# CHAPTER 14

# Early (uncomplicated) Parkinson's disease

*W. H. Oertel,[1] A. Berardelli,[2] B. R. Bloem,[3] U. Bonuccelli,[4] D. Burn,[5] G. Deuschl,[6] E. Dietrichs,[7] G. Fabbrini,[2] J. J. Ferreira,[8] A. Friedman,[9] P. Kanovsky,[10] V. Kostic,[11] A. Nieuwboer,[12] P. Odin,[13] W. Poewe,[14] O. Rascol,[15] C. Sampaio,[16] M. Schüpbach,[17] E. Tolosa,[18] C. Trenkwalder[19]*

[1]Philipps-University of Marburg, Centre of Nervous Diseases, Germany; [2]Sapienza, Università di Roma, Italy; [3]Donders Institute for Brain, Cognition and Behavior, Radboud University Nijmegen Medical Center, The Netherlands; [4]University of Pisa, Italy; [5]Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK; [6]Christian-Albrechts-University Kiel, Germany; [7]Oslo University Hospital and University of Oslo, Norway; [8]Institute of Molecular Medicine, Lisbon, Portugal; [9]Medical University of Warsaw, Poland; [10]Palacky University, Olomouc, Czech Republic; [11]Institute of Neurology CCS, School of Medicine, University of Belgrade, Serbia; [12]Katholieke Universiteit Leuven, Belgium; [13]Central Hospital Bremerhaven, Germany, and University Hospital, Lund, Sweden; [14]Innsbruck Medical University, Austria; [15]University Hospital and University of Toulouse, Toulouse, France; [16]Laboratório de Farmacologia Clinica e Terapeutica e Instituto de Medicina Molecular, Faculdade de Medicina de Lisboa, Portugal; [17]INSERM CIC-9503, Hôpital Pitié-Salpétrière, Paris, France, and Bern University Hospital and University of Bern, Switzerland; [18]Universitat de Barcelona, Spain; [19]Paracelsus-Elena Hospital, Kassel, and University of Goettingen, Germany

## Background

In the initial stages of disease, levodopa is the most effective therapy for improving motor symptoms in Parkinson's disease (PD). However, long-term treatment is accompanied by the development of 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, postural instability, falling, 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 reliable standards for patient care that are based on current scientific knowledge.

This chapter provides these scientifically supported treatment recommendations.

If the level of available evidence is only Level IV, i.e if the evidence is based on expert opinion and scientific evidence is lacking and therefore the rating of recommendation is below C, best practice is recommended (GPP).

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## Methods

### Search strategy

Searches were made in MEDLINE, the full database of the Cochrane Library, and the International Network of Agencies for Health Technology Assessment (INAHTA). The databases were also searched for existing guidelines and management reports, and requests were made to EFNS societies for their National Guidelines. For the 2010 update, the Movement Disorder Society's Evidence Based Medicine Task Force conducted systematic checking of reference lists published in review articles and other clinical reports, and provided the results of a literature search for articles published until September 2009.

### 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. If the level of available evidence is only Level IV, i.e if the evidence is based on the experience of

the guidelines development group (expert opinion) and/or scientific evidence is lacking and therefore the rating of recommendation is below C, best practice is recommended (GPP).

Meetings of the original author group were held in Chicago in June 2008 and in Paris in May 2009 to agree the strategy for revision of the original review, and additional members were invited to join the author group. Two authors were assigned to review the recent publications relating to each section of the original document, grade the evidence, and make any necessary revisions.

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) Parkinson's disease

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 and disease modification

To date, no adequate clinical trial has provided unequivocal 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: [2], coenzyme Q10 (CoQ) (Class II: [3], and glial-derived neurotrophic factor (GDNF) (Class II: [4] do not support the use of any of these drugs for neuroprotection in routine practice. Although a meta-analysis of seven observational studies suggested that dietary intake of vitamin E protects against PD (Class III: [5], vitamin E did not have a neuroprotective effect in patients with PD (Class I: [6]).

