

EFNS TASK FORCE ARTICLE

Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies and the Movement Disorder Society–European Section. Part I: early (uncomplicated) Parkinson's disease

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The aim of the study was to provide evidence-based recommendations for the management of early (uncomplicated) Parkinson's disease (PD), based on a review of the literature. Uncomplicated PD refers to patients suffering from the classical motor syndrome of PD only, without treatment-induced motor complications and without neuropsychiatric or autonomic problems. MEDLINE, Cochrane Library and International Network of Agencies for Health Technology Assessment (INAHTA) database literature searches were conducted. National guidelines were requested from all European Federation of Neurological Societies (EFNS) societies. Non-European guidelines were searched for using MEDLINE. Part I of the guidelines deals with prevention of disease progression, symptomatic treatment of motor features (parkinsonism), and prevention of motor and neuropsychiatric complications of therapy. For each topic, a list of therapeutic interventions is provided, including classification of evidence. Following this, recommendations for management are given, alongside ratings of efficacy. Classifications of evidence and ratings of efficacy are made according to EFNS guidance. In cases where there is insufficient scientific evidence, a consensus statement (good practice point) is made.

Background

In the initial stages of disease, levodopa therapy is the most effective for improving motor symptoms in Parkinson's disease (PD). However, long-term treatment is accompanied by fluctuations in motor performance, dyskinesias, and neuropsychiatric complications. Furthermore, as PD progresses, patients develop features that do not respond well to levodopa therapy, such as freezing episodes, autonomic dysfunction, falling, and dementia, and symptoms related to the administration of other drugs. The increasingly diverse possibilities in the therapy of PD, and the many side effects and complications of therapy, require the formulation of

reliable standards for patient care that are based on current scientific knowledge.

This document provides these scientifically supported treatment recommendations. If the available evidence is less than level C, or if scientific evidence is lacking, best practice (good practice point) is recommended, based on the experience of the guideline development group.

Methods

The authors were invited by European Federation of Neurological Societies (EFNS) and Movement Disorder Society–European Section (MDS–ES) to prepare an evidence-based review.

Search strategy

Searches were carried out in MEDLINE, the full database of the Cochrane Library, and the International

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Network of Agencies for Health Technology Assessment (INAHTA), up to the first complete draft in May 2005. During the following discussions, relevant articles could be added up to January 2006. The databases were also searched for existing guidelines and management reports, and requests were made to EFNS societies for their National Guidelines. Reference lists from (review) articles and other reports were also checked.

Method for reaching consensus

Classification of scientific evidence and the rating of recommendations are made according to the EFNS guidance [1]. This report focuses on the highest levels of evidence available and, when only class IV evidence is available, or there is no scientific evidence, a good practice point is given.

After an initial meeting, held to discuss the principal format and methodology, six members of the task force provided a first draft of the report, which was commented on by all members via e-mail and through discussion at four EFNS and MDS congress meetings, until a consensus was reached (informative consensus approach). At a final meeting in September 2005, the six primary authors finalized the text for approval by all members of the task force.

For recommendations concerning drug dosage, method and route of administration, and contraindications the reader is referred to the local formulary or manufacturer's instruction, except when provided within the guidelines' recommendation itself.

Interventions for the management of early (uncomplicated) PD

This section discusses drug classes used in the pharmacological treatment of PD. Following this, there is consideration of the non-pharmacological interventions in early (uncomplicated) PD.

Neuroprotection

To date, no adequate clinical trial has provided definitive evidence for pharmacological neuroprotection. While many agents appear to be promising based on laboratory studies, selecting clinical endpoints for clinical trials that are not confounded by symptomatic effects of the study intervention has been difficult. As matters stand at present, neuroprotective trials of riluzole (class II: Ref. [2]), coenzyme Q10 (CoQ) (class II: Ref. [3]), and glial-derived neurotrophic factor (GDNF) (class II: Ref. [4]) do not support the use of any of these drugs for neuroprotection in routine practice. Although a meta-analysis of seven observational studies suggests that dietary intake of

vitamin E has a protective effect against PD (class III: Ref. [5]), vitamin E did not have a neuroprotective effect in patients with PD (class I: Ref. [6]). The sections below describe the neuroprotective use of drugs primarily known for their symptomatic effect.

MAO-B inhibitors

Studies in early PD (class I and II: Refs [6–10]) show that selegiline postpones the need for dopaminergic treatment by >6 months, indicating a delay in disability progression. However, the initial advantages of selegiline were not sustained [11]. Furthermore, evidence is insufficient to make a conclusion on the neuroprotective, as opposed to the symptomatic, effect of selegiline in PD. Rasagiline had been shown to have a symptomatic effect in the TEMPO study [12]. However, these patients were followed up thereafter in a so-called late-start design, showing that patients treated with rasagiline for 12 months showed less functional decline than subjects whose treatment was delayed for 6 months, suggesting a neuroprotective effect [13].

Levodopa

The only available placebo-controlled study of levodopa in relation to neuroprotection is inconclusive about any neuroprotective, as opposed to symptomatic, effect (class I: Ref. [14]). Mortality studies suggest improved survival with levodopa therapy (class III: Ref. [15]; review: [16]).

Dopamine agonists

Class I randomized, controlled trials with bromocriptine, pramipexole, and ropinirole produced no convincing evidence of neuroprotection [9,17,18]. Starting treatment of PD patients with bromocriptine, rather than with levodopa, is not effective in improving mortality (class II: Refs [19,20]).

Anticholinergics, amantadine, COMT inhibitors

For these medications, either clinical studies are not available or the agents are unable to prevent the progression of PD.

Symptomatic pharmacotherapy of parkinsonism

Anticholinergics

Mechanism of action

Anticholinergics are believed to act by correcting the disequilibrium between striatal dopamine and acetyl-

choline activity. Some anticholinergics, e.g. benztropine, can also block dopamine uptake in central dopaminergic neurons. The anticholinergics used to treat PD specifically block muscarinic receptors.

Symptomatic treatment of parkinsonism (monotherapy)

Three class II trials found anticholinergic monotherapy to be more effective than placebo in improving motor function in PD (bornaprine [21], benzhexol [22,23]). Biperiden is as effective as apomorphine in patients with parkinsonian tremor (class III: Ref. [24]). However, the studies are conflicting over whether anticholinergic drugs have a better effect on tremor than on other outcome measures. These results are consistent with reviews concluding that anticholinergics have only a small effect on PD symptoms, and that evidence for a special effect on tremor is inconclusive [25,26].

Adjunctive therapy of parkinsonism

Class II studies of trihexyphenidyl [27], benztropine [28] and bornaprine [29] in levodopa-treated patients, and two reviews, indicate that adjunctive anticholinergics have only a minor effect on PD symptoms in patients on levodopa therapy, and that the tremor-specific data are inconclusive [25,26].

Prevention of motor complications

No studies available.

Symptomatic treatment of non-motor problems

Because of the risk of side effects (see below), centrally acting anticholinergics are usually not advised for the therapy of non-motor, i.e. autonomic, dysfunctions.

Safety

The clinical use of anticholinergics has been limited by their side-effect profiles and contraindications. The most commonly reported side effects are blurred vision, urinary retention, nausea, constipation (rarely leading to paralytic ileus), and dry mouth. The incidence of reduced sweating, particularly in those patients on neuroleptics, can lead to fatal heat stroke. Anticholinergics are contraindicated in patients with narrow-angle glaucoma, tachycardia, hypertrophy of the prostate, gastrointestinal obstruction, and megacolon.

Impaired mental function (mainly immediate memory and memory acquisition) is a well-documented central side effect that resolves after drug withdrawal (class IV: Ref. [30]). Therefore, if dementia is present, the use of anticholinergics is contraindicated.

The abrupt withdrawal of anticholinergics may lead to a rebound effect with marked deterioration of parkinsonism. Consequently, anticholinergics should be discontinued gradually and with caution [31,32].

Amantadine

Mechanism of action

Amantadine's mechanism of action remains unclear. A blockade of N-methyl-D-aspartate (NMDA) glutamate receptors and an anticholinergic effect are proposed, whereas other evidence suggests an amphetamine-like action to release presynaptic dopamine stores.

Symptomatic treatment of parkinsonism (monotherapy)

Class II studies [22,33–35] and reviews [25,36] show that amantadine induces symptomatic improvement.

Adjunctive therapy of parkinsonism

The addition of amantadine to anticholinergic agents is superior to placebo, with the improvement more pronounced in severely affected patients (class II: Refs [37,38]).

Over 9 weeks, amantadine was beneficial as an adjunctive treatment to levodopa (class II: Ref. [39]), with a more noticeable improvement in patients on low levodopa doses (class II: Ref. [40]). Together with the results of low class evidence studies (reviews: Refs [25,36]), data suggest that amantadine is probably effective as adjunct therapy, with an unproven long-term duration of effect.

Prevention of motor complications

No studies available.

Symptomatic treatment of non-motor problems

Not applicable.

Safety

Side effects are generally mild, most frequently including dizziness, anxiety, impaired coordination and insomnia (> 5%), nausea and vomiting (5–10%), and headache, nightmares, ataxia, confusion/agitation, drowsiness, constipation/diarrhea, anorexia, xerostomia, and livedo reticularis (< 5%). Less common side effects include psychosis, abnormal thinking, amnesia, slurred speech, hyperkinesia, hypertension, urinary retention, decreased libido, dyspnoea, rash, and orthostatic hypotension (during chronic administration) [25].

