

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

The opinions and views expressed in the paper are those of the authors and not necessarily those of the MDS or its Scientific Issues Committee (SIC).

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