cme: The Current Treatment of Parkinson's Disease

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SUMMARY

Introduction: Parkinson's disease is a neurodegenerative disease characterized by akinesia, rigidity, tremor and postural instability. Degeneration of dopaminergic neurons in the substantia nigra plays a major role in the pathophysiology of Parkinson's Disease (PD), which has a prevalence of 100 to 200 per 100,000 population. No causal treatment is yet available, but motor deficits can be treated symptomatically and efficiently for many years. Non-motor symptoms emerge in the later stages of the disease. Methods: Selective literature review, taking account of the German Neurological Society's guidelines. Results: Dopaminergic replacement is the mainstay of treatment for motor symptoms. Younger patients (under 70) are given dopamine agonists whereas older patients receive levodopa. Glutamate antagonists are also effective. Fluctuations in levels of motor functioning require measures to provide continuous dopaminergic receptor stimulation. Levodopa induced dyskinesias and tremor refractory to pharmacological treatment respond well to deep brain stimulation.

Key words: Parkinson's disease, motor fluctuations, levodopa, dopamine agonists, deep brain stimulation

Parkinson’s Disease (PD, idiopathic parkinsonian syndrome) is one of the most common neurologic diseases, with a prevalence of 100 to 200 cases per 100,000 individuals. The percentage of the population suffering from PD increases with age; in Europe, 1.8% of persons over age 65 and about 2.6% of persons over age 85 have PD (1). Thus, in Germany, the number of persons with PD can be expected to rise over the next few decades as the population continues to grow older.

The term “parkinsonian syndromes” encompasses a number of different diseases whose common clinical features is slowing of voluntary and involuntary movement (akinesia) in addition to at least one of the following "cardinal symptoms": resting tremor, rigidity and postural instability (box 1).

Parkinson's disease is due to marked degeneration of dopaminergic neurons in the pars compacta of the substantia nigra. It is to be distinguished from other, much rarer parkinsonian syndromes that differ from PD, and from one another, in their etiology, prognosis, and treatment. These include both symptomatic (secondary) parkinsonian syndromes and atypical parkinsonian syndromes in connection with other neurodegenerative diseases (box 2). In accordance with the diagnostic criteria that are currently used around the world (2, 3), the German Neurological Society, in its Guidelines (4), recommends the following steps to establish the diagnosis of Parkinson's disease:

- The general diagnosis of a parkinsonian syndrome should be made (box 1).
- Exclusion of a symptomatic or atypical Parkinson syndrome based on anamnestic or current clinical evidence.

Classification of parkinsonian syndromes

- idiopathic
- atypical
- secondary
The characteristic features of Parkinson’s disease in the strict sense of the term (PD) include a unilateral onset of the symptoms and a positive response to L-dopa or dopaminergic agonists, either in a single L-dopa test or over the course of treatment.

The diagnosis is thus made on clinical grounds. Confirmatory diagnostic evaluation by a neurologist should be obtained in case of doubt to rule out the presence of a non-idiopathic parkinsonian syndrome. A further evaluation might include any or all of the following:

- brain imaging (CT or MRI),
- an L-dopa test,
- tests for autonomic dysfunction,
- additional neuropsychological testing,
- ultrasonographic and nuclear medical imaging studies.

Definitive establishment of the diagnosis is important for both treatment and prognostication.

**Treatment**

There is still no curative causal treatment for Parkinson’s disease. At present, the goals of treatment are

- improvement of the quality of life,
- improvement of motor, autonomic, cognitive, and psychiatric symptoms of the disease (depending on disease stage),

Parkinson’s disease is characterized by a slowly progressive course that may, however, be highly variable. Patients tend to become dependent on nursing care after an average of 20 years from disease onset (5).

The onset of the disease is typified by the cardinal motor symptoms, which are due to the dopaminergic deficit. Thus, dopaminergic substances are the mainstays of treatment in the early stages. The principles of treatment that will be presented here (diagram 1) are the product of the authors’ selective review of the current literature, including the Guidelines of the German Neurological Society. All statements regarding the effectiveness of treatment are based on at least one valid clinical study of adequate quality (at least evidence level II); for older medications, the supporting evidence is also derived from comparative studies (evidence level III). The recommendations provided here are thus type A and type B recommendations.
The mainstays of treatment: levodopa and dopamine agonists

The dopamine precursor substance L-3,4-dihydroxyphenylalanine (L-dopa), given in a fixed combination with a peripheral inhibitor of amino acid decarboxylase (benserazide or carbidopa), is still the optimally effective drug for dopamine substitution therapy. It is particularly recommended as standard treatment for patients over 70 years of age. L-dopa has been in clinical use since the 1960’s.

