine and exert an anti-apoptotic effect. These agents have mild effect on symptoms and persis for up to one year after disease onset.

1. Rasagiline is a second-generation, irreversible, highly-selective MAO-B inhibitor. Unlike selegiline, it is not metabolized to amphetamine-like derivatives. The agent is applied of dose 1 mg once daily. It affects rigidity, bradykinesia and tremor favorably. It is preferred to selegiline due to the more reliable data concerning its neuroprotective activity and its fewer side effects.

2. Selegiline is a first-generation, selective, irreversible MAO-B inhibitor. It may be used as a monotherapy at doses of 10 mg daily but is no longer commonly used in clinical practice.

II. Dopamine agonists are added after exhaustion of the symptomatic effects of MAO-B inhibitors. In patients with marked Parkinson-like symptoms at the time of diagnosis, in young and working adults and in patients with prevalent tremor, the immediate initiation of dopamine agonist therapy is recommended. In patients with early Parkinson's disease, dopamine agonists as single-agent treatment may be successful in controlling the symptoms for five years.

These agents are classified as ergotamine based (bromocriptine, pergolide and cabergoline) and non-ergotamine based (pramipexole, ropinirole, apomorphine and rotigotine) dopamine agonists. Non-ergotamine agonists have an advantage over ergotamine agonists because of missing side effects nausea and vomiting. The most serious side effects, which have resulted in this group of dopamine agonists being almost out of use nowadays, include lung infiltrations, pleural-pulmonary and retroperitoneal fibrosis.

They stimulate predominantly the D_2 and D_3, but not the D_1 (which leads to dyskinesia with long-term use), dopaminergic receptors in the striatum. They have a good symptomatic

and neuroprotective effect, which slows the progression of the disease, and are associated with few side effects. The neuroprotective effect is mediated through the reduction of free radicals generated during dopamine metabolism. They also have a direct antioxidative effect as they reduce nitrogen-oxide radicals, they do not form free radicals and do not cause oxidative stress.

1. Pramipexole is a non-ergotamine based dopamine agonist that acts selectively on the D_2 and D_3 receptors when used at daily dose of 4.5 mg, acting on Parkinson's symptoms; unlike the other dopamine agonists, it markedly improves resting tremor, the latter being a source of anxiety for patients and difficult to control by other medication. The dose is increased gradually to reach the desired effect using the minimal effective dose. The dose-titration period covers 3-4 weeks. Sustained-release tablets may be used as well, at a daily dose of up to 3.15 mg (equivalent to 4.5 mg of standard tablets).

2. Ropinirole is a non-ergotamine dopamine agonist with a 6-8 hours half-life which stimulates D_2 and D_3 receptors and acts on non-dopamine receptors. It is used at a daily dose of 7.5 to 24 mg (9 mg on average) as standard tablets or as sustained-release tablets.

3. Rotigotine is a non-ergotamine dopamine agonist that activates predominantly the D_1 and D_2 receptors and is administered in the form of a transdermal system (a silicone patch), placed on the skin once a day. The advantages of this route of administration are the more stable plasma levels, one-off daily application and in patients with swallowing disorders. Food intake and stomach emptying do not affect the drug's plasma concentrations. It improves all symptoms of the disease at daily dose of 4 - 16 mg.

4. Apomorphine hydrochloride hemihydrate 10 mg/ml solution for injections is a non-ergotamine dopamine agonist that activates predominantly the D_1 and D_2 receptors. It is administered subcutaneously in patients with Advanced Parkinson's disease and marked Off periods without significant dyskinesia. It is injected during the off periods and the total daily dose should not exceed 100 mg. The onset of effect is in 10 minutes and it lasts for about 1 hour. The patient should take domperidone 10 mg 3 times daily to suppress the side effects: nausea and vomiting. When a patient requires more than 10 injections a day, it is recommended to apply a continuous subcutaneous infusion using a mini-pump, with a dose not exceeding 10 mg/hour.

III. Levodopa agents are added on after the symptomatic effect of the above listed groups of medicines wears off. The combination of MAO-B inhibitors and a dopamine agonist used until that moment may be reduced or remain unchanged which would allow for a lower levodopa dose.

1. Standard levodopa medication is used for the continuation of treatment. The lowest possible doses of the agent able to sufficiently improve the symptoms are used. Treatment is initiated with 3 doses of 62.5 mg a day and, if needed, the dose is then gradually increased, up to 750 mg daily. It is recommended not to exceed that dose, and if it is insufficient to improve the symptoms, dopamine agonists should be added if they have not been included so far.

2. Levodopa sustained-release formulations (levodopa/benserazide and levodopa/carbidopa) were expected to maintain a more stable serum concentration (for an average of 4 hours) and delay disease progression. Clinical practice did not confirm that they have any advantage over the standard levodopa formulations, which was attributed to their complicated pharmacokinetics. Further to these data, they are recommended for use only in strictly individually specified indications. They may be used in sleep disturbances caused by the difficult movements in bed, at a dose of 125–250 mg at bedtime.

Due to their lower bioavailability (50-70%), the dose administered should be 30-50% higher than that of standard levodopa formulations. This results in an increase in the total daily levodopa intake. Treatment is initiated with 125 mg 3 times a day. It is obligatory to use the lowest possible dose, which brings sufficient relief of symptoms. In the beginning, it is desirable to keep the dose lower than 1000 mg, while in later stages it may reach up to a maximum of 1500 mg daily. The slower absorption results in a slower increase in levodopa's peak plasma levels, which delays clinical improvement. Response time is about 1 hour following administration and therefore patients do not feel the rapid improvements they are used to with standard medication. This requires adding 125 mg of standard or dispersed levodopa to the first morning dose.

IV. Anticholinergique agents (up to 4 mg of biperiden a day and up to 6 mg of trihexyphenidyl a day) were the first drugs used for the treatment of Parkinson's disease. They normalize decreased dopamine/acetylcholine ratio, lowering the acetylcholine levels. This group of medicines has disadvantages and its use is limited. They are absolutely contraindicated for use in patients over 65 years of age or where evidence of dementia and cognitive disorders is present regardless of age, in prostate hypertrophy and in glaucoma. Even in younger individuals they may cause behavioural changes and hallucinations. Bearing in mind that the onset of the disease is most commonly after the age of 60 and the large percentage of patients with comorbidity of dementia, it is clear how very limited their scope of application is. Furthermore, those medicines, like levodopa, cause motor fluctuations and dyskinesia similar to late-onset dyskinesia. They may be used only in patients under 65 years of age with prevalent resting tremor signs because these rarely

develop dementia. In such cases, they may be used as adjunct treatment to enhance the symptomatic response. Before the initiation of treatment, a psychological examination is necessary. Careful monitoring for the onset of hallucinations or dementia is required as these would necessitate emergency discontinuation of the medicine. In the event of strange changes in behavior or suspected cognitive disorders, the medicine should be discontinued gradually, over a few days, to avoid deterioration of the Parkinson's disease.

V. Antidepressants should be prescribed by the neurologist if evidence of depression is present. The patient needs to be interviewed regarding symptoms of depression and anxiety (bad mood, depressive thoughts, loss of appetite, nightmares, tenseness, headache, etc.). Treatment is initiated with tricyclic or other types of medication from the SNRI group (serotonin-noradrenaline re-uptake inhibitor), provided the particular patient has no somatic contraindications.

Amitriptyline up to 75 mg a day is relatively well tolerated, has a sedative effect and improves insomnia. It is preferred in agitated patients. In view of the numerous somatic contraindications in this age group, it is not commonly used.

Venlafaxine up to 150 mg a day suppresses noradrenaline and serotonin re-uptake and is suitable for patients with orthostatic hypotension because it causes an increase in blood pressure.

Mirtazapine up to 30 mg a day suppresses noradrenaline and serotonin re-uptake and is suitable for patients with sleeping disorders.

Selective serotonin re-uptake inhibitors (SSRI) increase the tremor and deteriorate the other Parkinsonism symptoms. They increase the risk of developing serotonin syndrome among patients treated with Selegiline.