Likewise, no adequate clinical trial has provided unequivocal evidence for a disease-modifying effect of any available pharmacotherapy. The sections below describe the investigations on the neuroprotective and disease-modifying effect of drugs primarily known for their symptomatic effect.

#### MAO-B inhibitors

Studies in early PD (Class I and II: [6–10] showed that selegiline postpones the need for dopaminergic treatment by >6 months, suggesting a delay in disability progression. However, the initial advantages of selegiline were not sustained [11]. Rasagiline had been shown to have symptomatic effect in early *de novo* PD patients in the TEMPO study (Class I: [12]. These patients were followed in a so-called delayed-start design[1] with 1 mg or 2 mg rasagiline for 12 months. They showed less functional decline (UPDRS-score) than subjects whose treatment with rasagiline was delayed for 6 months, suggesting that a disease modification may be present (Class I: [13]. In the ADAGIO study (Class I: [14]; delayed start design) rasagiline was studied in less affected patients under randomized double-blind placebo-controlled conditions for 18 months. The combined primary endpoint was reached for 1 mg, but not for 2 mg. The authors themselves advise caution in the interpretation of the results, given they were not replicated in the 2 mg/day arm. The long-lasting beneficial effect of the 1 mg dose may be interpreted as being due to a potential 'disease-modifying effect', or a symptomatic effect combined with other confounding factors [14]. A disease modifying effect of 1 mg rasagiline can be hypothesized, but is currently not proven.

In summary, the delayed-start results are compatible with the concept that 1 mg/day rasagiline is possibly efficacious for disease modification. However, in the absence of long-term follow-up, such trials do not provide sufficient evidence to conclude on any potential disease-modifying – as opposed to the symptomatic – effect of rasagiline in PD in respect to its usefulness in the practical management of early PD.

#### Levodopa

The only available placebo-controlled study of levodopa in relation to neuroprotection is inconclusive about any neuroprotective, as opposed to symptomatic, effect

[1]The introduction of the 'delayed start design' for studying a potential disease-modifying effect has not resolved the issues that: (1) the primary endpoint(s) are not confounded by a symptomatic effect of the intervention under study; (2) the study duration may not be long enough; and (3) the enrolled group of PD patients may already be too far in the course of the disease to address the issue of disease modification.

(Class I: [15]. Mortality studies suggest improved survival with levodopa therapy (Class III: [16]; review: [17]).

### Dopamine agonists

Class I randomized, controlled trials with bromocriptine, pergolide, pramipexole, and ropinirole produced no convincing evidence of neuroprotection or disease modification [9, 18–20].

Starting treatment of PD patients with bromocriptine, rather than with levodopa, is not effective in improving mortality (Class II: [21, 22]).

### 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 acetylcholine neurotransmission. Some anticholinergics, e.g. benzotropine, 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 more effective than placebo in improving motor function in PD (bornaprine [23], benzhexol [24, 25]). Biperiden is as effective as apomorphine in patients with parkinsonian tremor (Class III: [26]). However, data conflict over whether anticholinergic drugs have a better effect on tremor than on other outcome measures or a better effect on tremor than other antiparkinsonian agents. 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 [27, 28].

#### Adjunctive therapy of parkinsonism

Class II studies of trihexyphenidyl [29], benzotropine [30], and bornaprine [31] 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 [27, 28].

#### 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 (see Part II of the review).

#### 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) and acute confusional state are a well-documented central side effect that resolves after drug withdrawal (Class IV: [32]. 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 [33, 34].

### Amantadine

#### Mechanism of action

Amantadine's mechanism of action appears to be multiple. A blockade of 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 [24, 35–37] and reviews [28, 38] 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: [39, 40].