MAO-B inhibitors

Mechanism of action

Selegiline and rasagiline inhibit the action of monoamine oxidase isoenzyme type B (MAO-B). MAO-B prevents the breakdown of dopamine, leading to greater dopamine availability. Mechanisms besides MAO-B inhibition may also contribute to the clinical effects [41].

Unlike selegiline, rasagiline is not metabolized to amphetamine, and has no sympathomimetic activity.

Symptomatic treatment of parkinsonism (monotherapy)

Five of six studies with a typical follow-up period of 3–12 months (class I and II: Refs 6,8,10,42–44) and a meta-analysis [45] demonstrated a small symptomatic effect of selegiline monotherapy (class I). One study of rasagiline also showed significant improvements on the PD Quality of Life questionnaire and although there was no difference in Unified PD Rating Scale (UPDRS) versus baseline at 6 months, there was a significant improvement versus placebo on UPDRS at 6 months (class I: Ref. [17]).

Adjunctive therapy of parkinsonism

In clinical studies (class I: Refs [46–50]) and a meta-analysis [45], investigating the addition of selegiline to other antiparkinsonian therapies (mainly levodopa), no consistent beneficial effect was demonstrated on the core symptoms of PD in non-fluctuating patients. Rasagiline has not been studied in this context.

Prevention of motor complications

Selegiline has shown no effect in preventing motor fluctuations including wearing-off, ON–OFF fluctuations and dyskinesia (class I: Ref. [51; class II: [52,53]). Rasagiline has not been studied in this context.

Symptomatic treatment of non-motor problems

A class II study detected no effect of selegiline on depression in PD [54]. MAO-B inhibitors have not been investigated for the treatment of other non-motor problems.

Safety

As with any dopaminergic drug, MAO-B inhibitors can induce a variety of dopaminergic adverse reactions. At the daily doses currently recommended, the risk of tyramine-induced hypertension (the ‘cheese effect’) is low [55]. Concerns that the selegiline/levodopa combination increased mortality rates [56] have been allayed [57].

COMT inhibitors

Mechanism of action

Catechol-*O*-methyltransferase (COMT) inhibitors reduce the metabolism of levodopa, extending its plasma half-life and prolonging the action of each levodopa dose. Therapeutic doses of entacapone only act peripherally and do not alter cerebral COMT activity.

Symptomatic treatment of parkinsonism (monotherapy)

Not applicable (COMT inhibitors should always be given with levodopa).

Adjunctive therapy of parkinsonism

There are four published studies (class I and II) where the issue of efficacy in non-fluctuating patients is addressed. Two of these tested tolcapone [58,59], and the other two examined entacapone [60,61]. All trials showed a small benefit in the control of the symptoms of parkinsonism, mostly reflected in UPDRS part II (activities of daily living), but the results were not consistent across all endpoints.

Prevention of motor complications

No studies available.

Symptomatic treatment of non-motor problems

No studies available.

Safety

Catechol-*O*-methyltransferase inhibitors increase levodopa bioavailability, and hence they increase the incidence of dopaminergic adverse reactions, including nausea, and cardiovascular and neuropsychiatric complications. Diarrhoea and urine discoloration are the most frequently reported non-dopaminergic adverse reactions.

Tolcapone can elevate liver transaminases, and fatal cases of liver injury are reported. The European Agency for the Evaluation of Medicinal Products (EMA) lifted the suspension of tolcapone for use in patients on levodopa who fail to respond to other COMT inhibitors, but imposed strict safety restrictions [62]. Tolcapone can only be prescribed by physicians experienced in the management of advanced PD, with a recommended daily dose of 100 mg three times daily. Patients must have fortnightly blood tests for liver function in the first year, at four-weekly intervals for the next 6 months and, subsequently, every 8 weeks. Patients with abnormal liver function or a history of neuroleptic malignant syndrome, rhabdomyolysis or hyperthermia have to be excluded. The combination with selective MAO-B inhibitors (selegiline) is allowed if the dose of MAO-B inhibitor does not exceed the recommended dose.

Levodopa

Standard levodopa formulation

Mechanism of action. Levodopa exerts its symptomatic benefits through conversion to dopamine, and is routinely administered in combination with a decarboxylase inhibitor (carbidopa, benserazide) to prevent its

peripheral conversion to dopamine and the resultant nausea and vomiting.

Symptomatic treatment of parkinsonism (monotherapy)

The efficacy of levodopa is firmly established from over 30 years of use in clinical practice [25,63]. A recent class I trial confirmed a dose-dependent significant reduction in UPDRS scores with levodopa versus placebo [14].

In terms of symptomatic effects, levodopa proved to be better than the dopamine agonists. Levodopa was better than bromocriptine, at least during the first year (class II: Ref. [19]), and a Cochrane review found comparable effects of bromocriptine and levodopa on impairment and disability [64]. Levodopa's symptomatic effect also proved better than ropinirole (class I: Ref. [18]), pramipexole (class I: Ref. [65]), pergolide (class III: Ref. [66]), lisuride (class III: Ref. [67]), and cabergoline (class I: Ref. [68]). The results of these individual studies are confirmed by systematic reviews showing that levodopa monotherapy lead to better UPDRS scores than cabergoline, pramipexole and ropinirole [25,63], and bromocriptine, lisuride and pergolide [63].

Adjunctive therapy of parkinsonism

Supplementation of levodopa with other antiparkinsonian medications in stable PD is a common clinical practice to improve symptomatic control (class IV).

Prevention of motor complications (risk reduction)

The prevention of motor complications (i.e. fluctuations and dyskinesia) by levodopa seems contradictory because these complications are actually caused by levodopa. Usually, levodopa is started three times daily, which offers symptomatic control throughout the day, but after several months or years of chronic treatment, motor complications may arise (see the section 'Safety', below). However, by carefully shortening the dose interval in order to compensate for shortening of the duration of effect of each levodopa dose (wearing-off), and by reducing the dose of each levodopa intake to reduce the magnitude of the effect (peak-dose dyskinesia), the clinical emergence of these motor problems can be postponed.

Symptomatic treatment of non-motor problems

Whether or not levodopa improves mood in PD is a matter of debate [69–71], as is the influence of levodopa on cognition (reviews: Ref. [72–74]). Off-period psychiatric symptoms (anxiety, panic attacks, and depression) and other non-motor symptoms (drenching sweats, pain, fatigue, and akathisia) may be alleviated by modifying the treatment schedule of levodopa (class IV: Refs [75–78]).

Safety

Most studies in animal models and humans failed to show accelerated dopaminergic neuronal loss with long-term levodopa therapy at usual clinical doses (reviews: Ref. [25,79,80]). A meta-analysis reported no treatment-related deaths or life-threatening events [63]. Peripheral side effects include gastrointestinal and cardiovascular dysfunction (reviews: Ref. [25,63,77,81,82]).

Central adverse effects include levodopa motor problems such as fluctuations, dyskinesia and dystonia, and psychiatric side effects such as confusion, hallucinations and sleep disorders (reviews: Refs [63,77,81]). A meta-analysis found ~40% likelihood of motor fluctuations and dyskinesias after 4–6 years of levodopa therapy [83]. Risk factors are younger age, longer disease duration, and levodopa ([14,84–89]; for reviews: Ref. [63,77,81]). In individual studies, the percentage of fluctuations and dyskinesia may range from 10% to 60% of patients at 5 years, and up to 80–90% in later years [63,77]. Neuropsychiatric complications occur in <5% of *de novo* patients on levodopa monotherapy (reviews: Ref. [63,77]).

CR levodopa formulations

Mechanism of action. Levodopa has a short half-life, which eventually results in short-duration responses with a wearing-off (end-of-dose) effect. Controlled-release (CR) formulations aim to prolong the effect of a single dose of levodopa, and reduce the number of daily doses.

Symptomatic treatment of parkinsonism (monotherapy)

Standard and CR levodopa maintain a similar level of control in *de novo* PD after 5 years (class I: Ref. [90]), and also in more advanced PD with a duration of about 10 years and without motor fluctuations (class I: Ref. [91]).

Prevention of motor complications

Controlled-release levodopa has no significant preventive effect on the incidence of motor fluctuations or dyskinesia, when compared with standard levodopa (class I: Ref. [90,92,93]).

Dopamine agonists

Mechanism of action

Of the nine dopamine agonists presently marketed for the treatment of PD, five are ergot derivatives (bromocriptine, cabergoline, dihydroergocryptine, lisuride, and pergolide) and four are non-ergot derivatives (apomorphine, piribedil, pramipexole, and ropinirole).

It is generally accepted that the shared D₂-like receptor agonistic activity produces the symptomatic

antiparkinsonian effect. This D₂ effect also explains peripheral (gastrointestinal nausea and vomiting), cardiovascular (orthostatic hypotension) and neuropsychiatric (somnia, psychosis, and hallucinations) side effects. In addition, dopamine agonists have other properties (e.g. anti-apoptotic effect) that have prompted their testing as putative neuroprotective agents.

Apart from apomorphine, which can only be used via the subcutaneous route (penject and pumps) [94], all dopamine agonists are used orally. A transdermal patch of a new non-ergot dopamine agonist, rotigotine, is currently under development for the treatment of PD [95].