Depression also responds to increased doses of anti-Parkinson therapy. Pramipexole, Ropinirole and Selegiline have antidepressant effects, too.

VII. A moderate physical activity is recommended. Use of physiotherapeutic procedures, acupuncture, laser treatment, moxa and diets have no impact on early Parkinson's disease.

Vasodilators, anti-platelet and nootropic drugs or myorelaxant agents have no effect on therapy of the disease.

The General practitioners should check the patient on monthly basis or when symptoms deteriorate. Patient should be monitored for:

- symptoms of therapeutic overdose (involuntary movements associated with the peak of the dose)
- onset of hallucinations and confusion (particularly in the elderly)
- onset of motor fluctuations or dyskinesia
- symptoms deterioration due to inadequate dosing. Intercurrent diseases or surgical interventions require an increase of the daily dose of the drugs.

If any of the above symptoms occur, patient should be referred to a neurologist for an emergency consultation. Therapeutic pauses should never be recommended. The therapy should only be prescribed after personal examination of the patient.

The patient should be examined by a neurologist every 6 months or when symptoms deteriorate.

- In case of drug overdose that present with dyskinesia and dystonia associated with dose peaks, the dose of the levodopa-based products should be reduced.
- In case of hallucinations and confusion, the following withdrawal sequence should be observed until the hallucinations are completely resolved: anti-cholinergic agents, glutamate antagonists, MAO-B inhibitors, dopamine agonists, levodopa. This should not be done abruptly; withdrawals should be done by groups of medicines in 3-4-day intervals.
- The onset of motor fluctuations or dyskinesia means that the patient has entered the complicated phase of Parkinson's disease and the relevant therapeutic guidelines should be followed.
- In cases of symptom deterioration due to inadequate dosing, new groups of medicines should be added or the dose should be cautiously increased. It is obligatory to use the lowest possible dose, which brings sufficient relief of symptoms.

II. Advanced (complicated) Parkinson's disease

After the diagnosis has been confirmed and appropriate treatment has been started, the symptoms are well controlled for a different period of time that varies in every patient. The duration differs for each case and depends both on the type of the disease and on the type of treatment provided. The initial clinical effect has a long duration (more than 4 hours), despite the short serum half-life of levodopa (60-90 minutes), and patients do not experience the effect of the separate doses separately. If levodopa is discontinued during this period, a

1-week wash out is necessary to recover patient's condition at baseline. The presynaptic storage of the dopamine synthesized, as a result of levodopa, confers the long-term pharmacological effect, which far exceeds its pharmacokinetic profile, and the continuing pharmacodynamics post-synaptic effect supports a longer and smoother therapeutic response. Gradually, the effect becomes shorter with each dose and the initially good response to treatment shortens. Patients develop motor fluctuations after the intake of every single dose of the medicine. At this point, they enter the stage of **late Parkinson's disease**, which is characterized by the onset of various complications. Once developed, they gradually progress and do not respond to the levodopa therapy. Complications are grouped in two large categories:

1. Complications associated with disease progression:

- Freezing episodes
- Dysautonomia
- Dementia
- Falls

2. Complications due to long-term levodopa therapy:

- *Motor:* motor fluctuations and dyskinesia
- *Neuropsychiatric*

The form of the disease determines the individual speed of disease progression. Parkinson's disease is a progressive neurodegenerative disorder because of the progressive loss of nigrostriatal neurons. The intensity of signs increases by 8-9% annually. Progression is uneven: it is faster during the first 4-8 years and slower in the later years following the onset of the disease. It is slow if the onset of the disease is before the age of 50 years and when the initial symptom is a tremor. Progression is faster if the onset of the disease comes at a later stage, in cases of predominantly - bradykinetic–rigid syndrome and when there is accompanying dementia.

The treatment determines the time of onset of complications from the levodopa therapy. The severity of complications is greater and their onset comes earlier if the patient has undergone previous high-dose levodopa treatment. Pulse release of levodopa and dopamine in the brain is the reason for dyskinesia and motor fluctuations to occur. Usually, after 5 years on levodopa treatment complications of Parkinson's disease occur in 50% of patients and within 10 years from the start of treatment complications are found in 80% of patients. Apart from motor fluctuations, levodopa treatment causes oxidative stress and accelerates neurodegeneration in the substantia nigra due to free radicals generated.

To diagnose advanced Parkinson's disease, neurologist needs a targeted disease history to determine the duration of the effect of a single dose of levodopa, the presence of motor fluctuations in the patient throughout the entire day and the onset of dyskinesia, as well as whether those are associated with the use of medication. It is also necessary to determine the duration of decreased motor activity and/or dyskinesia and dystonia.

The neurologist should be certain whether the onset of dyskinesia and dystonia is associated with levodopa overdose, by carefully and slowly decreasing the doses used.

Motor complications

Motor fluctuations and dyskinesia

The most common motor complications are motor fluctuations and dyskinesia.

Motor fluctuations are disruptions of the "on" periods (when patients respond well to treatment), by "off" periods (when the treatment effect on the disease symptoms is sub-optimal). Motor fluctuations develop through central pharmacokinetic and pharmacodynamics mechanisms. The nigrostriatal dopaminergic system in healthy individuals is responsible for the continuous mediator release to the striatal receptors. Brain dopamine synthesized from exogenous levodopa is produced by the Dopa decarboxylase in the dopaminergic neurons of the striatum, which have a low storage capacity and release the mediator. On the other hand, levodopa storage is decreased in Parkinson's disease in proportion to the severity of the disease; therefore, periodical intake of levodopa results in abrupt increases and decreases of its levels and pulse synthesis of dopamine in the brain. At the start of the disease, when 80% of nigrostriatal dopaminergic neurons have degenerated, this condition may be mitigated by the dopamine reserves in the remaining nigrostriatal neurons. With the progressive loss of nigra neurons - when more than 90% of these have failed to function - this buffering capacity is reduced. As a result, pulse release of dopamine to the striatal receptors occurs. In such circumstances, the duration of levodopa effects decreases and the variations in levodopa plasma levels cause motor fluctuations. Levodopa medicines have a short half-life, with rapid increases and drops in plasma levels. This pharmacodynamic profile is partially the reason for their decreased efficacy and for motor fluctuation.

Changes in the central pharmacodynamic mechanisms modify the basal ganglion response to dopamine. The progressive loss of nigrostriatal neurons leads to denervational hypersensitivity on the part of dopamine receptors. On the other hand, dopamine pulse release causes receptor damage. These two factors change the sensitivity of dopamine receptors, the balance between the D_1 and D_2 receptors and the post-synaptic translation

pathways. Additionally, they alter the activity of striatal neurons, which are loaded with dopamine receptors. As a result of the impact of these factors, changes in the central pharmacodynamic response to levodopa occur. The threshold at which improvement from levodopa occurs remains relatively unchanged, but the threshold for the onset of dyskinesia progressively decreases. Thus, the dose of levodopa required for improving Parkinson's symptoms nearly equals the dose causing the abnormal involuntary movements. Further on, the curve reflecting the improvement vs the levodopa dose undergoes qualitative change. Initially, with increasing the dose, a linear improvement occurs, but later the curve assumes a sigmoid shape – the patient is either mobile (in an "on" period) or almost immobile (in an "off" period), or somewhere in between the two conditions depending on plasma levodopa levels and brain dopamine levels.

At this stage, the levodopa dose reaches critical levels, with the lower doses failing to provide sufficient plasma levels for transit into the "on" phase. The higher doses reaching the threshold for improvement of the condition may also fail to produce effect, due to the interplay of various external factors. Delayed stomach emptying or protein rich foods impair levodopa absorption and its uptake by the brain, which may cause rapid switching from an "on" to an "off" phase.