Over 9 weeks, amantadine was beneficial as an adjunctive treatment to levodopa (Class II: [41]), with a more noticeable improvement in patients on low levodopa doses (Class II: [42]. Together with the results of low class evidence studies (reviews: [28, 38]), 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 co-ordination and insomnia (>5%), nausea and vomiting (5–10%), peripheral distal oedema (unresponsive to diuretics), and headache, nightmares, ataxia, confusion/agitation, drowsiness, constipation/diarrhoea, anorexia, xerostomia, and livedo reticularis (<5%). Less common side effects include psychosis, abnormal thinking, amnesia, slurred speech, hyperkinesia, epileptic seizures (rarely, and at higher doses), hypertension, urinary retention, decreased libido, dyspnoea, rash, and orthostatic hypotension (during chronic administration) [28].

## MAO-B inhibitors

**Mechanism of action**
Selegiline and rasagiline inhibit the action of monoamine oxidase isoenzyme type B (MAO-B). MAO-B inhibition prevents the breakdown of dopamine, producing greater dopamine availability. Mechanisms besides MAO-B inhibition may also contribute to the clinical effects [43]. 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: [6, 8, 10, 44–46], and a meta-analysis [47], demonstrated a small symptomatic effect of selegiline monotherapy (Class I).

Two large scale placebo-controlled trials with rasagiline monotherapy in early PD with a follow-up of 6–9 months (Class I: TEMPO-study [12, 13]; ADAGIO-study [14]) provided consistent and significant results for a modest symptomatic benefit of early use of 1 mg and 2 mg/daily to early *de novo* PD patients.

**Adjunctive therapy of parkinsonism**
In clinical studies (Class I: [48–52]) and a meta-analysis [47] 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: [53]; Class II: [54, 55]). 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 [56]. 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 of selegiline currently recommended, the risk of tyramine-induced hypertension (the 'cheese effect') is low [57]. The tyramine-effect does not need to be taken into consideration when using rasagiline. Concerns that the selegiline/levodopa combination increased mortality rates [58] have been allayed [59].

## 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. Entacapone is administered together with each dose of levodopa. Entacapone is not approved for use in early (uncomplicated) and non-fluctuating PD patients (see Part II).

Tolcapone (a second-line drug – see safety in Part II) also acts peripherally; in addition a small central effect is

discussed. Due to its stronger and longer action, tolcapone is recommended to be taken three times a day. Tolcapone is not approved for use in early (uncomplicated) and non-fluctuating PD patients (see Part II).

**Symptomatic treatment of parkinsonism (monotherapy)**
Not applicable (COMT inhibitors should always be given with levodopa).

**Adjunctive therapy of parkinsonism**
There are six published studies (Class I and II) where the issue of efficacy in non-fluctuating patients is addressed. Two of these tested tolcapone [60, 61] and the further two examined entacapone [62, 63]. 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.

In two recent trials, levodopa/cerbidopa/entacapone showed only borderline significance when compared to levodopa/carbidopa alone in the UPDRS parts II and III in patients with no or minimal fluctuations in the QUEST-AP study [64]. In the FIRST STEP STUDY [65], a 39-week, randomized, double-blind, multicentre study, the efficacy, safety, and tolerability of levodopa/carbidopa/entacapone (LCE, Stalevo®) was compared with levodopa/carbidopa (LC, Sinemet IR) in patients with early, *de novo* PD. A significant difference was present in the combined UPDRS II and III, but not in the UPDRS part III between the two treatment arms (Class I: [65]).

**Prevention of motor complications**
In addition the FIRST STEP study assessed as secondary endpoints the occurrence of motor fluctuations and dyskinesias. When the initiation of treatment with levodopa/carbidopa/entacapone was compared to that with levodopa/carbidopa, no difference was found between the two treatment arms [65].

**Symptomatic treatment of non-motor problems**
No studies available.

**Safety**
COMT inhibitors increase levodopa bioavailability, so they can increase the incidence of dopaminergic adverse reactions, including nausea, and cardiovascular and neuropsychiatric complications. Diarrhoea and urine discolouration are the most frequently reported non-dopaminergic adverse reactions.