After being treated with L-dopa for 5 years, 30% of patients have fluctuations of the effect of the drug on their motor symptoms (“motor fluctuations” for short), including a loss

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**BOX 2**

**Inclusion and exclusion criteria for Parkinson’s disease**

- **Important positive evidence for Parkinson’s disease**
  - unilateral onset and persistent asymmetry
  - progression over more than 10 years
  - resting tremor
  - good response to L-dopa for more than 5 years
  - L-dopa-induced dyskinesia

- **Important evidence for the presence of another type of parkinsonian syndrome**
  - stroke-like course or severe vascular encephalopathy revealed by cranial CT/MRI
    - vascular parkinsonism
  - hydrocephalus revealed by cranial CT/MRI associated with the clinical triad of gait disturbance, urinary incontinence, and cognitive dysfunction
    - normal pressure hydrocephalus
  - history of neuroleptic or antiemetic agent use
    - drug-induced parkinsonism
  - hallucinations independent of drug use, early development of dementia
    - Lewy body dementia
  - supranuclear gaze palsy, frequent falls at onset (particularly backwards)
    - progressive supranuclear palsy
  - symmetrical onset, marked autonomic dysfunction at onset or cerebellar ataxia
    - multisystem atrophy of parkinsonian type (MSA-P) or cerebellar type (MSA-C)
  - apraxia, “alien limb” phenomenon, pyramidal tract signs, marked asymmetry of bradykinesia, and lack of good response to L-dopa
    - corticobasal degeneration (CBD)

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**Principles of treatment of motor symptoms**

- L-dopa and dopamine agonists are the first line of symptomatic treatment.
### TABLE 1

**Principles of treatment of motor disturbances**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Maintenance dose</th>
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</thead>
<tbody>
<tr>
<td><strong>L-Dopa</strong></td>
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<tr>
<td>Oral L-dopa</td>
<td>Initial treatment in patients over age 70, maintenance treatment if symptoms are progressive</td>
<td>50 mg tid or up to 100 mg several times a day, with maximum intake of about 1000 mg/d</td>
</tr>
<tr>
<td>Duodenal L-dopa</td>
<td>Severe motor fluctuations (long-term L-dopa syndrome)</td>
<td>By pump, 1-10 mL/hr (20–200 mg/hr)</td>
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<tr>
<td>(plus carbidopa)</td>
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<tr>
<td>(plus carbidopa)</td>
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<tr>
<td><strong>Dopamine agonists</strong></td>
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<tr>
<td>Ergot derivatives:</td>
<td>Initial monotherapy for patients under age 70, maintenance therapy in combination with L-dopa</td>
<td></td>
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<tr>
<td>Bromocriptine</td>
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<tr>
<td>Cabergoline</td>
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<td>Dihydroergocryptine</td>
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<td>Lisuride</td>
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<td>Pergolide</td>
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<tr>
<td>Non-ergot derivatives:</td>
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<tr>
<td>Pramipexole</td>
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<tr>
<td>Ropinirole</td>
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<td>Rotigotine (patch)</td>
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<td>Apomorphine</td>
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<tr>
<td>(subcutaneous injection/infusion)</td>
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<tr>
<td>MAO-B inhibitors</td>
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<tr>
<td>Selegiline</td>
<td>Initially as monotherapy for mild symptoms, later on for end-of-dose fluctuations in combination with L-dopa</td>
<td>5 mg qd or bid or as a sublingual tablet, 1.25 mg qd 1–2 mg/d</td>
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<td>Rasagiline</td>
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<td><strong>NMDA antagonists</strong></td>
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<tr>
<td>Amantadine</td>
<td>Initial treatment before L-dopa administration, for L-dopa-induced dyskinesia, or IV for akinetic crises...</td>
<td>50–400 mg/d 10–30 mg tid</td>
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<tr>
<td>Budipine*1</td>
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<td></td>
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<tr>
<td><strong>COMT inhibitors</strong></td>
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<tr>
<td>Entacapone</td>
<td>End-of-dose fluctuations in combination with L-dopa or as a fixed combined preparation</td>
<td>200 mg with each L-dopa dose, up to 1000 mg/d 100 mg tid</td>
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<tr>
<td>Tolcapone*2</td>
<td></td>
<td></td>
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<tr>
<td><strong>Anticholinergic drugs</strong>*3</td>
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<tr>
<td>Biperidene</td>
<td>Resting tremor</td>
<td>2–4 mg tid 2–4 mg tid 2.5–5 (10) mg tid 2–5 mg tid</td>
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<tr>
<td>Bornaprine</td>
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<td>Metixene</td>
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<td>Trihexphenidyl</td>
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<tr>
<td>Beta-blockers</td>
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<tr>
<td>Propranolol</td>
<td>Resting and postural tremor</td>
<td>20–80 mg tid</td>
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<td>Primidone</td>
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<tr>
<td>Clotidine*4</td>
<td>Resting tremor, reserve (backup) medication</td>
<td>12.5–75 mg/d</td>
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<td><strong>Deep brain stimulation</strong></td>
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<td></td>
<td>Severe motor fluctuations (long-term L-dopa syndrome) or medically intractable tremor</td>
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</table>