Motor fluctuations initially take the shape of a *"wearing off" effect,* or a "short-lived response," which is a fluctuation in motor activity associated with taking a high levodopa dose. The effect of the medicine wears off before the next dosing. Decreased motor activity at the end of the dose correlates with the low serum levodopa levels. The daily motor fluctuations become clinically evident when the therapeutic activity of each levodopa dose is shorter than 4 hours. Initially, motor fluctuations appear in the morning and in the afternoon. The effect of the single dose gradually becomes very short and almost coincides with the plasma half-life of the medicine.

The *"on-off" phenomenon,* or "unpredictable off periods," can occur at any time. With continued treatment and in the course of the disease, motor fluctuations become abrupt, unpredictable and not associated with the time of dosing and the levodopa serum levels. They have a sudden onset, last for seconds or minutes and are manifested by severe deterioration of the Parkinson's symptoms. The periods of no effect may cover up to 50% of the daytime and severe dyskinesia may be observed during the "on" periods.

Akinetic crises are extremely dangerous and occur when patients remain in an "off" period longer. They may be triggered by concomitant illness, discontinuation of treatment or may not have a clear cause. They are characterized by extremely severe deterioration of Parkinson's symptoms and impaired swallowing.

The "delayed on" or suppressed to lacking ("no-on") motor response following a single dose of levodopa is associated with poor drug absorption. Proteins in the food are decomposed to large amino acids, which compete with levodopa for intestinal absorption and transport to the brain. This results in a minimal but sufficient decrease of striatal dopamine levels because the storage capacity for dopamine becomes extremely limited or absent as the disease progresses.

Motor fluctuations are almost always accompanied by dyskinesia and dystonia associated with or without the intake of the medicine.

Dyskinesia refers to abnormal involuntary movements that are chorea-like or resemble dystonia, tics or myoclonus. They are triggered by the change in post-synaptic sensitivity and the disrupted balance between the D_1 and D_2 dopamine receptors in the striatum. The disrupted balance between dopamine, a suppressive neurotransmitter, and glutamate, an excitatory neurotransmitter, towards a relatively higher glutamate level due to the decrease in dopamine levels contributes to the onset of dyskinesia. Dyskinesia and motor fluctuations are closely related, yet involuntary movements may have an earlier onset than fluctuations. It should be noted that the onset of dyskinesia or dystonia may be a manifestation of a levodopa treatment overdose.

They are more common in younger patients and are particularly marked during the “on” periods. They are usually associated with the levodopa or anticholinergic therapy but may also develop with any anti-parkinsonian agent used in patients previously treated with levodopa. In the beginning, dystonia involves the distal portions of the limbs, with chorea-like dyskinesia appearing later. Those may affect any part of the body but the ones caused by levodopa involve the head, the neck, the limbs and the respiratory muscles, while the ones associated with anticholinergic medicines affect the oropharyngeal muscles.

“Peak-dose dyskinesia” is the most common and the earliest to appear. It is chorea-like and less commonly dystonic in nature. It is triggered by high levels of plasma levodopa and brain dopamine exceeding the threshold of improved motor function. In patients with advanced Parkinson’s disease, the therapeutic window is narrowed so the intake of the levodopa dose, which improves Parkinson’s symptoms, causes dyskinesia, too.

“Diphasic dyskinesia” is less common. It develops later with the progression of the disease, after patients have already experienced peak-dose dyskinesia. It may be chorea-like or dystonic in nature and most commonly affects the lower limbs. It is more severe and is poorly tolerated by patients. Its onset is in the beginning and at the end of the “on” phase. It develops when plasma levodopa levels increase after the intake of a single dose. With reaching the threshold concentration for triggering the “on” phase, the dyskinesia decreases

or resolves only to appear again when the drug plasma levels decrease.

Dystonia is caused by levodopa or by the progression of the disease. It presents as painful and excruciating dystonia affecting the large toe and, less commonly, as blepharospasm, cervical or limb dystonia. It occurs at low plasma levodopa levels.

Early morning dystonia appears at the time the patient wakes up, before the first morning tablet is taken. It is a characteristic sign in untreated patients, too.

The *"off" dystonia* occurs while the effect of the single dose wears off.

The freeze phenomenon may occur with any single movement, but its impact is the greatest if it interferes with walking. It may be associated with insufficient or excessive levodopa doses. In the majority of patients, it is independent of treatment and is suspected to be a non-dopamine mediated phenomenon. Freezing episodes are transitory; they last for several seconds to several minutes. They occur when the patient steps forward (hesitation at the start), when turning (hesitation of turning), when passing through a narrow space (e.g. a door) or when distracted.

Dysautonomia

Dysfunction of the autonomous nervous system is a common complication. These disorders are moderate and rarely marked. The most common symptoms are constipation, urinary, sexual or sensory disorders, orthostatic hypotension, impaired body temperature regulation, aches and dysphagia.

Constipation is associated with impaired colon muscles contractions, leading to slow passage and dystonic impairment of the coordinated contractions of the rectum and the anal sphincter and the relaxation of the anal sphincter.

Urination disorders are first and most commonly manifested by nocturia, followed by frequent voiding, voiding urges and difficult voiding. They are due to a hyper-reflexive detrusor and late and incomplete relaxation of the pelvic floor muscles.

Sexual dysfunction presents as impotence in males due to erectile dysfunction. Often, the cause is depression. Sexual dysfunction in females is not known. In some cases, treatment with high dose anti-parkinsonian medicines causes hyper sexuality.

Orthostatic hypotension is due to peripheral and central autonomous nervous system impairment. The main cause is decrease in sympathetic tone and vasoconstriction. Due to excessive renal sodium loss and mild anemia, the intravascular volume is decreased. Sodium loss is due to lower renin release and decreased renal sodium reabsorption, while anemia is due to decreased renal erythropoietin secretion. It should be noted that high supine blood pressure values are common that may lead to arterial hypertension

hyperdiagnosis.

Thermoregulatory dysfunction in patients with advanced Parkinson's disease is due to dysregulation of the central dopaminergic systems. The most common signs are excessive sweating, abnormal sensations of cold and warm and hypothermia. They frequently occur during motor fluctuations ("on" or "off" phases).

Sensory disorders occur in 50% of patients. They present as pain, paresthesia, dysesthesias, feeling cold or a sense of tingling and deep-running pain, mostly in the lower limbs, resembling polyneuritis. They are often associated with the "off" periods.

Dysphagia may be present in 40% of patients depending on the severity of the disease. It occurs mostly during the "off" periods and is associated with the involvement of the oropharyngeal muscles and abnormal control of the tongue, which leads to difficulties in pushing food towards the pharynx. Impaired esophageal motility is also common. Those changes cause saliva discharge from the mouth and aspiration of food.

Seborrhea that affects the head, face and neck, as well as **blepharitis**, are common conditions. Blepharitis is due to rare blinking and may lead to keratitis.

Falls

Falls are associated with postural instability, freezing phenomenon, dyskinesia and orthostatic hypotension. While walking, the weight of the patient's body shifts forward. That is why the patient tries to compensate with small and fast steps but fails to and often falls. The cause may differ in each patient and should be identified.

Neuropsychiatric disorders

Could be found in one third of patients and may be more disabling than motor impairment.

Cognitive disorders, with or without concomitant dementia, have been found in 19% of patients even in the early stages of the disease. Those include slow processing of information (bradyphrenia), impaired executive functions, memory disorders, attention disorders, inadequate behavior.

Dementia is found in 30% of patients, usually during the late stage of the disease, after the fifth year of onset.

Hallucinations and delirium may occur in 20% of patents spontaneously or due to anti-parkinsonian treatments, anxiolytics, antidepressants and sedatives. Hallucinations are more common among the elderly and in patients with cognitive disorders. These are visual hallucinations and seldom auditory ones. In the beginning, they are nocturnal and non-threatening; later they may become threatening to the patient. Hallucinations may expand

into delirium with disorientation, impulsiveness, and inadequate behavior, sleep, attention and memory disturbances. Delirium may have a sudden onset and deteriorate or may start gradually and continue to deteriorate.

Behavioral disorders present with anxiety, panic attacks, agitation and depression. In some patients, they may be seen only during the “off” period.