Symptomatic treatment of parkinsonism (monotherapy)

Agonists versus placebo. Dihydroergocryptine [96], pergolide [97], pramipexole [98], and ropinirole [99], are effective in early PD (class I). Bromocriptine and cabergoline are probably effective as monotherapy in early PD (class II and III: Refs [68,100–102]). Lisuride [67] and piribedil [103] are possibly effective (class IV).

Agonists versus levodopa

Levodopa is more efficacious than any orally active dopamine agonist monotherapy (see section 'Levodopa'). The proportion of patients able to remain on agonist monotherapy falls progressively over time to <20% after 5 years of treatment (class I: bromocriptine [52,101], cabergoline [102], pramipexole [104], and ropinirole [105]). For this reason, after a few years of treatment, most patients who start on an agonist will receive levodopa as a replacement or adjunct treatment to keep control of motor parkinsonian signs. Over the last decade, a commonly tested strategy has been to start with an agonist and to add levodopa later if worsening of symptoms cannot be controlled with the agonist alone. However, previously, it was common practice to combine an agonist like bromocriptine or lisuride with levodopa in the first months of treatment (early combination strategy) (class II: bromocriptine [106] and lisuride [107]). There are no studies assessing whether one strategy is better than the other.

Agonists versus agonists

From the limited data available (class II: bromocriptine versus ropinirole [108,109]; class III: bromocriptine versus pergolide [110]), the clinical relevance of the reported difference between agonists, if any, remains questionable.

Agonists versus other antiparkinsonian medications

There are no published head-to-head comparisons between agonist monotherapy and any other antiparkinsonian medication in early PD. Changes in UPDRS

scores reported for most agonists are usually larger than those reported with MAO-B inhibitors, suggesting a greater symptomatic effect with the agonists.

Adjunctive therapy of parkinsonism

Agonists versus placebo. Based on class I evidence, most agonists have been shown to be effective in improving the cardinal motor signs of parkinsonism in patients already treated with levodopa. This is true for apomorphine [111], bromocriptine [112,113], cabergoline [114], pergolide [115], piribedil [116], and pramipexole [117–119]. The available evidence is less convincing (class II) for dihydroergocryptine [120], lisuride [107], and ropinirole [121].

Agonists versus agonists

Several class I and II studies have compared the symptomatic effect of two different dopamine agonists on parkinsonism when given as adjunct to levodopa – with bromocriptine as the reference comparator. Such data cannot have a strong impact on clinical practice because of methodological problems in the reported studies (cabergoline [122], lisuride [123,124], pergolide [110,125–127], pramipexole [113], and ropinirole [128]). Switching from one agonist to another for reasons of efficacy or safety is sometimes considered in clinical practice. Most of the available data are based on open-label class IV trials with an overnight switch [129–136]. An empirical conversion chart of dose equivalence is usually proposed, with 10 mg bromocriptine = 1 mg pergolide = 1 mg pramipexole = 2 mg cabergoline = 5 mg ropinirole.

Agonists versus other antiparkinsonian medications

Bromocriptine [137] and pergolide [138] have been compared with the COMT inhibitor tolcapone (class II), and no significant difference was reported in terms of efficacy on parkinsonian cardinal signs.

Prevention of motor complications

Agonists versus levodopa. Class I randomized, controlled trials demonstrate how early use of an agonist can reduce the incidence of motor complications versus levodopa (cabergoline [102], pramipexole [104], and ropinirole [18,105]). Similar conclusions were reported with bromocriptine (class II: Refs [52,101,139]), and pergolide (class II: Ref. [140]). Conflicting results have been reported with lisuride [67,107].

Agonists versus agonists

There is no available indication that one agonist might be more efficacious than another in preventing or delaying 'time to motor complications'. The only published class II comparison (ropinirole versus bromo-

criptine: Ref. [109]) did not show any difference in dyskinesia incidence at 3 years.

Agonists versus other antiparkinsonian medications

No studies available.

Symptomatic treatment of non-motor problems

There is no indication that symptoms such as anxiety, sleep disturbance or pain are responsive to dopamine agonists. It is conceivable that such symptoms, if partly 'dopa-responsive' and occurring or worsening during OFF episodes, might be improved by dopamine agonists, as with any dopaminergic medication, but no convincing data are available. Conversely, dysautonomic parkinsonian symptoms, like orthostatic hypotension, are aggravated by dopaminergic medication, including agonists, probably through sympatholytic mechanisms (see also the 'Management Recommendations' section on neuropsychiatric complications in Part II of the guidelines).

Safety

Dopamine agonists and all other active dopamine-mimetic medications share a common safety profile reflecting dopamine stimulation. Accordingly, side effects such as nausea, vomiting, orthostatic hypotension, confusion, psychosis, and somnolence may occur with administration of any of these agents. Peripheral leg edema is also commonly observed with most agonists.

Hallucinations and somnolence are more frequent with some agonists than with levodopa (class I: Refs [141,142]). There is no convincing evidence that any agonist is better tolerated than bromocriptine. However, the rare but severe risk of pleuropulmonary/retroperitoneal fibrosis is greater with ergot agonists than with non-ergot agonists. The same is probably true for valvular heart disorders, although pergolide has been the most frequently reported drug at the present time [143]. For this reason, pergolide is presently only used as a second-line alternative option, when other agonists have not provided an adequate response.

Occupational, physical, and speech therapy

Mechanism of action

Occupational therapy, physical therapy, and speech therapy, are designed to teach patients how to cope with emotional problems, disabilities, and handicaps.

Prevention of disease progression

Higher levels of physical activity may lower the risk of PD in men (class IV: Refs [144–146]).

Symptomatic treatment of parkinsonism (monotherapy)

No studies available.

Adjunctive therapy of parkinsonism

Most studies of physical therapy, speech therapy, and rehabilitation programmes in PD report improvements in at least one outcome measure. However, it is often difficult to interpret the clinical importance of these improvements, and long-term effects remain unclear.

Some class II–III studies suggest that physical therapy, especially exercise, improves parkinsonian motor impairments or disabilities [147–154]. Several review articles also highlight the positive effects of physiotherapy [63,155–157], although others have found insufficient evidence to support or refute its efficacy in PD [25,63,158–160]. Practice and specific training strategies have been shown to improve motor performance (class III: Ref. [161,162]).

Sensory cue strategies such as walking sticks and auditory pacing can improve gait and reduce freezing in some patients (class III–IV: Refs [163–169]; review: Ref. [170]), but may reduce walking speed and be ineffective against ON-freezing in others (class III: Refs [171,172]).

The effect of non-pharmacological therapies on falls has been evaluated in elderly people, but no class I–III study specifically evaluates the effect in PD patients. In elderly people, health/environmental risk factor intervention, muscle strengthening and balance retraining, home hazard modification, and withdrawal of psychotropic medication, are all likely to be effective (class III–IV: Refs [173,174]).

Three reviews found insufficient evidence for the efficacy of speech and language therapy for dysarthria [25,175,176]. Ramig *et al.* [177,178] showed that Lee Silverman voice therapy (LSVT) improves vocal intensity and phonation. Pitch limiting voice treatment (PLVT) produces the same increase in loudness, but limits an increase in vocal pitch and prevents a strained voicing (class IV: Ref. [179]). No scientific evidence supports or refutes the efficacy of non-pharmacological swallowing therapy for dysphagia in PD [160,180].

Prevention of motor complications

No qualified studies in these areas.

Symptomatic treatment of non-motor problems

Not specifically addressed by class I–III studies. The good practice point is to adhere to the usual management rules in general practice.

Safety

Practice suggests that these therapies are safe.

Conclusion for patient care

Physical therapy, especially exercise and cueing strategies, are probably effective (level B). Speech therapy is possibly effective (level C). However, the long-term benefits of these therapies remain to be proven. The studies discussed above and the conclusion address physical and speech therapy as adjunctive therapy in PD. No recommendation can be made regarding the effect of physiotherapy as monotherapy in early PD.

Recommendations for the management of early (uncomplicated) PD

Early untreated patients

The optimal time frame for onset of therapy has not been clearly defined. Once parkinsonian signs start to have an impact on the patient's life, initiation of treatment is recommended. For each patient, the choice between the numerous effective drugs available is based on a subtle combination of subjective and objective factors. These factors include considerations related to the drug (efficacy for symptomatic control of parkinsonism/prevention of motor complications, safety, practicality, costs, etc.), to the patient (symptoms, age, needs, expectations, experience, co-morbidity, socioeconomic level, etc.), and to his/her environment (drug availability according to national markets in the European Union, variability in economic and health insurance systems, etc.). However, based on the available level of evidence alone, two main issues are usually considered when initiating a symptomatic therapy for early PD: the symptomatic control of parkinsonism, and the prevention of motor complications (see Table 1).