The combination with selective MAO-B inhibitors (selegiline) is allowed if the dose of MAO-B inhibitor does not exceed the recommended dose.

For tolcapone including safety see Part II.

## Levodopa

### (a) 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 (benserazide, carbidopa) to prevent its peripheral conversion to dopamine with the resultant nausea and vomiting. Levodopa passes the blood–brain barrier – in contrast to dopamine. Levodopa has a short half-life, which eventually results in short-duration responses with a wearing-off (end-of-dose) effect.

**Symptomatic treatment of parkinsonism (monotherapy)**
The efficacy of levodopa is firmly established from more than 30 years of use in clinical practice [28, 66]. A recent Class I trial confirmed a dose-dependent significant reduction in UPDRS scores with levodopa versus placebo [15].

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: [21]), and a Cochrane review found comparable effects of bromocriptine and levodopa on impairment and disability [67]. Levodopa's symptomatic effect also proved better than ropinirole (Class I: [19]), pramipexole (Class I: [68]), pergolide (Class I: [20, 69]; Class I: [20]), lisuride (Class III: [70]), and cabergoline (Class I: [71]). The results of these individual studies are confirmed by systematic reviews showing that levodopa monotherapy – in general – produced lower UPDRS scores than cabergoline, pramipexole, and ropinirole [28, 66], and bromocriptine, lisuride, and pergolide [66].

**Adjunctive therapy of parkinsonism**
Supplementation of levodopa to other antiparkinsonian medications in stable PD is 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 safety section, below). However, by carefully shortening the dose interval 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 may be postponed.

For a comment on non-disabling and disabling dyskinesia in studies with initial levodopa monotherapy versus initial dopamine agonist therapy, see below 'Dopamine agonist, Prevention of motor complications'.

### Symptomatic treatment of non-motor problems

Whether or not levodopa improves mood in PD is a matter of debate [72–74], as is the influence of levodopa on cognition (reviews: [75–77]). Off-period psychiatric symptoms (anxiety, panic attacks, depression) and other non-motor symptoms (drenching sweats, pain, fatigue, and akathisia) may be alleviated by modifying the treatment schedule of levodopa (Class IV: [78–81]).

**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: [28, 82, 83]). A meta-analysis reported no treatment-related deaths or life-threatening events [66]. Peripheral side effects include gastrointestinal and cardiovascular dysfunction (reviews: [28, 66, 80, 84, 85]).

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: [66, 80, 84]. A meta-analysis found ~40% likelihood of motor fluctuations and dyskinesias after 4–6 years of levodopa therapy [86]. Risk factors are younger age, longer disease duration, and levodopa [15, 87–92]; reviews: [66, 80, 84]. 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 [66, 80]. Neuropsychiatric complications occur in less than 5% of *de novo* patients on levodopa monotherapy (reviews: [66, 80].

### (b) Controlled-release (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: [93]), and also in more advanced PD with a duration of about 10 years and without motor fluctuations (Class I: [94]).

**Prevention of motor complications**
CR levodopa has no significant preventive effect on the incidence of motor fluctuations or dyskinesia, as compared with standard levodopa (Class I: [93, 95, 96].

### (c) Intrajejunal application of Levodopa

Not applicable; only approved for very advanced PD patients.

### Dopamine agonists

**Mechanism of action**
Of the 10 dopamine agonists presently marketed for the treatment of PD, five are ergot derivatives (bromocriptine, cabergoline, dihydroergocryptine, lisuride, and pergolide) and five are non-ergot derivatives (apomorphine, piribedil, pramipexole, ropinirole, and rotigotine).

It is generally accepted that the shared $D_2$-like receptor agonistic activity produces the symptomatic antiparkinsonian effect. This $D_2$ effect also explains peripheral (gastrointestinal – nausea and vomiting), cardiovascular (orthostatic hypotension), and neuropsychiatric (somnolence, 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 or rotigotine, which are used via the subcutaneous (penject and pumps) or transdermal (patch) routes respectively [97, 98], all dopamine agonists are used orally. A once-daily controlled-release formulation of ropinirole has recently became available

[99], while one such formulation for pramipexole is currently under development [100].