Depression is found in 40% of patients. It may be endogenous - due to the deficit of monoamines, or exogenous - associated with the awareness of a chronic disease and disability. Some of the patients present with a syndrome involving apathy, passivity and decreased energy, which is not combined with sadness, feeling of helplessness, remorse or guilt and does not respond to antidepressants.

Anxiety and panic attacks are common or in some cases during the “off” periods only. About 40% of patients experience solely anxiety, or anxiety in combination with depression. This may be in response to the disabling disease. Anxiety may be part of Parkinson’s disease resulting from the loss of stem dopaminergic, noradrenergic and serotoninergic neurons, and denervation of the subcortical circles. Panic attacks present with psychiatric, autonomous and somatic symptoms.

Agitation may be caused by anti-Parkinson treatment or it may be a component of anxiety. It is characterized by restlessness, irritability and dysphoria.

Sleep disorders are found in 75% of patients and may be associated with the disease, depression, cognitive disorders, nightmares, pain, difficulty turning in bed, nocturia, restless legs syndrome and levodopa therapy. As the disease progresses, numerous neurotransmitter systems are affected, three of which (dopaminergic, serotoninergic and noradrenergic) are important in sleep disturbances.

Insomnia presents as difficulty falling asleep and staying asleep.

Daytime drowsiness may be due to the treatment, to anxiolytics, depression, and dementia featuring disrupted circadian rhythm or due to insufficient night sleep.

Nightmares or vivid dreams may be idiopathic, caused by dementia or by medication (dopamine agonists or levodopa).

REM sleep behaviorral disorder is characterized by aggression, performing seemingly purposeful activities at night, and sleepwalking. The violent movements may harm the patient or their partner. This is associated with impaired motor suppression during the REM phase of sleep.

The Restless legs syndrome is a common and presents with paresthesia, pain, muscle cramps and the need for moving. Symptoms deteriorate late in the night and improve after movement. Periodic movements of the legs at night have been found in 50% of

patients. They resemble the Babinski reflex, continue for about 6 seconds and take place every 20-40 s. They may seriously disturb the sleep of patients and their partners. They are usually associated with insufficient treatment of Parkinson's disease.

By thorough interview, the neurologist should investigate the disease history and identify the presence and the characteristics of the neuropsychiatric disorders, dysautonomia, sleeping disorders and falls.

Differential Diagnosis

Usually, in the late stages, the diagnosis of Parkinson's disease has already been confirmed and is valid. It should be noted that some patients diagnosed with Parkinson's disease may later develop symptoms typical for multiple systemic atrophy or Progressive Supranuclear Palsy. They may respond to levodopa in the early stages of the disease, but later this effect wears off. In terms of differential diagnosis, CT and MRI of the cerebrum, neuropsychological, neuro-ophthalmological and neurophysiological tests may be used.

Management

Prevention of Parkinson's disease complications is most important and early DOPA-sparing therapy is recommended.

At late Parkinson's disease stages, levodopa as monotherapy is usually not effective enough. Combined treatment allows decreasing levodopa dosage. In cases of symptom deterioration due to inadequate dosing, the dose should be cautiously increased or new groups of medicines should be added. It is obligatory to use the lowest possible dose of the drug that offers sufficient relief of symptoms. In general, this results in a combination treatment with levodopa and a dopamine antagonist, i.e. if the patient has been on a levodopa-only regimen, a dopamine agonist is added or vice versa. If the patient has been taking controlled-release levodopa formulations, a switch to standard formulations is necessary. At a later stage, when the combination of levodopa and the dopamine antagonist has exhausted its potential, a COMT inhibitor may be added; this, however, offers only a mild improvement of motor disturbances. Adding on MAO-B inhibitors and glutamate antagonists rarely results in greater control over motor fluctuations. Amantadine affects dyskinesia favorably.

Treatment of motor fluctuations

I. Medicines

1. The dispersed levodopa formulation (levodopa/benserazide) offers the advantages of a rapid start of effect (in 15–20 minutes) associated with rapidly reaching the therapeutic plasma levels. It is appropriate for managing morning akinesias, freeze phenomenon, akinetic crises and swallowing disorders.

2. Controlled-release levodopa formulations should not be used except in nocturnal akinesias. The individual tailoring of the dose is far more difficult than with standard formulations because due to the prolonged action of the agent there is an overlapping of the effect with the previous dose and a slow increase in levodopa plasma levels. As a result, end-of-day dyskinesia may occur.

3. Dopamine agonist treatment reduces the complications in advanced Parkinson's disease. These agents directly stimulate dopamine receptors and do not require metabolic modification to an active product in order to exert their pharmacodynamic effects; thus, their action is independent of dopamine neurodegeneration. Their effect is not dependent on absorption and transportation to the brain because, unlike levodopa, they do not compete with nutritional amino acids. The majority of dopamine agonists have longer-lasting effects than levodopa, thus conferring long-term rather than pulse stimulation of dopamine receptors. Combination treatment with dopamine agonists allows for a reduction of the levodopa dose by 30-40%. In patients with late Parkinson's disease, dopamine agonists reduce "off" periods by about 30% and prolong "on" periods.

4. COMT inhibitors (entacapone) allow for increased bioavailability and levodopa transport to the brain. COMT inhibitors metabolize levodopa and dopamine to 3-O-methyldopa and to 3-methoxytyramine in the peripheral and in the central nervous system. COMT inhibitors suppress the COMT and the peripheral catabolism of levodopa to 3-O-methyldopa. There is a decrease in the formation of 3-O-methyldopa, which competes with levodopa for transportation via the pathway for large neutral fatty acids in the circulation and in the brain. Thus, the bioavailability of levodopa increases without a concomitant increase in maximum plasma levels. The above effect is present when COMT inhibitors are used concomitantly with standard or controlled-release levodopa formulations. In this way, levodopa peak plasma concentrations leading to motor fluctuations are avoided. They may be used only concomitantly with levodopa (200 mg with each dose) and often cause dyskinesia around 24 hours following the first dose used. It is therefore necessary to reduce the levodopa dose by about 30%. The drug may be used in patients with motor fluctuations and it may decrease "off" periods by 25 to 30%. Clinical experience shows no improvement

of motor disorders; the increase of dyskinesia is shown to result in deterioration of the patient's condition.

5. Combined levodopa + dopa-decarboxylase inhibitor + COMT inhibitor formulations, in a single tablet, are bio-equivalent to the concomitant use of the three components as separate formulations. Stalevo is a combination of levodopa, carbidopa and entacapone in different strengths. It is available as film-coated tablets in 100/25/200 mg, 150/37.5/200 mg or 200/50/200 mg. Patients on current treatment with a combination of levodopa and a COMT inhibitor may be switched to Stalevo, in view of ensuring greater convenience for patients. The triple combination allows decreasing the number of tablets taken. It is suitable for patients taking many different drugs and also for patients with swallowing disorders. On the other hand, such a combination reduces the flexibility of levodopa therapy.

6. MAO-B inhibitors rarely affect motor fluctuations positively and prolong "on" periods.

7. Anticholinergic agents are not recommended in patients with advanced Parkinson's disease due to their numerous side effects and patients' advanced age.

8. A physical activity regimen of moderate load is recommended. Use of physiotherapeutic procedures and neurorehabilitation improve motor activity.

II. Management of specific types of motor fluctuations

In **cases of wearing-off phenomenon**, the first option is to decrease the single doses of **standard levodopa** or to increase the frequency of intake. Such tactics are initially good but later become ineffective. Smaller doses help to achieve lower levodopa plasma levels that are below the threshold concentration for motor improvement. Even if the threshold is achieved, lower doses and lower plasma levels lead to a shorter period of improvement. The daily dose may reach up to 1,500 mg.

Dystonia during wearing off of the single dose effect is managed in the same way as the dose wearing-off phenomenon.