Currently, there is no uniform proposal across Europe on initiating symptomatic medication for PD. Options include starting treatment with:

- *MAO-B inhibitor*, like selegiline or rasagiline (level A). The symptomatic effect is more modest than that of levodopa and (probably) dopamine agonists, but they are easy to administer (one dose, once daily, no titration).
- *Amantadine or an anticholinergic* (level B). The impact on symptoms is smaller than that of levodopa. Anticholinergics are poorly tolerated in the elderly and their use is mainly restricted to young patients.
- *Levodopa*, the most effective symptomatic antiparkinsonian drug (level A). After a few years of treatment, levodopa is frequently associated with the development of motor complications. As older patients are more

Table 1 Recommendations for the treatment of early PD

| Therapeutic interventions | Recommendation level | |
|----------------------------------|-------------------------------------|-----------------------------------|
| | Symptomatic control of parkinsonism | Prevention of motor complications |
| Levodopa | Effective (level A) | Not applicable |
| Levodopa CR | Effective (level A) | Ineffective (level A) |
| Apomorphine | Not used ^a | Not used ^a |
| Bromocriptine ^b | Effective (level B) | Effective (level B) |
| Cabergoline ^b | Effective (level B) | Effective (level A) |
| Dihydroergocryptine ^b | Effective (level A) | No recommendation ^c |
| Lisuride ^b | Effective (level B) | Effective (level C) |
| Pergolide ^b | Effective (level A) | Effective (level B) |
| Piribedil | Effective (level C) | No recommendation ^c |
| Pramipexole | Effective (level A) | Effective (level A) |
| Ropinirole | Effective (level A) | Effective (level A) |
| Selegiline | Effective (level A) | Ineffective (level A) |
| Rasagiline | Effective (level A) | No recommendation ^c |
| Entacapone ^d | No recommendation ^c | No recommendation ^c |
| Tolcapone ^d | No recommendation ^c | No recommendation ^c |
| Amantadine | Effective (level B) | No recommendation ^c |
| Anticholinergics | Effective (level B) | No recommendation ^c |
| Rehabilitation | No recommendation ^c | No recommendation ^c |
| Surgery | Not used | Not used |

^aSubcutaneous apomorphine is not used in early PD.

^bPergolide, bromocriptine, cabergoline and, precautionarily, other ergot derivatives, cannot be recommended as a first-line treatment for early PD because of the risk of valvular heart disorder [189,190].

^cNo recommendation can be made due to insufficient data.

^dAs COMT inhibitors, entacapone and tolcapone should always be given with levodopa. Due to hepatic toxicity, tolcapone is not recommended in early PD.

sensitive to neuropsychiatric adverse reactions and are less prone to developing motor complications, the early use of levodopa is recommended in the older population (good practice point). The early use of CR levodopa formulations is not effective in the prevention of motor complications (level A).

- *Orally active dopamine agonist*. Pramipexole and ropinirole are effective as monotherapy in early PD, with a lower risk of motor complications than levodopa (level A). Older drugs like bromocriptine are supported by lower class evidence, giving a level B recommendation. However, there is no convincing evidence that they are less effective in managing patients with early PD. The benefit of agonists in preventing motor complications (level A, with data up to 5 years only) must be balanced with the smaller effect on symptoms and the greater incidence of hallucinations, somnolence, and leg edema, when compared with levodopa. Patients must be informed of these risks, e.g. excessive daytime somnolence is especially relevant to drivers. Younger patients are more prone to developing levodopa-induced motor complications, and therefore initial treatment with an agonist can be recommended in this population (good practice point). Ergot derivatives such as pergolide

lide, bromocriptine, and cabergoline are not recommended as first-line medication because of the risk of fibrotic reactions. Subcutaneous apomorphine is not appropriate at this stage of the disease. The early combination of low doses of a dopamine agonist with low doses of levodopa is another option, although the benefits of such a combination have not been properly documented.

- **Rehabilitation.** Because of the lack of evidence of the efficacy of physical therapy and speech therapy at this stage of the disease, a recommendation cannot be made.

Adjustment of initial monotherapy in patients without motor complications

Patients not on dopaminergic therapy

If a patient has started on an MAO-B inhibitor, anticholinergic, amantadine, or a combination of these drugs, a stage will come when, because of worsening motor symptoms, there is a requirement for:

- **Addition of levodopa or a dopamine agonist** (good practice point). Just like in *de novo* patients, at this stage, the choice between levodopa and an agonist again mainly depends on the impact of improving motor disability (better with levodopa) compared with the risk of motor complications (less with agonists) and neuropsychiatric complications (greater with agonists). In addition, there is the effect of age upon the occurrence of motor complications (more frequent in younger patients), and neuropsychiatric complications (more frequent in older and cognitively impaired patients). In general, dopaminergic therapy could be started with agonists in younger patients, whereas levodopa may be preferred in older patients (good practice point, see previous section).

Patients on dopaminergic therapy

Once receiving therapy with a dopamine agonist or levodopa, adjustments of these drugs will also become necessary over time because of worsening motor symptoms.

If on dopamine agonist therapy:

- **Increase the dopamine agonist dose** (good practice point). However, even when the dopamine agonist dose is increased over time, it cannot control parkinsonian symptoms for more than about 3–5 years of follow-up in most patients.
- **Switch between dopamine agonists** (level C).
- **Add levodopa** (good practice point).

If on levodopa:

- **Increase the levodopa dose** (good practice point).
- **Add a dopamine agonist** (good practice point), although the efficacy of adding an agonist has been insufficiently evaluated.

Patients with persistent, or emerging disabling, tremor

If a significant tremor persists despite usual therapy with dopaminergic agents or amantadine, the following treatment options exist for tremor at rest:

- **Anticholinergics** (good practice point: possibly useful, although no full consensus could be made). Cave: anticholinergic side effects, particularly cognitive dysfunction in older patients. (See section on Anticholinergics.)
- **Clozapine** (level B: Ref. [181–183]). Because of safety concerns (see Part II of the guidelines on the treatment of psychosis), clozapine is not advised for routine use, but it is considered as an experimental approach for exceptionally disabled patients requiring specialized monitoring (good practice point).
- **Beta-blockers** (propranolol). Beta-blockers can be effective in both resting and postural tremor (level C: Refs [184–187]). However, because of methodological problems, a Cochrane review found it impossible to determine whether beta-blocker therapy is effective for tremor in PD [188]. Further studies are needed to judge the efficacy of beta-blockers in the treatment of tremor in PD (no recommendation can be made).
- **Consider deep brain stimulation.** Usually subthalamic nucleus stimulation, rarely thalamic stimulation (good practice point, see Part II of the guidelines).

Statement of the likely time when the guidelines will need to be updated

No later than 2009.

Conflicts of interest

M. Horstink has not received any departmental research grants or honoraria since starting this guidelines project.

E. Tolosa has received honoraria for research funding and consultancy from Novartis, Boehringer Ingelheim, Teva, Medtronic, Schwarz, and Servier.

U. Bonuccelli has acted as scientific advisor for, or obtained speaker honoraria from, Novartis, Boehringer Ingelheim, Pfizer, Chiesi, Schwarz, and GlaxoSmithKline. During the past 2 years he has received departmental grants and performed clinical studies for GlaxoSmithKline, Novartis, Teva, Chiesi, Boehringer, Schwarz, and Eisai.

G. Deuschl has acted as scientific advisor for, or obtained speaker honoraria from, Orina, Novartis, Boehringer Ingelheim, and Medtronic, during the past 2 years.

J.P. Larsen has received honoraria and research support from Orion Pharma and Pfizer, and has acted as a consultant for Lundbeck.

A. Lees has received honoraria for lectures from Novartis, Orion, Valeant, Britannia, GE-Amersham,

Servier, Teva, GlaxoSmithKline, Boehringer Ingelheim, and Lundbeck.

W. Oertel has received honoraria for research funding and consultancy from Novartis, Boehringer Ingelheim, Schwarz, Medtronic, Teva, Orion, GlaxoSmithKline, Pfizer, and Solvay.

W. Poewe has received honoraria for lecturing and advisory board membership from Novartis, GlaxoSmithKline, Teva, Boehringer Ingelheim, Schwarz, and Orion.

O. Rascol has received honoraria for research funding and/or consultancy from GlaxoSmithKline, Novartis, Boehringer Ingelheim, Eli Lilly, Teva, Lundbeck, Schwarz, and Servier.

C. Sampaio has received departmental research grants from Novartis Portugal. Her department has also charged consultancy fees to Servier and Lundbeck, and she has received honoraria for lectures from Boehringer Ingelheim.

A. Friedman and P. Kanovsky have nothing to declare.

Disclosure statement

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EFNS TASK FORCE ARTICLE

Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies (EFNS) and the Movement Disorder Society-European Section (MDS-ES). Part II: late (complicated) Parkinson's disease

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To provide evidence-based recommendations for the management of late (complicated) Parkinson's disease (PD), based on a review of the literature. Complicated PD refers to patients suffering from the classical motor syndrome of PD along with other motor or non-motor complications, either disease-related (e.g. freezing) or treatment-related (e.g. dyskinesias or hallucinations). MEDLINE, Cochrane Library and INAHTA database literature searches were conducted. National guidelines were requested from all EFNS societies. Non-European guidelines were searched for using MEDLINE. Part II of the guidelines deals with treatment of motor and neuropsychiatric complications and autonomic disturbances. For each topic, a list of therapeutic interventions is provided, including classification of evidence. Following this, recommendations for management are given, alongside ratings of efficacy. Classifications of evidence and ratings of efficacy are made according to EFNS guidance. In cases where there is insufficient scientific evidence, a consensus statement ('good practice point') is made.

Methods

For background, search strategy and method for reaching consensus, see Part I of these guidelines.