*1 Risk of life-threatening arrhythmia; *2 risk of hepatotoxicity; *3 cognitive side effects in elderly patients; *4 risk of agranulocytosis.

### Other treatment options

- Further options are available for
  - the early stage of the disease,
  - the late stage of the disease,
  - tremor.
of drug effect, “wearing off,” and L-dopa-induced dyskinesia (6). To avoid these complications of treatment with L-dopa, it is recommended that patients under 70 be initially treated with dopaminergic agonist monotherapy instead. These medications exert a direct effect on the striatal dopamine receptors. In Germany, at present, 8 preparations of this type are available, as well as a new preparation in patch form (table 1). The effectiveness of monotherapy has been demonstrated in placebo-controlled studies, at least for the more recently introduced preparations (7–9) and for the rotigotine patch (10). A study with a follow-up interval of 5 years has revealed that initial treatment with a dopaminergic agonist is associated with a later onset of dyskinesia than initial L-dopa monotherapy (9). Potential side effects of dopaminergic therapy include nausea, orthostatic circulatory dysregulation, and medication-induced psychosis. It has been found that patients with Parkinson’s disease who develop hallucinations are more likely to be taking dopamine agonists than patients who have no hallucinations (11). Thus, L-dopa is considered to be preferable for elderly patients.

In recent years, there has been increasing discussion of the side effects of dopamine agonists, including fibrosis, leg edema, and daytime fatigue. The latter is a problem particularly with pramipexole and ropinirole; for other types of dopaminergic agonist, the evidence remains unclear. Nevertheless, the German Neurological Society’s guidelines recommend that the prescribing physician should warn the patient of the risk of sleep attacks and change the medication if these should occur. Patients reporting somnolence should also be told not to drive a car (4). For the group of ergot-derived dopaminergic
agonists, Raynaud's phenomenon as well as pleuropulmonary and retroperitoneal fibrosis are recognized complications that have occurred to date only rarely and in the setting of long-term treatment, though their precise incidence has not yet been systematically studied. The risk of cardiac valvular fibrosis must also be mentioned in this context. Current studies reveal that treatment with pergolide and cabergoline is associated with a 5- to 7-fold elevation of risk (12, 13). Thus, especially patients who already suffer from valvular heart disease should be given only non-ergot-derived dopaminergic agonists. If an ergot-derived drug is used, echocardiography should be performed before treatment is begun and annually thereafter. Because of the current study data, pergolide was withdrawn from the market in the USA in March 2007.

**Treatment in the early stage: MAO-B inhibitors**
Selective inhibition of intra- and extraneuronal monoamine oxidase B raises the striatal concentration of dopamine. MAO-B inhibitors have a mild symptomatic effect in the early stage of the disease (16). In addition to selegiline, rasagiline was approved in Germany in 2005 as a monotherapeutic agent and for the treatment of end-of-dose fluctuations, because there is positive evidence for its effectiveness in combination therapy for this indication (17). A possible neuroprotective effect is currently under study. Even though selegiline and rasagiline are very selective inhibitors of MAO-B, their use can nonetheless raise the pulse and blood pressure; they can also potentiate the tendency of L-dopa to cause orthostatic hypotension when given in combination with L-dopa. Furthermore, these drugs can cause agitation. Their use in combination with an antidepressant of the SSRI type (selective serotonin reuptake inhibitor) is contraindicated because of the danger of serotonin syndrome.

**Treatment of fluctuations: COMT inhibitors**
Motor fluctuations such as end-of-dose hypokinesia can be treated with inhibitors of catechol O-methyl transferase, an enzyme that catalyzes the degradation of L-dopa to 3-O-methyldopa. Entacapone and tolcapone are two drugs of this type that are currently available in Germany. Their effectiveness against motor fluctuations has been documented by randomized, double-blinded, placebo-controlled studies (14, 15), but no studies of their prophylactic use against fluctuations have yet been completed. COMT inhibitors are, therefore, not yet recommended as standard treatment at the onset of the disease.