The unpredictable "**on and off syndrome**" responds in the same way as the dose wearing-off phenomenon but treatment of such cases is much more difficult. Controlled-release levodopa formulations should be avoided because they may lead to further dyskinesia. Apart from dose fractioning for standard levodopa, adding on a dopamine agonist or a COMT inhibitor may improve the patient's condition. A diet of rescheduled protein intake is desirable, with proteins taken mostly in the evening.

Early morning dystonia responds to the add-on of a dopamine agonist with the

evening dose. The morning dose of levodopa should be taken before the patient gets off the bed.

The lack of response or sub-optimal response to a single dose of levodopa is managed by increasing the dose but the latter may cause dyskinesia. The protein diet regimen, taking levodopa 1 hour before meals or use of medication increasing intestinal motility may improve the patient's condition.

Akinetic crisis should be rapidly treated, because failure to rescue the patient from such a crisis may be fatal. If the patient is able to drink liquids, 125 mg of the dispersible levodopa formulation should be given right away, dissolved in about 100 ml of water. In the event of lack of response or if the patient is completely unable to swallow, amantadine sulfate 200 mg/500 ml is administered in the form of slow intravenous infusions, up to 3 times a day. After swallowing is recovered, patient is switched to the usual levodopa therapy, which may need to see an increase in dose.

The **freeze phenomenon** is difficult to treat. Because it may be associated either with treatment sub-dosing or overdosing, increasing the dose of levodopa or adding a dopamine agonist should be tried. If no improvement occurs, the dose should be decreased. If patients do not respond, they should be helped to design a voluntary programmed motor pattern, to stand in for the involuntary automatic one. The patient should learn to take their first step forward towards a certain target on the floor or to step forward with the leg stretched, as if marching. Diverse visual and auditory (music) challenges also may help the patient overcome freezing.

Management of dyskinesia

Likewise motor fluctuations, dyskinesia is a serious therapeutic challenge.

I. Glutamate antagonists – amantadine (amantadine sulfate or amantadine hydrochloride) reduce glutamate transmission in the internal part of the Globus pallidum and affect dyskinesia favorably. They achieve their symptomatic effects through normalizing the dopamine/glutamate ratio, lowering the glutamate levels. There is no information about their efficacy when used alone in the early phases of the disease but they improve dyskinesia in the late stages of the disease.

1. Amantadine sulfate is used at an average daily dose of 400 mg, but higher doses may be used as well (up to 600 mg). The dose is gradually increased over several months by increments of 100 mg until the desired response is achieved at the minimal effective dose. The detection of any side effects prompts for discontinuation of treatment, with gradual withdrawal.

2. Amantadine hydrochloride is used in daily doses of 100 to 400 mg.

Dyskinesia during peak plasma levels respond to lowering the every single dose of levodopa. The therapeutic window is too narrow in such patients and even minimal reductions of levodopa may deteriorate motor activity. If the patient has been taking controlled-release levodopa formulations, switching to the standard formulations should improve dystonia. Decreasing the levodopa dose and adding on dopamine antagonists or increasing the dose of the latter are helpful, particularly if the dyskinesia episodes are of dystonic nature. The use of MAO-B inhibitors should be discontinued.

Diphasic dyskinesia may be managed by increasing the frequency of levodopa intake or by switching from controlled-release formulations to standard levodopa formulations. Increasing the dose of levodopa may be tried. If the frequency of dosing is increased, the timing should be selected in such a way as to allow the single doses to overlap in order to avoid fluctuations in plasma levels. After the overlapping of 4-5 doses, dyskinesia episodes will start again but their timing will be predictable, the patient will be familiar with them and may plan to be at home. It is recommended to discontinue the MAO-B inhibitors. Where the intervention fails, a dopamine agonist or glutamate antagonist may be added.

Treatment of motor complications is performed by a neurologist in the following sequence:

1. Decreasing the single doses of standard levodopa (125 mg) and increasing the frequency of dosing to 5-6 intakes.

2. Switching from controlled-release levodopa formulations to standard formulations.

3. Before a night's sleep, a single dose of dopamine agonist or controlled-release levodopa formulation may be prescribed.

4. If the effect is unsatisfactory, combined treatment is initiated by adding the following to the levodopa therapy:

- non-ergotamine dopamine agonist
- COMT inhibitor
- dispersible levodopa formulation of 125 mg if needed for akinesias, akinetic crisis, freeze phenomenon or disturbed swallowing.
- dispersible levodopa formulation of 125 mg instead of the standard formulation for daily early morning akinesia.
- glutamate antagonists for dyskinesia and akinetic crisis (intravenous infusions).
- in poorly responding dyskinesia or dystonia, an add-on of up to 60 mg of baclofen

a day may be considered.

- MAO-B inhibitors, to address motor fluctuations and prolong the “on” period.

- in cases of poor response, taking the doses before meals and using low-protein diet are recommended.

5. Anticholinergic medication is not recommended.

6. Treatment of depression continues in the same way as during the early stages of the disease.

7. Moderate physical activities are recommended.

III. Terminal Parkinson’s disease

Regardless of the applied treatment within 14 of onset, on average, patients become heavily disabled and hardly get off the bed. They may become severely disabled because they either have dyskinesia or have become akinetic and difficult to manage via medication. The immobilization and its associated somatic complications are the most common reason for the end. Some of these patients, in whom the disease started at earlier age, are somatically healthy and still relatively in good physical condition.

Management

There are three methods for management of patients developing severe motor complications and wearing off of their response to oral treatments – using Lecodopa/carbidopa Intestinal Gel (LCIG), Apomorphine or Deep Brain Stimulation (DBS). These device assisted methods automatically deliver required dosage of medicine or stimulate certain structures in the brain. The criteria for assessing whether patient is suitable for device-assisted therapy include: intake of levodopa more than 5 times a day, off-periods of 2 hours a day and troublesome dyskinesia - 1 hour daily. The three management methods are used when all other options have been exhausted and the motor complications have proven life-threatening for the patients. Past treatment with sustained-release levodopa formulations or with COMT inhibitors, anticholinergic agents and COMT inhibitors is not mandatory. Such patients’ condition requires continuous monitoring in specialized centers. The added value of such methods includes their favorable effect on nocturnal impairment in patients’ condition, a decrease in day-time drowsiness and a reduced risk of developing psychoses and behavioral disorders. Non-dopaminergic signs do not respond to any of the three methods; an exception is tremor, that might slightly improve in response to subthalamic deep brain stimulation.

1. Deep brain stimulation by electrodes implanted in specific cerebral areas is used

during the last stage of Parkinson's disease. *Subthalamic deep brain stimulation*, which is most commonly used, and the *globus pallidus internus stimulation* imitate the effects of levodopa by positively affecting rigidity, bradykinesia, the off-periods and dyskinesia. The two types of stimulation have similar effects, but subthalamic nucleus stimulation has better effects on Parkinson's symptoms and allows for a reduction of oral levodopa intake. The need for additional oral levodopa intake is greater than in treatment with apomorphine or a duodenal levodopa infusion. Response to treatment is not greater than during the "on" phase of levodopa use but is associated with fewer dyskinesia episodes. Axial Parkinson's symptoms, such as dysarthria, postural instability and the freezing-of-gait phenomena are not affected. The effect of electrostimulation persists for 5 years, which is when adaptation leads to a decrease in effectiveness. Where unilateral signs are present, contralateral stimulation is used; this may nevertheless have bilateral effects. Bilateral deep brain stimulation is more effective but is associated with more side effects. The stimulation has impulse duration of 60 ms and a frequency rate of 130-180 Hz. The amplitude of stimulation (2–5 V) is increased slowly until an optimal ratio of the clinical effectiveness vs. side effects is achieved.

The nucleus ventralis intermedius stimulation in the thalamus, that acts only on tremor, is more rarely used.

Eligible patients are between 65 and 70 years of age and have no cognitive or psychiatric disorders, but suffer prevalent dyskinesia. Patients should have a good therapeutic response to levodopa treatment with mild axial symptoms. Patient selection should be the responsibility of a multidisciplinary team, including a neurologist, a neurosurgeon and a clinical psychologist.