Patients with advanced Parkinson's disease (PD) may suffer from any combination of motor and non-motor problems. Doctors and patients must make choices and decide which therapeutic strategies should prevail for each particular instance.

Interventions for the symptomatic control of motor complications

Motor complications are divided into motor fluctuations and dyskinesia. With advancing PD, patients may

begin to fluctuate in motor performance, i.e. they experience a wearing-off (end-of-dose) effect because the motor improvement after a dose of levodopa becomes reduced in duration and parkinsonism reappears. However, wearing-off can also manifest in symptoms such as depression, anxiety, akathisia, unpleasant sensations and excessive sweating. Besides fluctuations, dyskinesias may occur, which are involuntary movements in response to levodopa and/or dopamine agonist intake. Most dyskinesias emerge at peak-dose levels and are typically choreiform, but may involve dystonia or myoclonus. A minority of patients may experience diphasic dyskinesia, in which they exhibit dyskinesia at the beginning of turning ON and/or at the beginning of turning OFF, but have different and less severe or absent dyskinesias at the time of peak levodopa effect. Eventually, patients may begin to experience rapid and unpredictable fluctuations between ON and OFF periods, known as the ON-OFF phenomenon.

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The diagnosis and therapeutic management of motor complications depends on detecting the type of movement involved and the time of day when they occur in relation to the timing of levodopa and the resulting ON-OFF cycle. Diaries may be helpful in assessing this course over time. It must be noted that many patients prefer being ON with dyskinesia rather than OFF without dyskinesia.

Pharmacological interventions

Mechanisms of action: if not mentioned, see Part I of the guidelines.

Amantadine

Using patient diaries, one study found that the duration of daily OFF time decreased significantly (class I: [1]), whereas a second study found no significant differences in ON or OFF duration (class I: [2]).

During 3 weeks of steady-state infusion with amantadine, dyskinesia was reduced by 60%, with a similar effect observed at 1-year follow-up (class I: [1,3]). In patients on chronic levodopa, oral amantadine significantly reduced the dyskinetic effect of an orally administered acute levodopa/decarboxylase inhibitor challenge of 1.5 times their usual dose (class I: [4]). Similar results were found by Luginger *et al.* [2] (class I). However, the antidyskinetic effect of oral amantadine may only last for 3–8 months, according to one study (class I: [5]), in which, several subjects experienced a rebound in dyskinesia severity after discontinuation.

MAO-B inhibitors

Short-duration studies (<3 months) showed no consistent effect of selegiline in the reduction of OFF time, although an improvement in PD symptoms was observed (class I and II: [6–8]). Zydys selegiline, which dissolves on contact with saliva, reduces daily OFF time when used as adjunctive therapy with levodopa (class I: [9]).

Rasagiline produced a significant reduction in OFF time in patients on levodopa (class I: rasagiline 1 mg, -0.78 h/day [10] and -0.94 h/day [11]). In the study by Rascol *et al.*, [10] rasagiline achieved a similar magnitude of effect to the active comparator, entacapone, which reduced OFF time by 0.80 h/day (class I).

Selegiline might increase or provoke dyskinesia in levodopa-treated patients, but this was not the primary outcome measure in the studies referred to (class I: [6,12]). Golbe *et al.* [8] noted that dyskinesia abated after levodopa was reduced (class I). Rasagiline increased dyskinesia in one study [11], whereas it had no

significant impact in another [10]. The reason for this difference remains unknown, as levodopa dose adjustment was allowed equally in both trials.

Catechol-O-Methyltransferase (COMT) inhibitors

Because of their mechanism of action, COMT inhibitors should always be given with levodopa.

Class I studies demonstrated that tolcapone was efficacious in reducing OFF time [13–16]. The effect size of tolcapone and dopamine agonists (bromocriptine, pergolide) may be similar (class II: [17–19]), but these studies lacked the power to be fully conclusive [20]. The overall conclusion from four studies of entacapone was a reduction in OFF time of 41 min/day (95% CI: 13 min, 1 h 8 min) as compared with placebo (class I: [21]). Entacapone reduces mean daily OFF time in levodopa-treated patients by a similar extent to rasagiline (class I: [10]).

In the trials quoted above, dyskinesias were more frequent with entacapone groups than with placebo. In the majority of the trials, entacapone produced an improvement in Unified PD Rating Scale (UPDRS) motor scores.

Levodopa

It is common practice to lower the individual doses of levodopa in cases of peak-dose dyskinesia, whereas the dose interval is shortened in wearing-off [22,23].

In order to lower the occurrence of delayed ON, no ON, or reduced symptomatic effect because of gastrointestinal absorption failure, methods are being developed to improve levodopa absorption. Fluctuations and wearing-off could be reduced by methods providing more constant gastrointestinal delivery (reviews: [22,24]).

Controlled-release levodopa formulations

Controlled-release (CR) levodopa has been shown to have a significant beneficial effect on daily ON time in a minority of studies, but the improvement is often only minor and transient. No class I study shows long-lasting (>6 months) daily improvement of >1 h ON, or a reduction in hours with dyskinesia as measured by diaries, although some studies found an improvement using 1–4 ratings similar to the UPDRS-Complications scale [22,25–27].

Alternative levodopa formulations and delivery routes

In fluctuating PD, oral dispersible levodopa/benserazide significantly shortened time to peak plasma levels compared with the standard formulation (class III: [28]).

Continuous duodenal infusions of levodopa/carbidopa resulted in statistically significant increases in ON time (class III: [29]). Continuous intraduodenal infusion of levodopa/carbidopa enteral gel resulted in a significant improvement in motor function during ON time, accompanied by a significant decrease in OFF time and no increase in dyskinesia. Median total UPDRS score also decreased (class III: [30]).

Dopamine agonists

Several dopamine agonists have been shown to reduce the duration of OFF episodes. There is class I evidence for pergolide [31], pramipexole [32,33], ropinirole [34,35] and for apomorphine as intermittent subcutaneous injection (class I: [36,37]) or continuous infusion (class IV: [38]). There is class II evidence for bromocriptine [32,39,40] and cabergoline [41], and class IV evidence for other agonists such as lisuride or piribedil [22].

The available comparative class II–III trials showed no major differences between bromocriptine and other agonists such as cabergoline [42], lisuride [43], pergolide [44] and pramipexole [32]. The same was true when comparing bromocriptine [18] and pergolide [19], to the COMT inhibitor tolcapone (class II).

When levodopa-treated patients with advanced PD receive an agonist to reduce OFF episodes, dyskinesia may occur or, if already present, worsen. In clinical practice, when an agonist is given as adjunct in patients with dyskinesias, the levodopa dose is usually reduced to minimize this problem.

Dopamine agonists can deliver more continuous dopamine stimulation than levodopa, because of their longer plasma elimination half-life. Therefore, high doses of dopamine agonists might allow a reduction in levodopa daily dose and, consequently, lessen the duration and severity of levodopa-induced dyskinesias. There are only a few open-label reports to support this practice (class IV), involving small cohorts of patients with continuous subcutaneous infusions of apomorphine [45–48] or oral administration of high doses of pergolide [49] or ropinirole [50].

Functional neurosurgery

Pallidotomy and deep brain stimulation (DBS) are discussed in detail here, as they are the only surgical treatments frequently used to treat PD symptoms. Other treatments are covered only briefly and the reader is referred to special reviews [51].

All surgical interventions for PD involve lesioning or stimulating nuclei or fibre connections of the basal ganglia loop (direct or indirect loop) [52]. Lesioning of these nuclei destroys the circuit, and continuous elec-

trical stimulation is probably to reversibly block the neuronal activity in the loop.

Pallidotomy

This section focuses on unilateral pallidotomy. Bilateral pallidotomy is only rarely performed and there are insufficient studies to allow a conclusion on the safety of the technique.

Adjunctive therapy of parkinsonism

Unilateral pallidotomy has been tested in prospective studies with control groups receiving best medical treatment or subthalamic nucleus (STN) stimulation (class II: [53–56]) and was found to be efficacious for the treatment of PD.

Symptomatic control of motor complications

The improvement of dyskinesia on the body side contralateral to pallidotomy is usually 50–80% (class III: [53,56,57–61]).

Safety

Side-effects with unilateral pallidotomy are generally limited, but the potential for severe complications because of haemorrhage or peri-operative complications is common to all stereotactic procedures. Symptomatic infarction was found in 3.9% of patients and the mortality rate was 1.2%. Speech problems were found in 11.1% of patients and facial paresis in 8.4% (reviews: [54,58]). Neuropsychological functioning is usually unaffected [62,63], but frontal lobe functions and depression may show a modest deterioration (class III: [64,65]). Visual field defects were common in earlier series, but have decreased to < 5% with modification of the surgical technique [66].

Deep brain stimulation

Stimulation of the STN (reviews: [23,67–71]) has become the most frequently applied surgical procedure for PD (at least in Europe), because treating neurologists and neurosurgeons consider it more efficient than pallidal stimulation. However, this is not scientifically proven.

Stimulation of the posteroventral pallidum

Adjunctive therapy of parkinsonism. Pallidal DBS may improve the symptoms of advanced PD, as assessed by the UPDRS-Motor score, by 33% for study periods of up to 6 and 12 months (class II: [72]). Over time, deterioration occurs in some patients who are subsequently successfully reoperated on, with implantation of electrodes into the STN (class III: [67]).