A fixed combination of L-dopa, carbidopa, and entacapone has been available on the market in Germany since late 2003. This fixed combination simplifies the dosing schedule of patients with Parkinson's disease for whom entacapone is indicated because of motor fluctuations.

The COMT inhibitor tolcapone was not approved in Germany for a few years because of its hepatotoxicity, but was then re-evaluated and approved in 2005 as a second-line COMT inhibitor for the treatment of patients in the advanced stage of the disease. During the first 12 months of tolcapone therapy, the hepatic transaminases should be regularly checked.

**Non-dopaminergic substances: NMDA antagonists, budipine, anticholinergic drugs**
The N-methyl-D-aspartate (NMDA) antagonist amantadine is effective against hypokinesia both as monotherapy and in combination with other medications. Furthermore, it is moderately effective, for a certain period of time, against L-dopa-induced dyskinesia (18, 19). Amantadine can thus be used in the early stage of the disease in place of L-dopa, as well as in the advanced stage to treat motor fluctuations. Because of the risk of agitation, it should
not be given at night. Amantadine is also available in an intravenous preparation that can be used to treat akinetic crises.

Although anticholinergic agents are the oldest type of antiparkinsonian medication, their use has not been studied systematically. Clinical experience suggests that they are particularly effective against resting tremor. Anticholinergic side effects such as agitation, cognitive dysfunction, tachycardia, and dry mouth are often dose-limiting, so that these substances are no longer recommended for the standard treatment. The same is true of budipine, which not only has effects on monoaminergic systems, but also exerts an NMDA-antagonist effect. This drug is recommended only for the treatment of tremor that does not respond to dopaminergic agents. It can produce life-threatening arrhythmia and its use therefore requires careful cardiological monitoring over the course of treatment.

**Pharmacotherapy of severe motor fluctuations: apomorphine, duodenal levodopa**

Apomorphine is a mixed D1- and D2-receptor agonist that is given subcutaneously. Initial reports of its efficacy were published as early as the 1950’s (20). Currently, apomorphine is indicated for the treatment of complex motor fluctuations in the setting of L-Dopa long-term-syndrome. L-dopa syndrome that can no longer be adequately managed with oral medications alone. Apomorphine is injected subcutaneously by pen for the rapid treatment of akinetic states; it can also be infused through a miniaturized pump system to achieve continuous dopaminergic stimulation. Peripheral dopaminergic side effects, such as nausea and hypotension, can be treated in the initial stage by the adjuvant administration of peripheral dopamine antagonists (domperidone) (21). In addition to subcutaneously infused apomorphine, motor fluctuations can also be treated with L-dopa administered duodenally through a tube implanted via percutaneous endoscopic gastrostomy (PEG). The principle here is the same: the drug is given continuously in order to produce a constant level of dopamine receptor stimulation.

**Surgical treatment alternatives: deep brain stimulation**

Deep brain stimulation (DBS) has now almost fully replaced the earlier functional neurosurgical treatment of PD with lesions in the brain, because DBS, unlike lesion-making, is reversible. When DBS is performed to treat Parkinson’s disease, the stimulation electrodes are stereotactically implanted usually in the subthalamic nucleus bilaterally (diagram 2). Individually programmable electrical stimulation is performed by means of an impulse generator implanted under the clavicle.

All of the cardinal symptoms of Parkinson’s disease can be treated symptomatically with DBS. The current indication for deep brain stimulation consists of long-term L-dopa syndrome with medically intractable motor fluctuations or medically intractable tremor (box 3). The extent of improvement of hypokinesia ("off" symptoms), the reduction of dyskinesia, and the reduction of medication dose are all in the neighborhood of 50% (22).

A recent controlled study demonstrated a clear therapeutic advantage of DBS as compared to optimal medical treatment for improving the quality of life of patients with long-term L-dopa syndrome in advanced Parkinson’s disease (23). The risk of permanent, severe complications from surgery varies from center to center in the range of 0.5% to 3%; the rate of reversible perioperative complications is under 5%. Psychiatric side effects may last for several weeks after surgery. Presurgical evaluation for DBS should be performed in specialized centers by experienced neurologists and neurosurgeons.