Serious complications are associated with neuropsychiatric and cognitive disorders (28%), strokes (2%), internal cerebral hemorrhage (10%), postoperative infections (1.6%), epileptiform seizures (2.4%), electrode displacement (20%) and mortality (up to 5%) associated with the surgical intervention. Neurological symptoms may appear (dysarthria, diplopia, apraxia of opening the eyes, phosphenes, paresthesia, muscle contractions), associated with the electrostimulation of adjacent anatomical structures. In 8% of patients, weight gain has been observed, which may return to normal in 2 years. Restrictions during the future life of patients include the lack of options for using magnetic fields, e.g. magnetic resonance imaging investigations, transcranial magnetic stimulation and physiotherapy.

2. Apomorphine hydrochloride hemihydrate 10 mg/ml solution for continuous subcutaneous infusion using a mini-pump is an alternative to the intestinal route of levodopa administration. Its effectiveness on Parkinson's symptoms is equal to that of levodopa

because it is the most potent dopamine agonist. It decreases “off” periods and, to a lesser extent, dyskinesia, it affects apathy and mood favorably. For dyskinesia to respond, it is necessary to decrease the levodopa daily dose. When used alone, apomorphine should be given in very high doses (greater than 100 mg daily), that is associated with serious side effects. Infusion is initiated at a dose of 1 mg/hour, which is increased by 0.5 mg/hour every 2-4 hours depending on tolerability.

It is suitable for patients of all age groups with prevalent prolonged “off” periods and who have caregivers residing with them. Apomorphine is not suitable for elderly patients, patients with cognitive disorders, orthostatic hypotension, severe systemic conditions (liver, renal or heart failure) or a history of dopaminergic psychosis.

Side effects include nausea and vomiting (10%), nodules (70%), somnolence and sedation (23%), orthostatic hypotension (5%), renal disorder (6%) and a positive Coombs test. Patients using apomorphine 24 hours a day may develop impaired control over impulsivity (pathological gambling or internet addiction, compulsive eating), pathological libido and acute paranoia with suicidal attempts.

3. The Levodopa Intestinal Gel is delivered by means of a portable pump through a permanent tube inserted via percutaneous endoscopic gastrostomy (PEG). The long-term and continuous infusion of levodopa aims to deliver a stable and optimal dose consistent with the individual therapeutic window. The drug is delivered directly in the duodenum, avoiding thus the problems associated with gastric passage and amino acids competition. The pulse delivery of levodopa is avoided too by continuously automated delivered controlled by computer.. Response to the suspension is pre-tested by administering the suspension through a temporary naso-duodenal tube.

The dose should be titrated to achieve the optimal clinical response in the individual patient, which involves maximizing the functional ON-time during the day by minimising the number and duration of OFF episodes (bradykinesia) and minimising ON-time with disabling dyskinesia. The total dose/day is composed of three individually adjusted doses: the morning bolus dose, the continuous maintenance dose, and extra bolus doses. Treatment is usually limited to the patient's awake period. If medically justified, treatment can be administered up to 24 hours/day

Used as monotherapy, the drug decreases “off” periods, the time periods of dyskinesia and motor fluctuations. The decrease of “off” periods is similar to that of deep brain stimulation and apomorphine use. The drug improves nocturnal symptoms, sleep, fatigue, daily drowsiness, and the gastrointestinal, urinary and sexual disorders. It also reduces the risk of developing psychosis or behavioral changes.

It is suitable for patients of all age groups with clear “on-off” periods, prolonged “off” periods (longer than 2 hours) and prevalent dyskinesia.

3.1. The Levodopa/carbidopa Intestinal Gel (20/5 mg/ml)-**Duodopa** is administered each day using one cassette of 100ml (2000 mg levodopa/500mg carbidopa)

Side effects occur during the first two weeks of administration and are associated with abdominal pain (42%), nausea (28%), peritonitis (2.8%), pneumoperitoneum, tube obstruction or displacement and pump failure. 2.8% of patients develop mild sensorimotor axonal polyneuropathy.

3.2. The levodopa/carbidopa/entacapone Intestinal Gel (20/5/20 mg/ml) – **Lecigon** is administered each day and maximum recommended daily dose is 100 ml (2000 mg levodopa/500 mg carbidopa/2000 mg entacapone). Lecigon contains entacapone, which enhances the effect of levodopa. It may therefore be necessary to reduce the total daily intake of Lecigon by, on average, 20–35% compared to the patient's previous dose of levodopa and carbidopa. The continuous maintenance dose should be based on the patient's daily levodopa intake and initially reduced to 65% of the previous daily levodopa intake. Entacapone reduces clearance of levodopa, resulting in prolonged clinical response of levodopa. Reduces the risk of accruing side effects related with prolonged levodopa usage (polyneuropathy, dimension, cardiovascular disorders).

The most commonly reported adverse reactions with oral levodopa/carbidopa/entacapone are dyskinesias (19%), gastrointestinal symptoms including nausea and diarrhea (15% and 12% respectively), muscle and connective tissue disorders (12%), chromaturia (10%)

Treatment of the terminal stage of the disease should be performed by a neurologist:

1. Deep brain stimulation, levodopa intestinal gel or apomorphine hydrochloride are used when motor complications fail to be treated by any other method.

2. Deep brain stimulation is the preferred method of treatment in patients up to 65 - 70 years of age with prevalent dyskinesia but with a good response to levodopa therapy and lack of cognitive and psychiatric disorders. Patient selection should be the responsibility of a multidisciplinary team, including a neurologist, a neurosurgeon and a clinical psychologist.

3. Apomorphine is preferred in cases of patients with prevailing prolonged “off” periods and no cognitive disorders.

4. The levodopa Intestinal Gel is preferred in patients with clear “on-off” periods, prolonged “off” periods (longer than 2 hours) and prevalent dyskinesia.

5. Such patients’ condition requires continuous monitoring in specialized centers.

Management of dysautonomia

In cases of chronic **constipation**, it is recommended that patients increase their physical activity, use more liquids (at least 8 glasses of water a day) as well as increase the dietary intake of vegetables and the volume of the food consumed. Laxatives may be used once a week.

Urinary disorders resulting from bladder detrusor hyper-function respond to 2 to 4 mg of tolterodine a day. If, due to increased tone of the external sphincter, myorelaxants (up to 60 mg of baclofen a day) may be used. The intake of fluids after suppertime should be reduced. Consultation by a urologist is needed for the urinary tract disorders.

Sexual dysfunction, if associated with depression, respond to antidepressants. Tricyclic antidepressants, SSRI and MAO-A inhibitors should not be used because they lead to impotence. Anxiety, if present, responds well to anxiolytics. Increasing the dose of anti-parkinsonian therapy may favorably affect sexual dysfunction.

Orthostatic hypotension may be affected positively by the intake of food rich in salt, by the frequent intake of small meals and raising the upper part of the body at $30\text{-}40^0$. Sodium loss in the supine position is greater due to decreased renin release. Domperidone 10 mg three times a day may prevent the development of orthostatic hypotension and of the postprandial syndrome.

Thermal regulation impairments respond to increasing levodopa levels or to adding-on dopamine agonists - if their onset is during the “off” period - and to decreasing the dose of anti-parkinsonian treatment - if they occur during the “on” period.

Sensory disorders respond to increasing levodopa levels or adding-on dopamine agonists, if their onset is during the “off” period.

Dysphagia responds to increasing the doses of anti-parkinsonian therapy.

Seborrhea and blepharitis respond to topical application of steroid creams.

Management of falls

Management will depend on the particular cause for the falls. It is necessary to eliminate all medication that may cause hypotension or lead to greater postural instability. The frequent use of a wheel chair is the only solution to this problem.