Symptomatic control of motor complications. One of the most consistent effects of DBS upon the pallidum is the reduction of dyskinesias and the reduction of OFF time. In class II and III studies, the reduction in OFF time was shown to be 35–60% [67,72]. The few long-term observations available show no loss of effect on dyskinesias [69].

Symptomatic control of non-motor problems. Under stimulation, there is a mild but significant improvement in mood [73], but the symptomatic control of non-motor complications has not been primarily studied.

Safety. The general surgical risks for pallidal stimulation are the same as for STN DBS (see next section). However, stimulation-specific side-effects are less frequent. The incidence and severity of the neuropsychological and psychiatric effects of this technique are understudied [67,74–77]. A recent review found neuropsychiatric complications in 2.7% of patients, speech and swallowing disturbances in 2.6%, sensory disturbances in 0.9%, and oculomotor disturbances in 1.8% of patients [69].

Stimulation of the subthalamic nucleus

Adjunctive therapy of parkinsonism in patients with dyskinesia. The UPDRS-Motor score improved by 56% for STN stimulation, compared with 33% for pallidal stimulation (class III: [72]). This is consistent with a meta-analysis of 20 studies, showing an average improvement of 53% [67]. Smaller controlled studies found similar results [56,78,79]. At the same time, the levodopa equivalence dosage could be reduced by 50–60%. UPDRS-Motor scores during stimulation were clearly improved after 1 year, but had deteriorated slightly 5 years after the operation (class III: [80]).

Symptomatic control of motor complications. A class III study found a 61% reduction in OFF time [72] and dyskinesias have been reduced by 59–75% [72,81]. Thus, STN stimulation is as effective in reducing dyskinesia as pallidotomy or pallidal stimulation. A 5-year study showed an ongoing improvement of dyskinesia (class III: [80]).

Symptomatic control of non-motor problems. Depression scores improve at 6 and 12 months after the operation [80,82–84]. However, there is insufficient evidence to assume a consistent positive or negative effect of STN stimulation on mood or neuropsychological functions. See also safety section, below.

Safety. In general, reviews [23,81] and those studies referred to below, show that adverse effects of DBS may occur in about 50% of patients, but are permanent in about 20% only. However, the severity of adverse events seldom warrants suspension of DBS. The occurrence of *adverse effects related to the procedure* i.e. acute confusion, intracerebral bleeding,

stroke and seizures, or *to device dysfunction*, i.e. infection or stimulator repositioning, causing permanent severe morbidity or death, reaches up to about 4% (review: [81]).

However, *most adverse effects are related to the treatment* (either stimulatory or stimulatory in combination with pharmacological). Neuropsychological tests were not worsened or showed only slight deterioration in various areas of cognition [63,83,85–91]. Older patients or patients with moderate cognitive impairment prior to surgery may be at greater risk of cognitive deterioration [76,87–89,92]. Apathy, hypomania, psychosis, depression, anxiety, and emotional lability occur in up to 10% of patients [67,80,91,93,94], although many of these might instead be caused by a reduction in dopaminergic therapy.

Suicide has been reported in up to about 4% of patients with DBS [80,83,95–97]. Weight gain is reported in 13% of patients, speech and swallowing disturbances in 7.1%, sensory disturbances in 0.4%, and oculomotor disturbances (apraxia of eyelid opening) in 1.5% [71]. However, a number of these stimulation-associated side-effects can be corrected. Gait disorder, speech and swallowing difficulties, and disequilibrium are probably not related to the stimulation itself [80,94], but could in part result from disease progression or a reduction in levodopa dose.

Surgical treatments that are rarely used in the treatment of PD

Thalamotomy

Thalamotomy has been performed in patients with tremor insufficiently controlled by oral medications. It improves tremor and rigidity is also reduced in 70% of patients, but it has no consistent effect on akinesia (class IV: [98]). Unilateral thalamotomy, as assessed in historical case series, has a permanent morbidity rate of 4–47% and bilateral thalamotomy is associated with a 30% chance of developing serious dysarthria [99].

Stimulation of the thalamus

Stimulation of the thalamus is frequently used for the treatment of tremors, especially essential tremor [100,101]. Stimulation of the thalamus improves tremor (and rigidity) in PD, but not akinesia [101,102] and is therefore rarely employed. Thalamotomy and stimulation of the thalamus were found to be equally efficient, but DBS had fewer side-effects (class I: [103]).

Lesioning of the subthalamic nucleus

Lesioning of the STN has only been used in experimental protocols in small patient series with a high incidence of persistent dyskinesias (class III: [104,105]).

Therefore, presently, this technique is not recommended if STN DBS is an available option.

Foetal mesencephalic grafts

Two class I studies found that the symptoms of parkinsonism were not improved by foetal mesencephalic grafts and some patients developed serious dyskinesias [106,107]. However, in the study by Freed *et al.*, [106] the younger group, but not the older, showed an improvement of UPDRS-Motor OFF scores of 34%, and of Schwab and England OFF scores of 31%, whilst sham surgery patients did not improve. Subsequent analysis showed that it was not patient age, but the preoperative response to levodopa that predicted the magnitude of neurological change after transplant. Some patients in open studies (class IV) have also shown major improvement [108–110]. Therefore, although transplantation of mesencephalic cells has, at the moment, to be considered ineffective as routine treatment for PD (level A), further investigation is probably warranted.

Recommendations for the symptomatic control of motor complications

Motor fluctuations

Wearing-off

- *Adjust levodopa dosing.* In an early phase, when motor fluctuations are just becoming apparent, adjustments in the frequency of levodopa dosing during the day, tending to achieve four to six daily doses, might attenuate the wearing-off (good practice point).
- *Switch from standard levodopa to CR formulation.* CR formulations of levodopa can also improve wearing-off (level C).
- *Add COMT inhibitors or MAO-B inhibitors.* No recommendations can be made on which treatment should be chosen first – on average, all reduce OFF time by about 1–1.5 h/day. The only published direct comparison (level A) showed no difference between entacapone and rasagiline. Tolcapone is potentially hepatotoxic, and is only recommended in patients failing on all other available medications (see Part I of the guidelines). Rasagiline should not be added to selegiline (level C) because of cardiovascular safety issues.
- *Add dopamine agonists.* Oral dopamine agonists are efficacious in reducing OFF time in patients experiencing wearing-off. Currently, no dopamine agonist has proven better than another, but switching from

one agonist to another can be helpful in some patients (level B/C). Pergolide and other ergot agonists are reserved for second-line treatment, because of their association with valvulopathy.

- *Add amantadine or an anticholinergic.* In patients with disabling recurrent OFF symptoms that fail to improve further with the above mentioned strategies, the addition of an anticholinergic (in younger patients), or amantadine, may improve symptoms in some cases (good practice point).

Most patients will eventually receive a combination of several of these treatments because a single treatment fails to provide adequate control of fluctuations. There is insufficient evidence on the combination of more than two strategies and the choice of drugs is mainly based on safety, tolerability and ease of use. All the above options may provoke or increase dyskinesias, but usually this can be managed by decreasing the levodopa dose.

Note: Reduction or redistribution of total daily dietary proteins may reduce wearing-off effects in some patients. Restricting protein intake to one meal a day may facilitate better motor responses to levodopa following other daily meals during the day. A more practical approach could be to take levodopa on an empty stomach about 1 h before or at least 1 h after, each meal (class IV: [111,112]).

If oral therapy fails, the following strategies can be recommended.

- *DBS of the STN* (level B).
- *Subcutaneous apomorphine* as penject (level A) or pump (level C).
- *Alternative delivery routes or alternative formulations of levodopa:*
 - *oral dispersible levodopa* might be useful for delayed ON (level C).
 - *levodopa/carbidopa enteric gel* administered through percutaneous gastrostomy (PEG) can also be considered to stabilize patients with refractory motor fluctuations (level B).

Unpredictable ON–OFF

In the large studies of wearing-off, patients with unpredictable ON–OFF were either not included or constituted <5% of the total population. Therefore, insufficient evidence exists to conclude whether the results that are valid for wearing-off are also valid for unpredictable ON–OFF. There are only a few small studies specifically including patients suffering from unpredictable ON–OFF, although studies evaluating continuous dopaminergic stimulation also include patients suffering concomitantly from wearing-off and

unpredictable ON–OFF. The same is true for concomitant dyskinesia, which frequently occurs during the ON phase of ON–OFF. Thus, there is insufficient evidence to conclude on specific strategies for ON–OFF, although the strategies described for dyskinesia and for wearing-off should be considered for unpredictable ON–OFF (good practice point).

Unpredictable ON–OFF can have several components, one of which is delayed ON and, for which, oral dispersible levodopa formulations could have some value (level C).

Note: By shortening the interval between levodopa doses to prevent wearing-off, the relation between the moment of intake of each dose and the subsequent motor effect can become difficult to disclose, especially when inadequate absorption also occurs. The resulting pattern of fluctuation and dyskinesia may falsely suggest unpredictable ON–OFF. In such patients, the actual mechanism of wearing-off and peak-dose dyskinesia may reappear by increasing the levodopa intake interval to about 4 h. However, in some patients, the benefit may wane after weeks or months.