Only patients with Parkinson’s disease whose symptoms respond, in principle, to L-dopa (with the exception of tremor) stand to benefit from DBS. It is, therefore, imperative that

<table>
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<tr>
<th>Treatment of long-term L-dopa syndrome</th>
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<tbody>
<tr>
<td>• Apomorphine</td>
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<tr>
<td>• Duodenal L-dopa</td>
</tr>
<tr>
<td>• Deep brain stimulation</td>
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</tbody>
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<table>
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<tr>
<th>Adjuvant measure</th>
</tr>
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<tbody>
<tr>
<td>• Give L-dopa 1 hour after protein-rich meals</td>
</tr>
<tr>
<td>• Make early use of physiotherapy</td>
</tr>
<tr>
<td>• Speech therapy help patients retain their ability to communicate</td>
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</table>
the diagnosis should be accurately established. Careful clinical assessment of the patient's constellation of neurological manifestations is essential.

**Adjuvant measures: diet, physiotherapy, speech therapy**

As pointed out in the recommendations of the German Neurological Society, there are number of reasonable non-pharmacological interventions that can help patients. L-dopa is taken up into the bloodstream and central nervous system by active transport mechanisms for which it competes with neutral amino acids; protein-rich meals should therefore be avoided before and after L-dopa is taken, and the medication should be taken about 1 hour before or after meals.

Physiotherapeutic measures can lead to a sparing of medication and lower the frequency of orthopedic and general medical complications. Regular physical therapy should therefore be regarded as essential, particularly in the advanced stage of the disease. In particular, rhythmic training methods for freezing of gait, as well as special protective exercises against falls, can help precisely where pharmacotherapy alone is least useful.

Speech therapy directed against the common speech problems of Parkinson's disease should be initiated early. They are a prerequisite for the maintenance of the patient's ability to communicate verbally and allow him or her to maintain social contacts. Speech-therapeutic exercises should reinforce the volume of speech, breathing technique, and articulation and preserve these functions for as long as possible.

**Special therapeutic problems**

A number of special therapeutic problems can arise during the treatment of advanced Parkinson's disease. If possible, these should be treated by an experienced specialist, so that disease- and treatment-related complications can be avoided early on.

**Motor fluctuations**

These usually arise 5 years (6) after the onset of the disease and come in two types:

- **hypokinetic motor fluctuations** (loss of medication effect, "wearing off", end-of-dose effect, "sudden off", sudden blockage of gait: "freezing").
- **hyperkinetic motor fluctuations** (peak-dose dyskinesia, plateau dyskinesia, "off"-dystonia, biphasic dyskinesia).

The treatment of motor fluctuations aims at keeping the level of dopaminergic stimulation as constant as possible. This can be done by optimizing the timing of drug intake and shortening the interval between doses, giving dopamine agonists with a long half-life in optimal doses, adding timed-release L-dopa at night, adding a COMT inhibitor, or adding amantadine and/or MAO-B inhibitors.

A special, water-soluble L-dopa tablet as well as subcutaneous apomorphine injections are available for the treatment of sudden "off" states. The irregular motor fluctuations that frequently arise in the further course of the disease are often not adequately treatable by oral medication. At this point, the use of an apomorphine pump, duodenal L-dopa, or deep brain stimulation may be required.

**Tremor**

Parkinsonian tremor, like the other cardinal symptoms of the disease, should be treated initially with dopaminergic medication. If this does not achieve the desired symptomatic improvement, the guidelines of the German Neurological Society (4) recommend the use of the following substances, the choice among which can be made for the individual patient on the basis of their response to treatment.

<table>
<thead>
<tr>
<th>Motor fluctuations</th>
<th>Tremor</th>
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</thead>
<tbody>
<tr>
<td>● These can be of either of the following types:</td>
<td>● Tremor, like other cardinal symptoms of Parkinson's disease, should be treated initially with dopaminergic drugs.</td>
</tr>
<tr>
<td>– hypokinetic fluctuations (loss of drug effect)</td>
<td>● If the tremor fails to improve, then anticholinergic drugs, budipine, beta-blockers, primidone or clozapine should be used.</td>
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<tr>
<td>– hyperkinetic fluctuations (dyskinesia)</td>
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the basis of their side effect profiles: anticholinergic drugs, budipine, beta-blockers, primidone, clozapine (table 1).

Particular side effects that must be borne in mind include cognitive dysfunction due to anticholinergic drugs, cardiac arrhythmia due to budipine, and agranulocytosis due to clozapine.