### Symptomatic treatment of parkinsonism (monotherapy)

*Agonists versus placebo* Dihydroergocryptine [101], pergolide [102], pramipexole [103], ropinirole [104], piribedil [105], and rotigotine [106–108] are effective in early PD (Class I). Bromocriptine and cabergoline are probably effective as monotherapy in early PD (Class II and III: [71, 109–111]. Lisuride is possibly effective [70] (Class IV).

*Agonists versus levodopa* Levodopa is more efficacious than any orally active dopamine agonist monotherapy (see section on 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 [55, 110, 112]), cabergoline [111], pergolide [20], pramipexole [113, 114]), and ropinirole ([18a, 115]). 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 past 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 within the first months of treatment ('early combination strategy') (Class II: bromocriptine [116] and lisuride [117]). 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 [118, 119]; Class III: bromocriptine versus pergolide [120]), the clinical relevance of the reported difference between agonists, if any, remains questionable. On the other hand, ropinirole controlled-release was shown to be non-inferior to ropinirole immediate-release [99], while this was not demonstrated for rotigotine in comparison to ropinirole immediate release, possibly because of methodological issues [106] (Class I evidence).

*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 [121], bromocriptine [122, 123], cabergoline [124], pergolide [125], piribedil [126], pramipexole [127–129], and ropinirole [130] . The available evidence is less convincing (Class II) for dihydroergocryptine [131] and lisuride [117].

*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 [132], lisuride [133, 134], pergolide [120, 135–137], pramipexole [123], piribedil [138], rotigotine [139], and ropinirole [140]). 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 [141–150]). 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. There is Class I evidence that ropinirole can be switched overnight at the same dose from immediate- to controlled-release formulation [99].

*Agonists versus other antiparkinsonian medications* Bromocriptine [151] and pergolide [152] 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 [111, 153], pramipexole [113], pergolide [20], and ropinirole ([18a, 19]). Similar conclusions were

reported with bromocriptine (Class II: [55, 110, 154]. Conflicting results have been reported with lisuride [70, 117]. The risk of dyskinesia reappears once levodopa is adjunct to initial agonist monotherapy. From that time-point, the incidence of dyskinesia does not differ, after adjusting for disease duration and levodopa daily dose, among subjects initially randomized to levodopa or an agonist [155, 156]. Long follow-up (6–15 years) of patients initially randomized early to an agonist (bromocriptine, pramipexole, ropinirole) or levodopa are available [112, 114, 115, 157].

Overall, the risk of motor complications remains lower for those starting on an agonist, but the importance of this observation is controversial in such advanced cases because of: (1) methodological issues including high drop-out rate, (2) greater incidence of daytime somnolence, peripheral oedema, and psychiatric/behavioural changes on agonists (see below); and (3) greater impact of other symptoms than dyskinesia (falls, dementia) on patients' disability.

Finally it should be mentioned, that the frequency of disabling dyskinesias – as opposed to non-disabling dyskinesias – was found not to differ in the above listed Class I studies in early PD, which directly compared the effect of initial levodopa monotherapy versus initial dopamine agonist monotherapy on the latency to dyskinesia and the occurrence of dyskinesia over the course of 2–6 years.

*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 bromocriptine: [119] 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**

Dopamine agonists may improve depression, as indicated by clinical trials conducted in non-parkinsonian subjects with major or bipolar depression pramipexole, which showed to be superior to placebo [158, 159]. However, only uncontrolled or low-quality clinical trails of pergolide, pramipexole, and ropinirole have addressed this issue in PD patients [160–163].

The effect of dopamine agonists over Health-related Quality of Life (HRQuOL) has been explored in several clinical trials as secondary outcomes [164]. Rotigotine improved HRQuOL versus placebo at 6 months in early PD [107]. Pramipexole had a similar impact than levodopa on HRQuOL over 6 years of follow-up [114, 165, 166].