Dyskinesias

Peak-dose dyskinesia

- *Add amantadine* (level A) – most studies use 200–400 mg/day. The benefit may last < 8 months. The use of other antiglutaminergic drugs is investigational.
- *Reduce individual levodopa dose size*, at the risk of increasing OFF time. The latter can be compensated for by increasing the number of daily doses of levodopa or increasing the doses of a dopamine agonist (level C).
- *Discontinue or reduce dose of MAO-B inhibitors or COMT inhibitors* (good practice point), at the risk of worsening wearing-off.
- *Add atypical antipsychotics*, clozapine (level A: [113,114]), with doses ranging between 12.5 and 75 mg/day up to 200 mg/day, or quetiapine (level C: [115,116]). However, clozapine is associated with potential serious adverse events (agranulocytosis and myocarditis), which limits its use (good practice point).
- *DBS of the STN*, which allows reduction of dopaminergic treatment (level B).
- *Apomorphine continuous subcutaneous infusion*, which allows reduction of levodopa therapy (level C).

Biphasic dyskinesia

Biphasic dyskinesias can be very difficult to treat and have not been the subject of specific and adequate class

I–III studies. Usually, the strategies described for peak-dose dyskinesias can also be considered for biphasic dyskinesia (good practice point). Another option is increasing the size and frequency of levodopa dose, at the risk of inducing or increasing peak-dose dyskinesia. This latter strategy can be helpful, generally transiently, in those cases without peak-dose dyskinesia, or where they are considered less disabling than the biphasic type. A further option could be larger, less frequent doses, to give a more predictable response, which would better enable patients to plan daily activities (good practice point).

Off-period and early morning dystonias

- *Usual strategies for wearing-off* can be applied in cases of off-period dystonia (good practice point).
- *Additional doses of levodopa or dopamine agonist therapy at night* may be effective for the control of dystonia appearing during the night or early in the morning (good practice point).
- *DBS of the STN* (level B).
- *Botulinum toxin* can be employed in both off-period and early morning dystonia (good practice point).

Freezing

Freezing, particularly freezing of gait, often occurs during the OFF phase and less frequently in both OFF and ON. The latter scenario often does not respond to dopaminergic strategies.

Options for OFF freezing are the same as those described for wearing-off. In addition, the use of visual or auditory cues is empirically useful for facilitating the start of the motor act once freezing has occurred (level C).

In ON freezing, trying a reduction in dopaminergic therapy is recommended, although this may result in worsening of wearing-off.

Interventions and recommendations for the symptomatic control of non-motor problems

Neuropsychiatric complications

Dementia

Dementia is a late feature of PD, found in about 30–40% of patients [117–121], with reported frequencies up to 78.2% [122]. Besides abnormalities in monoaminergic functions, another neurochemical brain change associated with dementia in PD is cortical cholinergic denervation (Reviews: [120,123]).

Interventions for the treatment of dementia in PD

Several drugs, particularly anticholinergics, can impair cognitive function and considering discontinuation of such drugs is recommended. Another possible intervention is therapy with cholinesterase inhibitors (see below).

Cholinesterase inhibitors Several reports on cognitive dysfunction in patients with dementia in PD have claimed beneficial treatment effects with donepezil (class II: [124,125]), rivastigmine (class I: [126]), galantamine (class IV: [127]) and tacrine (class IV: [128,129]). However, it must be noted that the cognitive improvements are only modest, whilst tremor worsened in some patients, although UPDRS scores did not change [126]. Besides tremor, nausea and vomiting can also result in discontinuation of therapy in a minority of patients.

Recommendations for the treatment of dementia in PD

- **Discontinue potential aggravators.** Anticholinergics (level B), amantadine (level C), tricyclic antidepressants (level C), tolterodine and oxybutynin (level C) and benzodiazepines (level C).
- **Add cholinesterase inhibitors.** Rivastigmine (level A), donepezil (level C), galantamine (level C). Given the hepatotoxicity of tacrine, its use is not recommended (good practice point).

Psychosis

Psychosis is one of the most disabling non-motor complications of PD. Visual hallucinations have been observed in up to 40% of patients with advanced disease in hospital-based series [130].

Interventions for the treatment of psychosis in PD

Because of the prominent role of dopaminergic treatment-induced psychosis in PD, interventions are primarily based on reduction or withdrawal of the offending drugs, complemented by adjunct treatment with atypical antipsychotics, if necessary. However, infection and metabolic disorders can provoke psychosis and, in such cases, the underlying disorder should be treated.

Atypical antipsychotics

Clozapine. The efficacy of clozapine was documented in two 4-week trials (class I: [131,132]). There was no worsening of UPDRS-Motor scores and one study [131] found significant improvement of tremor in patients receiving clozapine versus placebo. In an open-label extension of one of these studies, efficacy was maintained over an additional 12 weeks [133]. Leucopenia is a rare (0.38%) but serious adverse event with clozapine [134]. Consistently reported side-effects (even with low-

dose clozapine) include sedation, dizziness, increased drooling, orthostatic hypotension, and weight gain.

Olanzapine. In two class I studies, olanzapine failed to show antipsychotic efficacy [135,136]. Both studies also found significant motor worsening with olanzapine, as did [137] (class I). Olanzapine is associated with unacceptable worsening of PD, and is no longer recommended because of the risk of cerebrovascular events in the elderly [138]. However, a relationship between olanzapine and stroke has been denied by others [139].

Quetiapine. A recent trial found no significant improvement in psychosis rating with quetiapine versus placebo (class I: [140]). This study contradicts previous encouraging results from several class III studies [141–147] and a study by [115] (class II), which found no difference between quetiapine and clozapine.

Risperidone. Risperidone improves hallucinations and psychosis in PD (class IV: [148–151]). However, motor worsening was observed in most of these reports and, therefore, risperidone is not recommended in patients with PD [152].

Cholinesterase inhibitors. Rivastigmine (class III: [153,154]) and donepezil (class IV: [155,156]) have been reported to improve psychosis in PD patients. In a study of dementia in PD, rivastigmine improved hallucinations (class III, as hallucination was analysed *post hoc* in this trial: [126]). Motor worsening was reported in two cases in one study only. A small minority of patients discontinued therapy because of increased tremor, nausea or vomiting.

Recommendations for the treatment of psychosis in PD

- **Control triggering factors** (good practice point). Treat infection and metabolic disorders, rectify fluid/electrolyte balance, treat sleep disorder.
- **Reduce polypharmacy** (good practice point). Reduce/stop anticholinergic antidepressants, reduce/stop anxiolytics/sedatives.
- **Reduce antiparkinsonian drugs** (good practice point). Stop anticholinergics, stop amantadine, reduce/stop dopamine agonists, reduce/stop MAO-B and COMT inhibitors, lastly, reduce levodopa. Stopping antiparkinsonian drugs can be at the cost of worsening motor symptoms.
- **Add atypical antipsychotics.** Clozapine (level A) – although it can be associated with serious haematological adverse events, requiring monitoring. There is insufficient data on quetiapine, but it is possibly useful (good practice point). Quetiapine is thought to be relatively safe and does not require blood monitoring. Olanzapine (level A) and risperidone (level C) are not recommended (harmful).

- *Typical antipsychotics* (e.g. phenothiazines, butyrophenones) should not be used because they worsen parkinsonism.
- *Add cholinesterase inhibitors*. Rivastigmine (level B), donepezil (level C).

Depression

Depression is one of the most common non-motor symptoms of PD and, overall, available studies suggest that it may be found in about 40% of patients [157,158]. Depressive episodes and panic attacks may occur before the onset of overt motor symptoms [159,160] and, in established PD, depression is a major determinant of quality of life [161,162]. There is consensus that PD-specific neurobiological changes also play a key role [123,163,164].

Interventions for the treatment of depression in PD

Despite its clinical importance, pharmacological interventions to treat PD-associated depression have been poorly studied.

Levodopa. There are no studies on the effects of chronic levodopa treatment on depressive symptoms in PD.

Dopamine agonists. There have been early anecdotal claims of antidepressant effects of the dopamine agonists, initially related to bromocriptine (class IV: [165]). In addition, a small study has compared the antidepressive efficacy of standard doses of pergolide and pramipexole as adjunct therapy. After 8 months, both treatments were associated with significant improvements in depression scores (class III: [166]).

MAO inhibitors. In a study of the effects of selegiline on motor fluctuations, [6] (class II) failed to detect any significant changes in depression score in a subgroup analysis. However, depression was not the primary target of this trial.

In another study, after 6 weeks of therapy, Hamilton Depression rating scale (HAM-D) scores showed significantly greater improvement in patients receiving combined MAO-A (moclobemide 600 mg/day) plus MAO-B (selegiline 10 mg/day) inhibition, as compared with treatment with moclobemide alone (class III: [167]). However, this study was confounded by motor improvement in the combined treatment group.

Tricyclic antidepressants. This class of agents with amongst other things an anticholinergic effect is an established treatment modality in major depression. The only randomized placebo-controlled study dates back more than 20 years and is related to nortriptyline (titrated from 25 mg/day to a maximum of 150 mg/day) (class II: [168]), which showed a significant improve-

ment over placebo, on a depression rating scale designed by the author. Recent evidence-based reviews [22,169] found little evidence supporting the use of tricyclic antidepressants in PD.