**Autonomic dysfunction**

Severe autonomic dysfunction at the onset of the disease is evidence against the presence of Parkinson’s disease, but its appearance later on in the course of PD is common. It may involve detrusor hyperactivity, erectile dysfunction, gastrointestinal motility disorders, and/or orthostatic circulatory dysregulation. These problems pose a serious challenge to the treating generalist physicians and neurologists; they can be treated with a variety of measures (table e1). Drooling, which is common, is mainly due to hypokinesia of swallowing and should therefore be treated mainly by raising the antidopaminergic medication and training the act of swallowing with special exercises. The second line of treatment of drooling consists of anticholinergic agents and injection of botulinum toxin into the salivary glands to lessen the volume of saliva.

**Depression**

About one-third of patients with Parkinson’s disease have a depressive tendency. If this tendency is mainly associated with phases of reduced mobility, then it can often be ameliorated by optimizing the dopaminergic medication. If, on the other hand, depression is independent of mobility, then treatment of the depression per se is indicated. In principle, any antidepressant can be used; selective serotonin reuptake inhibitors (SSRI) are generally

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**Treatment of depression**

- If motor function is poor, increase dopaminergic medication.
- SSRI’s are preferable to other types of antidepressants because of their favorable side-effect profile.
preferred because of the absence of anticholinergic side effects and the consequently low risk of psychosis and cognitive dysfunction. A disadvantage of SSRI is that they cannot be given in combination with MAO-B inhibitors.

**Dementia**
Marked cognitive dysfunction early on in the course of the patient’s illness speaks against the presence of Parkinson’s disease. Nonetheless, about one-third of all patients with PD develop an attention deficit, disturbances of executive functioning (planning and organization of action), and, ultimately, dementia later on in the course of the disease (generally about 10 years after onset). A randomized, double-blinded, placebo-controlled multicenter study (24) demonstrated that the cholinesterase inhibitor rivastigmine, given in a dose of 3 to 12 mg/d, moderately improves the cognitive functioning of patients with PD and dementia without significantly impairing their motor function.

Only small placebo-controlled or open studies are currently available to document the possible effectiveness of the cholinesterase inhibitors tacrine, donepezil, and galantamine. The administration of anticholinergic drugs should be avoided in demented patients because these can cause worsening of cognitive dysfunction as well as acute delirium.

**Psychosis**
About one-third of all patients develop hallucinations while being treated with antiparkinsonian medications. The hallucinations are usually visual. In principle, all antiparkinsonian medications, if given in high enough doses, can cause hallucinations or paranoid disturbances, particularly in the advanced stages of the disease.

The different classes of drugs differ, however, with respect to their tendency to induce psychosis. Once general medical psychosis-inducing factors such as dehydration or infection have been ruled out, medications should be cautiously successively discontinued in the following order: anticholinergic agents, tricyclic antidepressants, MAO-B inhibitors, amantadine, budipine, dopaminergic agonists, and COMT inhibitors.

The reduction of L-dopa to the lowest possible dose is the last step. If the hallucinations persist even under L-dopa monotherapy, atypical neuroleptic drugs that have no extrapyramidal side effects (clozapine or quetiapine) can be begun. The effectiveness of clozapine was documented in a controlled study (25), but it should be given only with careful follow-up because of the associated risk of agranulocytosis.

Alternatively, quetiapine can be given, but fewer data are available to document its effectiveness.

**Treatment of psychosis**
- Eliminate psychosis-inducing factors.
- Reduce dopaminergic medication.
- Clozapine
- Quetiapine

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**BOX 3**

**Indications for deep brain stimulation**

- Long-term L-dopa syndrome in idiopathic parkinsonian syndrome
- Severe, irregular motor fluctuations despite optimized medical treatment, or medically intractable tremor
- Good response of symptoms other than tremor to L-dopa
- Biological age 75 or lower
- Absence of generalized brain atrophy
- Absence of general medical contraindications to surgery
- Absence of severe cognitive dysfunction or psychiatric disturbances (other than those induced by medication)
The use of other, so-called atypical antipsychotic drugs is expressly not recommended in the guidelines of the German Neurological Society, because these medications can induce severe akinetic-rigid syndromes even when given in low doses.

**Practical treatment recommendations**

Rational therapy is ensured only if Parkinson’s disease is reliably distinguished from other, non-idiopathic parkinsonian syndromes.

Standard therapy at the onset of the disease is determined by the age of the patient: patients under age 70 are treated initially with a dopaminergic agonist as monotherapy, or, if the symptoms are only mild, with amantadine (100 to 400 mg/d) or selegiline/rasagiline. If the response to dopaminergic agonists in sufficient doses remains inadequate, combination therapy with L-dopa can be begun, but a failure to respond to dopaminergic agonists can also be an indication that a non-idiopathic parkinsonian syndrome is present; in such cases, the patient should be re-evaluated by a neurologist.