Management of neuropsychiatric complications

If **hallucinations and delirium** or confusion develop, all myorelaxants, tricyclic

antidepressants, anxiolytics, sedatives and spasmolytic agents should be withdrawn. When necessary, management of dehydration, electrolytic imbalance and metabolic disorders should be corrected, and if there is an infection it should be treated. In the event of no response, the anti-parkinsonian medication should be discontinued with caution to avoid dramatic deterioration of the signs and symptoms of Parkinson's. The patient should be given standard levodopa and the controlled-release levodopa formulations should be discontinued. This should not be done abruptly in any circumstances; withdrawal should be done by groups of medicines over 3-4-day intervals and, in case of no response, the next group of medicines should be discontinued. Abrupt discontinuation may lead to malignant neuroleptic syndrome. In case these measures prove insufficient, antipsychotic treatment with clozapine 12.5 mg at bedtime should be initiated, and the dose should be increased gradually to 25–75 mg, depending on the effect. The drug does not block dopamine receptors and causes no deterioration of Parkinson's disease. Complete blood counts should be performed weekly as agranulocytosis is the most serious complication.

In presence of **Cognitive disorders and Dementia** all tricyclic antidepressants, anxiolytics, sedatives and other anti-parkinsonians agents should be applied at a minimal effective dosage. A consultation by a neuropsychologist is required.

Depression may sometimes respond to increasing the dose of anti-parkinsonian therapy. Antidepressant treatment is required as well, and agents from the SNRI group (serotonin-noradrenalin re-uptake inhibitors) and tricyclic antidepressants should be preferred.

Anxiety and panic attacks respond to short-acting anxiolytics (alprazolam 0.5–1.0 mg daily) and tricyclic antidepressants.

Agitation is managed by reducing the dose of anti-parkinsonian therapy in the same order as the one used for hallucinations and to treatment with anxiolytics (alprazolam 0.5–1.0 mg daily).

Management of sleep disturbances

In **insomnia** associated with difficulties with rolling over in bed, adding-on levodopa as a controlled-release formulation at bedtime or adding-on a dopamine agonist should solve the issue. If it is due to the anti-parkinsonian treatment, the dose of the MAO-B inhibitors, glutamate antagonists, dopamine agonists and finally of levodopa should be reduced. If sleeping disorders are associated with depression, a tricyclic antidepressant is recommended (amitriptyline 25-75 mg) or mirtazapine 30-60 mg, and if they arise from anxiety – alprazolam 0.5–1.0 mg or clonazepam up to 2 mg at bedtime. In any other cases,

short-acting hypnotics are recommended (zolpidem 5-10 mg) at bedtime.

Daytime drowsiness, if associated with the therapy, will respond to switching the patient from controlled-release levodopa formulations to standard formulations. If a patient is on anxiolytics, their day-time dose should be reduced.

Nightmares respond to decreasing the night-time dose of tricyclic antidepressants, dopamine agonists and levodopa. If there is no response, add-on antipsychotic should be started (clozapine 12.5-25 mg) at bedtime.

REM behavioral changes are managed by clonazepam 0.25 to 1 mg at bedtime. Treatment with tricyclic antidepressants and MAO inhibitors should be discontinued.

The **restless legs syndrome** responds to increasing the dose and switching to controlled-release levodopa formulations, as well as by dopamine agonists. Clonazepam 0.25 up to 1 g at bedtime may be added.

Treatment Complications

The **Parkinsonism-hyperpyrexia syndrome** is a variation of the neuroleptic malignant syndrome.

Its etiology in patients with Parkinson's disease is associated with abrupt withdrawal of anti-parkinsonian therapy.

Its pathogenesis is associated with a functional deficit of dopamine due to the massive blocking of dopamine receptors in the striatum and in the thermoregulatory and vasomotor centers in the hypothalamus. This results in disinhibition of cortical and subcortical excitatory pathways. Noradrenaline and serotonin may be affected, too.

Clinical symptoms develop within 24 to 72 hours. Often, mental status disturbances and extreme muscle rigidity may be the first signs. It is characterized by the triad of autonomous dysfunction (high body temperature, paleness, profuse sweating, unstable blood pressure, tachycardia, tachypnea, and pulmonary congestion), changes in the mental status and motor dysfunction (akinesia, tremor, choreoathetosis, rigid myoclonus or dystonia). For a difference of serotonin syndrome, bradykinesia, axial muscle rigidity of the "lead tube" type not prevalent in the lower limbs, and hyperreflexia occur and no bladder disorders are present. Rhabdomyolysis, electrolyte imbalance, and metabolic disorders, myoglobinuria, renal and respiratory failure, respiratory distress syndrome, pulmonary embolism, myocardial infarction, coagulation disorders, disseminated intravascular coagulation, epileptiform seizures, and shock may occur. Consciousness may be impaired, leading to stupor or coma, and a lethal outcome may follow.

Laboratory results indicate leukocytosis and increased creatine phosphokinase and

liver enzyme levels. Acute phase indicators, e.g. albumin and iron serum levels, may have lower levels.

Differential diagnosis includes acute poisoning (cocaine, amphetamines, and ecstasy), metabolic disorders, encephalitis, meningitis and subarachnoid haemorrhage.

Management requires early diagnosis and is performed in emergency due to the high mortality rates (up to 20% of patients). Re-starting of the anti-parkinsonian therapy is required. Intravenous volume replacement and lowering of the body temperature are part of the treatment. Benzodiazepines, methylprednisolone, bromocriptine (5 mg 4 times daily, for a total of up to 50 mg), carbamazepine, amantadine or electroconvulsive treatment are administered. In cases of severe hyperthermia, dantrolene sodium (2-8 mg/kg 4 times daily, up to 10 mg/kg per dose) is used.

Dopamine dis-regulation syndrome with impairment of the control over impulses is an iatrogenic behavioral disorder associated with excessive stimulation of the central dopaminergic system linked to rewards.

Its *etiology* is related to patients with Parkinson's disease and with restless legs syndrome who are undergoing pramipexole, ropinirole, pergolide, bromocriptine or levodopa mono-therapy.

Its *clinical course* involves pathological addiction to gambling and shopping, travelling, hyperphagia, compulsive re-enactment of a certain automated repetitive action and hyper sexuality.

Its *management* requires correction of the anti-parkinsonian therapy.

The **compulsive syndrome of repeated mechanical activities** is triggered by dopaminergic medication in patients with Parkinson's disease and restless legs syndrome.

Clinically, the disease presents with performing automated stereotypic pointless activities which the patient likes or has learned to perform well. Usually, handling technical equipment (radio sets, machinery) is observed or repeated cleaning of rooms or objects, excessive attention to personal hygiene.

Its *management* requires correction of the anti-parkinsonian therapy.

The General practitioner

Should check the patient on monthly basis or when symptoms deteriorate. Patient should be monitored for:

- Onset of hallucinations and confusion
- Deterioration of the Parkinson's symptoms
- Rapid deterioration of the disease with swallowing disturbances (akinetic crisis)

- Signs for Treatment complications
- Patient's physical health

If any of these signs occur, the patient should be referred to a neurologist for an emergency consultation. Therapeutic pauses should never be recommended. The therapy should only be prescribed after personal examination of the patient.

The neurologist

Should examine the patient once in every 3 months or whenever deterioration occurs, to adjust treatment. Has to monitor for deterioration of motor activities and administer symptomatic treatments.

- Patients should be hospitalized in neurology wards by a neurologist in the event of akinetic crisis, a deterioration of motor fluctuations and dyskinesia or if other life-threatening symptoms are present, e.g., Parkinsonism-hyperpyrexia syndrome.
- Upon the onset of hallucinations and confusion, the same management procedures as in the early phases of the disease are applied.
- In cases of deterioration of symptoms, the dose should be increased with caution.
- In the event of akinetic crisis or manifestation of the Parkinsonism-hyperpyrexia syndrome, emergency treatment is provided.