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 such as orthostatic hypotension can be aggravated by dopaminergic medication, including agonists, probably through sympatholytic mechanisms (see also the management recommendations section on neuropsychiatric complications and autonomic dysfunction 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 oedema is also commonly observed with most agonists.

Hallucinations and somnolence are more frequent with some agonists than with levodopa, (Class I: [167, 168] even in healthy subjects, in the case of somnolence [169]. Similarly, leg oedemas appear to be more frequent on agonists than levodopa [18a, 153, 165]). Though there is no convincing evidence that any agonist is better tolerated than bromocriptine, a recent meta-analysis suggested that while frequencies of somnolence, hallucination, or anxiety cases were higher with non-ergot DAs, incidence of vomiting, arterial hypotension, or depression was higher with ergots [170]. The rare but severe risk of pleuropulmonary/retroperitoneal fibrosis is greater with ergot agonists than with non-ergot agonists. The same is true for valvular heart disorders [171–173]). As pergolide and cabergoline have been the most frequently reported drugs at the present time, they are only used as a second-line alternative option, when other agonists have not provided an adequate response. If

employed, regular monitoring of heart valves by ultrasound is mandatory.

Impulse-control disorders have recently been identified as a common adverse drug reaction to dopamine agonists. Prevalence ranges between 5 and 15% depending on the author [174]. The principal risk factor is treatment with dopamine agonists, although they can occur on levodopa as well [174]. Personal traits, disturbed decision-making abilities, and younger age have also been implicated [174, 175]. Comorbidities, cognitive impairment, disease severity, and polytherapy are sometimes also mentioned [176]. Up to the present there is no evidence about between-agonists difference in the frequency of these events.

## Neurosurgical management of early stage PD

There are no studies available on deep brain stimulation or lesional neurosurgery in patients with uncomplicated PD before the appearance of motor complications.

## Non-pharmacological/ non-neurosurgical management of early stage PD

In addition to medical management, many patients with PD receive one or more forms of non-pharmacological treatment during the course of their disease. This includes a broad range of disciplines, among others rehabilitation specialists, allied health professionals (physiotherapy, occupational therapy, speech-language therapy), PD nurse specialists, social workers, and sex therapists. These disciplines can be engaged either as monotherapy, or as part of a team approach (interdisciplinary or multidisciplinary rehabilitation [198]). Non-pharmacological management can be engaged both as an adjunctive treatment for symptoms that also respond to dopaminergic therapy and as the mainstay treatment for symptoms that are otherwise treatment-resistant.

Physiotherapy is the only allied health discipline that explicitly distinguishes the management of early- versus late-stage PD as documented in an evidence-based guideline [177, 178]. The guideline recommends that standard medical care should be complemented with early referral to physiotherapy services (GPP). The guideline also stresses that any physiotherapy interventions should be aimed at clear goals and outcomes, based on a thorough interview and physical assessment. Non-pharmacological management supports patients and their families in coping with the disability and in teaching them how to compensate for their motor and non-motor deficits caused by PD. In the early to middle stages of PD, physiotherapy is aimed mainly at increasing levels of physical activity to preserve or improve physical capacity and physical functioning. This requires expert decisions and adapted exercise programmes to ensure that those aspects of physical capacity that best increase safety and independence in the later stages are targeted.

The weight of the evidence points at positive effects of exercise-based interventions, particularly on motor signs and gait (Class II). A recent meta-analysis recommends exercise therapy as an effective approach to enhance general physical functioning and quality of life in PD (Class II) [179]. Evidence of effectiveness (Class II–III) has now emerged in the following areas.