Multimorbid patients, or patients over 70 years of age at the onset of the disease, should be treated initially with L-dopa (50 mg qam at first, then increasing by 50 mg every three days till a final dose of 100 to 200 mg tid or qid is reached). If the patient’s parkinsonian symptoms are only mild, then amantadine or an MAO inhibitor can be used for initial treatment here as well, as long as the physician remains vigilant with respect to the potential side effects.

When motor fluctuations arise, the patient’s further treatment should be by a specialized neurologist. The remaining treatment options to be explored include COMT inhibitors, MAO-B inhibitors, amantadine, apomorphine, duodenal L-dopa, and deep brain stimulation.

**Conflict of Interest Statement**

Professor Alfons Schnitzler has received lecture fees from Pfizer, Schwarz Pharma, TEVA-Pharma, Novartis, GSK, Medtronic, and Orion Pharma. Dr. Martin Südmeyer has received travel expenses and lecture fees from Medtronic. The Solvay company gave him financial support for the running of a workshop and paid him lecture fees. Valeant and Schwarz Pharma paid travel expenses.

Dr. Lars Wojtecki has received lecture fees, travel expenses and honoraria for writing patient brochures from Medtronic as well as sponsored continuing medical education and travel expenses from TEVA-Pharma. In addition, he received a research stipend from Schwarz Pharma and travel expenses from Pfizer.

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Translated from the original German by Ethan Taub, M.D.

**REFERENCES**


Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

**Question 1**
Parkinson's disease is to be distinguished from other, rarer types of parkinsonian syndrome. Evidence for the presence of Parkinson's disease includes the following:
(a) Bilateral onset.
(b) Severe autonomic dysfunction at onset.
(c) Frequent falls at onset.
(d) Good response to L-dopa.
(e) Severe cognitive dysfunction at onset.

**Question 2**
The initial treatment of Parkinson's disease for patients under age 70 and without any major comorbidity should consist of:
(a) L-dopa monotherapy.
(b) monotherapy with a dopamine agonist.
(c) monotherapy with a COMT inhibitor.
(d) combination therapy with a dopamine agonist and L-dopa.
(e) deep brain stimulation.

**Question 3**
Because of the risk of valvular heart disease, ergot-derived dopamine agonists
(a) should never be used.
(b) should be used only as a second-line agent with annual follow-up echocardiography.
(c) should not be used in combination with non-ergot-derived agonists.
(d) should be stopped immediately in any patients who are taking them.
(e) should be given preferentially to older patients.

**Question 4**
COMT inhibitors
(a) should be given as soon as possible after the onset of the disease.
(b) should be given as monotherapy.
(c) should be given in combination with L-dopa to treat incipient motor fluctuations.
(d) should generally not be given to older patients.
(e) should not be given to patients who already have valvular heart disease.

**Question 5**
MAO-B inhibitors
(a) can be used for monotherapy and for the treatment of regular motor fluctuations.
(b) are particularly suitable for elderly patients and are well tolerated in combination with SSRI.
(c) are now available in the form of a patch.
(d) should not be used in the early stage of the disease.
(e) have only a short duration of effect and must therefore always be given several times a day.

**Question 6**
Amantadine
(a) has a neuroprotective effect.
(b) is only available as an oral preparation.
(c) belongs to the dopamine agonist group of medications.
(d) can be reasonably used in patients with only mild manifestations at the onset of the disease, or later on in the course of the disease to treat dyskinesia.
(e) should be used instead of L-dopa in patients with a psychotic tendency.
Question 7
Resting tremor in Parkinson’s disease
(a) should be treated with anticholinergic drugs as agents of first choice.
(b) does not respond to L-dopa.
(c) cannot be influenced by deep brain stimulation.
(d) is always unilateral.
(e) should be initially treated with dopaminergic drugs.

Question 8
Apomorphine
(a) has become an obsolete drug in the last few years.
(b) should not be used because of the risk of valvular heart disease.
(c) is particularly useful for patients with circulatory dysregulation.
(d) is delivered in patch form.
(e) is delivered subcutaneously by pen or pump in patients with long-term L-dopa syndrome.

Question 9
Deep brain stimulation
(a) has a neuroprotective effect and should therefore be performed as early as possible in the course of the disease.
(b) is an experimental technique to be used in exceptional patients suffering exclusively from tremor.
(c) is effective against motor fluctuations in long-term L-dopa syndrome and against medically intractable tremor.
(d) only works for about 1 year.
(e) characteristically improves symptoms that cannot be influenced by L-dopa, such as autonomic dysfunction and falls.