Selective serotonin reuptake inhibitors (SSRIs). Although the use of SSRIs in PD-associated depression has been reported as beneficial in numerous small, open-label studies covering a variety of agents (fluoxetine, sertraline, paroxetine; class II–IV: see [170] for review), to date only one small double-blind placebo-controlled study of sertraline has assessed this approach. No statistically significant differences in the change of Montgomery Åsberg Depression Rating Scale (MADRS) scores was detected between treatment arms (class II: [171]).

The two largest uncontrolled trials of SSRIs in the treatment of depression in PD investigated the use of paroxetine in 33 and 65 patients over a period of 3–6 months (class III: [172,173]). In both studies, paroxetine was titrated to 20 mg/day and produced statistically significant improvements over baseline in HAM-D rating scores. There were no changes in UPDRS-Motor scores in either study but, in the Ceravolo study, one patient reported worsening of tremor and, in the Tesei study, there were two (3%) withdrawals related to worsened OFF time or tremor. Avila *et al.* [174] (class II) compared nefazodone with fluoxetine. Significant improvements in BDI scores were observed with both treatments. However, according to a recent review, large effect sizes have been seen with both active and placebo treatment in PD, but there is no difference between the two groups [170].

When added to dopaminergic therapy, SSRIs have the potential to induce a 'serotonin syndrome', which is a rare but serious adverse event.

'New' antidepressants. Reboxetine (class III: [175]) and venlafaxine (class III: [176]) have been reported beneficial in PD-associated depression. However, these studies have been small, and of short duration.

Non-pharmacological interventions. A recent review identified 21 articles, covering a total of 71 patients with PD receiving electroconvulsive therapy (ECT) to treat concomitant depression [22]. These data are insufficient to conclude on the efficacy and safety of ECT to treat depression in PD.

Two double-blind studies have assessed repetitive transcranial magnetic stimulation (rTMS) in PD depression. There was no difference between sham and effective stimulation with respect to depression and PD measures (class I: [177]). A class I study [178] found rTMS as effective as fluoxetine in improving depression at week 2 – an effect maintained to week 8. However, interpretation of this study is hampered by lack of a placebo.

Recommendations for the treatment of depression in PD

- *Optimize antiparkinsonian therapy* (good practice point).
- *Tricyclic antidepressants* (good practice point).
- *SSRIs* (good practice point). SSRIs are less probably to produce adverse effects than tricyclic antidepressants (good practice point).
- 'New' antidepressants – reboxetine, venlafaxine (no recommendation can be made).

Autonomic dysfunction

Autonomic dysfunction is a common complication of PD. However, it may also occur as a side-effect of standard medical therapy in PD. A significant minority of parkinsonian patients experience very severe and disabling autonomic impairment.

Orthostatic hypotension*Interventions for the treatment of orthostatic hypotension in PD*

Midodrine. Midodrine is a peripheral alpha-adrenergic agonist, without cardiac effect. Two class II studies of midodrine that included PD and other causes of neurogenic orthostatic hypotension revealed a significant increase in standing blood pressure [179,180]. Supine hypertension was found in up to 4% of patients [180].

Fludrocortisone. Fludrocortisone (also called fluoro-hydrocortisone) enhances sodium reabsorption and potassium excretion in the kidney. The rise in blood pressure is assumed to be due to an increase in blood volume and cardiac output. Only one study (class IV) evaluated PD patients and showed an increase in systolic pressure upon standing, as well as disappearance of orthostatic symptoms [181]. Hypertension, hypokalaemia and ankle oedema [182] are the main side-effects. Other studies find fludrocortisone effective in various other causes of orthostatic hypotension.

Dihydroergotamine, etilefrine hydrochloride, indometacin, yohimbine, L-DOPS (L-threo-3,4-dihydroxyphenylserine) and EPO (erythropoietin). Insufficient evidence is available in PD and in other disorders causing neurogenic orthostatic hypotension.

Recommendations for the treatment of orthostatic hypotension in PD

- *General measures:*
 - *avoid aggravating factors* such as large meals, alcohol, exposure to a warm environment and drugs known to cause orthostatic hypotension such as diuretics or antihypertensive drugs. Levodopa and dopamine agonists may also induce orthostatic hypotension.

- *increase salt intake* in symptomatic orthostatic hypotension.
- *head-up tilt of the bed at night*, which may be helpful.
- *wear elastic stockings.*
- *highlight postprandial effects.* In some patients, hypotension occurs only postprandially. Warning the patient about this effect and taking frequent small meals may be helpful.
- *Drug therapy:*
 - *Add midodrine* (level A).
 - *Add fludrocortisone* (good practice point: possibly effective, but note side-effects).

Urinary disturbance*Interventions for the treatment of urinary incontinence in PD*

Peripherally acting anticholinergics. Drugs with anticholinergic effects (oxybutynin, amytriptyline), antispasmodic agents (propiverine, tolterodine) and alpha-1 agonists (prazosin and derived drugs) have not been specifically evaluated in PD [22].

Intranasal desmopressin spray. Intranasal desmopressin spray showed a good response in PD patients with nocturia (class IV: [183]).

Recommendations for the treatment of urinary incontinence in PD

- *General measures for treating urinary urgency and incontinence.* Avoid coffee before bedtime, limit water ingestion before bedtime, etc.
- *Add peripherally acting anticholinergic drugs* (good practice point).
- *Add intranasal desmopressin spray* for nocturnal polyuria (insufficient evidence, no recommendation can be made).

Gastrointestinal motility problems

Constipation and reduced gastric motility are common problems in PD. Anorexia, nausea and vomiting frequently occur as side-effects of dopamine agonist therapy.

Interventions for the treatment of gastrointestinal motility problems in PD

Cisapride has been withdrawn from the market in several European countries because of its association with cardiac arrhythmias and death [184].

Domperidone. Domperidone blocks peripheral dopamine receptors, thus increasing gastric emptying. It reduces dopaminergic drug-related gastrointestinal symptoms in patients with PD (class II–IV: [185–188]).

Metoclopramide. Metoclopramide also blocks peripheral dopamine receptors. However, in contrast to domperidone, it crosses the blood–brain barrier and reduces nausea and vomiting [186] by blocking dopamine receptors in the area postrema. However, it can also increase parkinsonism [189–191], which is considered an unacceptable risk in patients with PD.

Recommendations for the treatment of gastrointestinal motility problems in PD

- *Apply general measures for treating constipation.* Diet, laxatives, etc.
- *Reduce or discontinue drugs with anticholinergic activity* (good practice point).
- *Add domperidone* (level B).

Erectile dysfunction

Interventions for the treatment of erectile dysfunction in PD

Sildenafil. On the basis of trials using validated questionnaires, sildenafil was found to be efficacious in the treatment of erectile dysfunction (class I: [192; class IV: [193,194]). Side-effects of this drug include a group of mild and transitory adverse reactions (headache, transient visual effects, flushing) and, occasionally, severe reactions (hypotension, priapism, cardiac arrest).

Alprostadil. Insufficient evidence.

Dopamine agonists. Apomorphine, administered 30 min before sexual activity, may improve erectile function (class IV: [195]). Nausea, headache, yawning and orthostatic hypotension are the most common side-effects of apomorphine. Pergolide may improve sexual function in younger male patients (class IV: [196]).

Recommendations for the treatment of erectile dysfunction in PD

- *Add sildenafil* (level A).
- *Add dopamine agonists.* Apomorphine and pergolide (insufficient evidence, no recommendation can be made).

Statement of the probable time when the guidelines will need to be updated

No later than 2009.

Conflicts of interest

M Horstink has not received any departmental research grants or honoraria since starting this guidelines project.

E Tolosa has received honoraria for research funding and consultancy from Novartis, Boehringer Ingelheim, Teva, Medtronic, Schwarz and Servier.

U Bonuccelli has acted as scientific advisor for, or obtained speaker honoraria from, Novartis, Boehringer Ingelheim, Pfizer, Chiesi, Schwarz and GlaxoSmithKline. During the past 2 years he has received departmental grants and performed clinical studies for GlaxoSmithKline, Novartis, Teva, Chiesi, Boehringer, Schwarz and Eisai.

G Deuschl has acted as scientific advisor for, or obtained speaker honoraria from, Orina, Novartis, Boehringer Ingelheim and Medtronic, during the past 2 years.

JP Larsen has received honoraria and research support from Orion Pharma and Pfizer and has acted as a consultant for Lundbeck.

A Lees has received honoraria for lectures from Novartis, Orion, Valeant, Britannia, GE-Amersham, Servier, Teva, GlaxoSmithKline, Boehringer Ingelheim and Lundbeck.

W Oertel has received honoraria for research funding and consultancy from Novartis, Boehringer Ingelheim, Schwarz, Medtronic, Teva, Orion, GlaxoSmithKline, Pfizer and Solvay.

W Poewe has received honoraria for lecturing and advisory board membership from Novartis, GlaxoSmithKline, Teva, Boehringer Ingelheim, Schwarz and Orion.

O Rascol has received honoraria for research funding and/or consultancy from GlaxoSmithKline, Novartis, Boehringer Ingelheim, Eli Lilly, Teva, Lundbeck, Schwarz and Servier.

C Sampaio has received departmental research grants from Novartis Portugal. Her department has also charged consultancy fees to Servier and Lundbeck and she has received honoraria for lectures from Boehringer Ingelheim.

A Friedman and P Kanovsky have nothing to declare.

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