Medication used for the treatment of Parkinson's disease

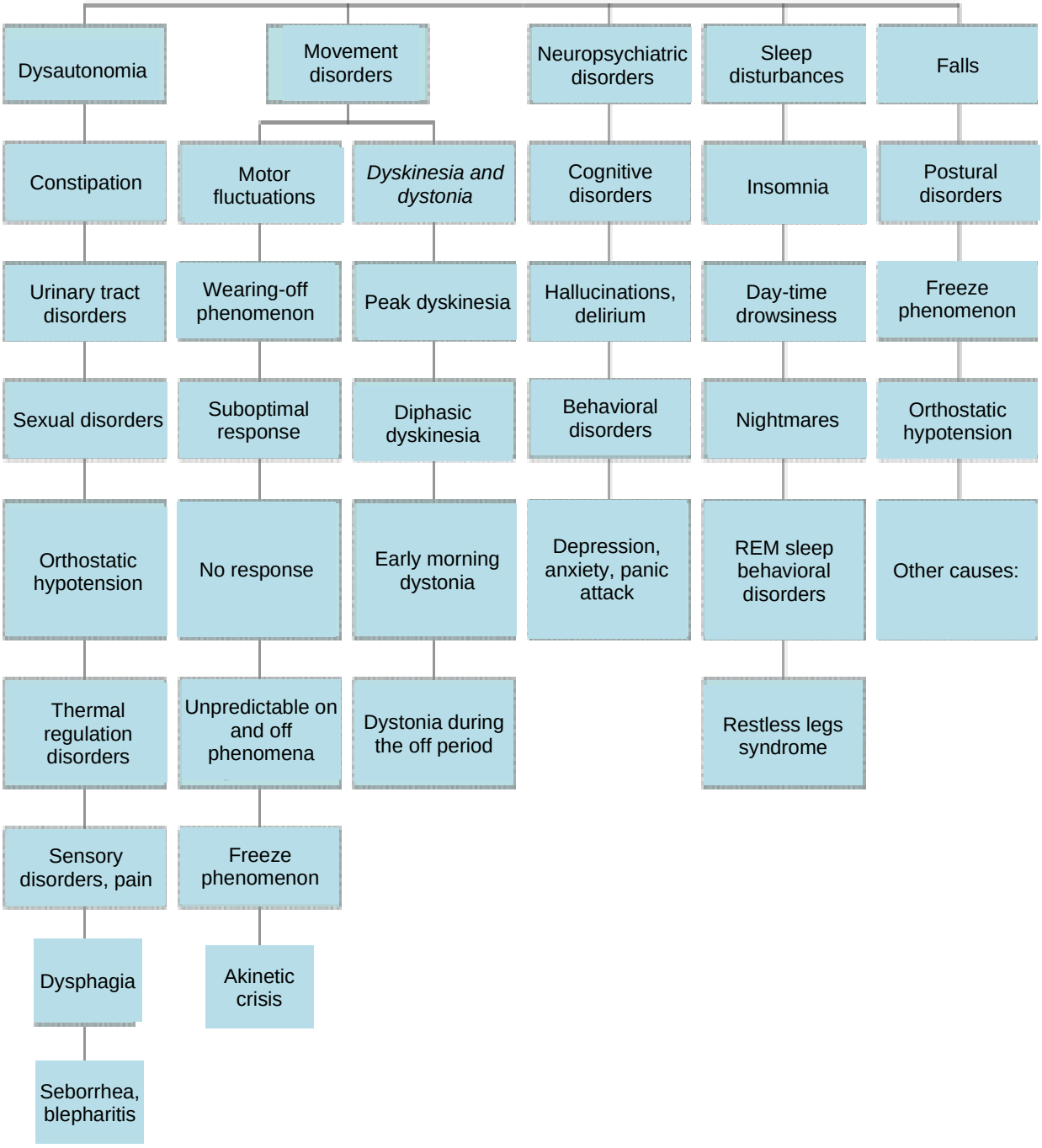
International Nonproprietary Name (INN)	**Packages** tablets, mg	**Mean dose,** mg	**Maximum dose,** mg
Levodopa/benserazide		750	1,500
Standard formulation Sustained release Dispersible formulation	125, 250 caps. 125 125		
Levodopa/carbidopa		750	1,500
Standard formulation Sustained release Gel for intestinal application	250 250 Cassette 100 ml (2,000 mg levodopa)	2,000	
Pramipexole		1.5	4.5
Standard formulation Sustained release formulation	0.25 and 1 0.52; 2.1; 3.15		
Ropinirole		9	24
Standard formulation Sustained release formulation	0.25; 0.5; 1; 2 2; 4; 8		
Cabergoline	1; 2	2 - 5	5
Rotigotine	Transdermal patch 2-8 mg/24 hours	8 mg/24 hours	16 mg/24 hours
Apomorphine hydrochloride hemihydrate	ampoules 10 mg/ml		100
Entacapone	200	600	800
Levodopa/ carbidopa/entacapone	100/25/200, 150/37.5/200 200/50/200		

Selegiline	5	10	10
Rasagiline	1	1	1
Amantadine hydrochloride	caps. 100	200	300
Amantadine sulfate	Infusion 200 mg/500 ml tabl. 100 mg	400 300	600 400
Biperiden	2	6	16
Trihexyphenidyl	2	6	15

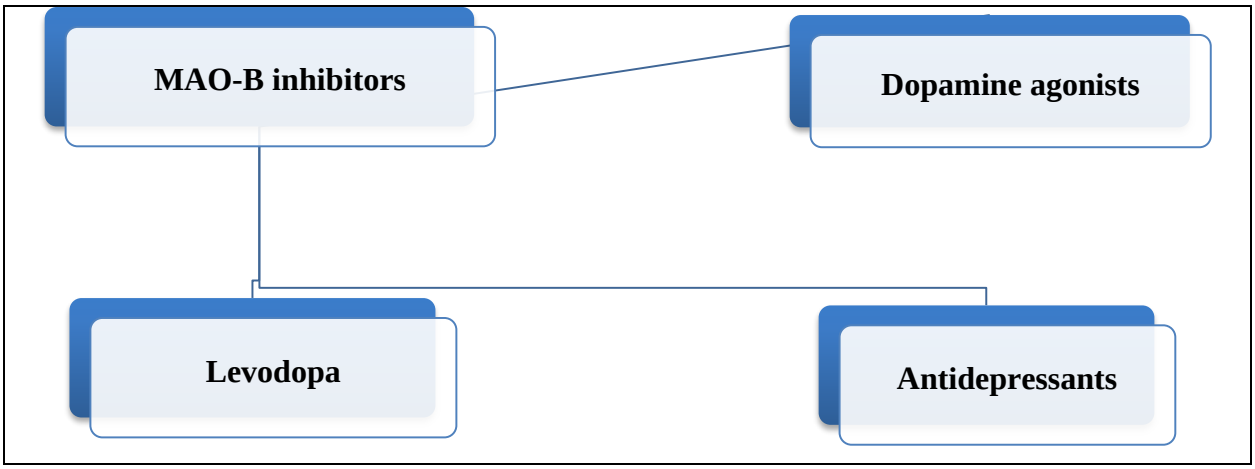
Medication for symptomatic management of Parkinson's disease

Symptom	**INN**	**Packages,** Tablets, mg	**Mean dose,** mg	**Maximal dose,** mg
Urinary tract disorders 1. Bladder detrusor hyper-function 2. External sphincter tone increased	Tolterodine Baclofen	1 and 2 10	2 30	4 60
Insomnia	Zolpidem Zopiclone Clonazepam Amitriptyline Mirtazapine	10 7.5 0.25; 1; 2 25 30 and 45;	5 7.5 1 12.5 30	10 7.5 2 25 60
Nocturnal nightmares Hallucinations	Clozapine	25; 100	12.5 25	25 75
Restless legs syndrome	Clonazepam	0.25; 1; 2	0.25	1
Anxiety	Alprazolam	0.25; 0.5; 1	0.5	1
Depression	Amitriptyline Venlafaxine Mirtazapine Duloxetine	25 75 and 150 30 and 45 30 and 60	25 150 30 30	75 300 60 60

Complications in Advanced Parkinson's disease



Algorithm for treatment of early Parkinson's disease



Algorithm for treatment of Advanced Parkinson's disease