Question 10
Patients with Parkinson’s disease and dementia
(a) should be treated with anticholinergic drugs if possible.
(b) can be treated effectively with rivastigmine to improve cognitive function.
(c) should not take L-dopa.
(d) should be treated early on in the course of disease with deep brain stimulation.
(e) should be given MAO-B inhibitors to improve cognitive function.

ADDITIONAL MATERIAL SEE NEXT PAGES
### TABLE e1

**Principles of treatment of non-motor disturbances in Parkinson's disease**

<table>
<thead>
<tr>
<th>Autonomic dysfunction</th>
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| Orthostatic hypotension | domperidone (10–20 mg tid)  
alternatively, fludrocortisone (0.05–3 mg Hs)  
supportive measures: compressive stockings, salt-rich diet |
| Urinary dysfunction, detrusor hyperactivity | oxybutynine (2.5–5 mg bid) – beware of anticholinergic side effects |
| Gastrointestinal dysfunction  
impaired gastric emptying | domperidone (10–20 mg tid)  
increased fluid and fiber intake  
increased physical activity  
polyethylene glycol (macrogol) in an initial dose of 1–3 sachets per day; reduce after a few weeks to ½–1 sachet per day |

<table>
<thead>
<tr>
<th>Constipation</th>
<th></th>
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<tbody>
<tr>
<td>Sialorrhea/dysphagia</td>
<td></td>
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</tbody>
</table>
optimization of dopaminergic therapy to improve akinesia  
anticholinergic drugs (e.g. biperidene 2 mg/d, scopolamine patch)  
local injections of botulinum toxin into the salivary glands |
| Erectile dysfunction | yohimbine, sildenafil, tadalafil |

### Depression

Medical treatment of akinesia-independent depression:

- **Selective serotonin reuptake inhibitors (SSRI)**[^1] [^2]
  - paroxetine (up to 40 mg/d)  
sertaline (up to 50 mg/d)  
citalopram (20–60 mg/d)

- **Tricyclic antidepressants**
  - amitriptyline (75–150 mg/d)  
doxepine (75–150 mg/d)  
desipramine (up to 100 mg/d)  
nortriptyline (up to 150 mg/d)

- **MAO-A inhibitors**
  - moclobemide (600 mg/d)[^1]

- **Others agents:**
  - mirtazapine (15–30 mg/d; promotes sleep in low doses)  
venlafaxine (up to 150 mg/d)[^1]  
reboxetine (up to 12 mg/d)[^1]

### Dementia

- Cholinesterase inhibitors
  - rivastigmine (3–12 mg/d)  
alternatively, tacrine, donepezil, and galantamine

### Psychosis

- Rule out acute episode of comorbid psychiatric disease.

- Slow successive discontinuation of medications, in the following order: anticholinergic drugs, tricyclic antidepressants, MAO-B inhibitors, amantadine, bupropine, dopaminergic agonists, COMT inhibitors. Leave L-dopa at the lowest possible dose.
  - clozapine (6.25–100 mg, with 2/3 of the dose given Hs)  
alternatively, quetiapine (25–125 mg Hs)

[^1]: Not to be used in combination with MAO-B inhibitors  
[^2]: Preferred for use because of lack of anticholinergic side effects
A 63-year-old office worker initially noted impairment of fine motor control of his right hand, particularly when writing. His handwriting appeared smaller than normal. A neurological examination revealed mild right-sided rigidity, bradykinesia of hand movements, and reduced arm swing during walking.

The patient's motor manifestations became barely noticeable after he began taking the dopamine agonist ropinirole. They progressed over the ensuing 3 years, however, and spread to involve the left side of the body.

The ropinirole dose was increased at first, and then L-dopa was prescribed. After a further 2 years, end-of-dose hypokinesia appeared. During these “off” phases, the patient suffered from difficulty initiating movements and a marked gait disturbance.

The interval between L-dopa doses was shortened and, additionally, entacapone was prescribed. This had the effect of flattening out the motor fluctuations. Over the next 2 years, however, the fluctuations became more severe and irregular. The patient had rather severe peak-dose hyperkinesia and was no longer able to walk independently during the phases of reduced mobility.

Apomorphine treatment was begun. The patient's movements became more regular for 1 year and the patient was once again able to pursue his everyday activities independently. A few months afterward, apomorphine had to be discontinued because of cutaneous reactions at the injection sites.

Deep brain stimulation was performed via electrodes implanted in the subthalamic nucleus on both sides. The motor fluctuations were hardly present any more and the medication dose could be cut by half.