- There is evidence that cueing strategies improve the quality of gait and increase the confidence to carry out functional activities (Class II) [180]. Cueing does not increase the risk of falling. However, effects are not retained at 6 weeks follow-up without cues. Cued training is likely to improve gait during performance of a secondary motor task (Class III) [181].
- Increases of muscle power can be achieved through resistance exercise (several Class III studies [182]).
- Aerobic training with an appropriate duration (7 weeks) and intensity (50–60% of maximum heart rate reserve) induces significant changes in several cardiorespiratory measures of endurance (Class II) [183].
- Treadmill training for patients with PD results in sustained gains in gait speed (Class II) [184, 197]. Alternative forms of exercise such as Tai Chi (Class II) [185] or Qijong (Class II) [186] have beneficial effects on balance and gait measures, and Unified Parkinson Disease Rating Scale scores.

Other disciplines may also be used in the non-pharmacological management of early stage PD. Similar to physiotherapy, early referral is felt to be useful for occupational therapy and speech-language therapy (Expert opinion), but this is not yet grounded in international guidelines (see also Part II).

### Recommendations

#### 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, comorbidity, socioeconomic level, etc.), and to their 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 14.1).

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),and well tolerated (especially rasagiline)
- *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 sensitive to neuropsychiatric adverse reactions and are less prone to developing motor complications, the early use of levodopa is recommended in the older population (GPP). The early use of controlled-release levodopa formulations is not effective in the prevention of motor complications (Level A)
- orally active dopamine agonist. Pramipexole, piribedil, and ropinirole immediate- or controlled-release are effective as monotherapy in early PD (Level A), with a lower risk of motor complications than levodopa for pramipexole or ropinirole (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, impulse-control disorders, somnolence, and leg oedema, as 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 (GPP). Ergot derivatives such as pergolide, bromocriptine, and cabergoline are not recommended as first-line medication because of the risk of fibrotic reactions. Rotigotine is administered transdermally using a patch and ropinirole CR once daily orally, as opposed to the other agonists that are administered orally three times a day. 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*. Due to the lack of evidence of the efficacy of physical therapy and speech therapy in the early 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* (GPP). 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 in the first 3–5 years) and neuropsychiatric complications (greater with agonists). In addition, there is the effect of age on the occurrence of motor complications (more frequent in younger patients) and neuropsychiatric/behavioural complications (more frequent in older and cognitively impaired patients). In general, dopaminergic therapy may/could be started with agonists in younger patients, whereas levodopa may be preferred in older patients (GPP, see previous section) and in multimorbid patients of any age.

**Table 14.1** 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) |
| Pramipexole CR[e] | not available | not available |
| Ropinirole | effective (Level A) | effective (Level A) |
| Ropinirole CR[e] | effective (Level A) | no recommendation[c] |
| Rotigotine[f] | effective (Level A) | no recommendation[c] |
| 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 |

[a]Subcutaneous apomorphine is not used in early PD.
[b]Pergolide, bromocriptine, cabergoline and, precautionarily, other ergot derivates, cannot be recommended as a first-line treatment for early PD because of the risk of valvular heart disorder [187, 188].
[c]No recommendation can be made due to insufficient data.
[d]As COMT inhibitors, entacapone and tolcapone should always be given with levodopa. Due to hepatic toxicity, tolcapone is not recommended in early PD.
[e]Controlled-release.
[f]Transdermal patch delivery system.

## 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.

### Recommendations

If on dopamine agonist therapy:

- *increase the dopamine agonist dose* (GPP). 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* (GPP).

If on levodopa:

- *increase the levodopa dose* (GPP)
- *add a dopamine agonist* (GPP), although the efficacy of adding an agonist has been insufficiently evaluated
- *add a COMT-inhibitor* to levodopa at the transition of a non-fluctuating to a fluctuating status, i.e. if motor fluctuations evolve (GPP) – preferably in older patients and multimorbid patients of any age.

### 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.

**Recommendations**

- *Anticholinergics* (GPP: 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: [189–191]). Due to 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 specialised monitoring (GPP).
- *Beta-blockers (propanolol)*. Beta-blockers can be effective in both resting and postural tremor (Level C: [192–195]). However, due to methodological problems, a Cochrane review found it impossible to determine whether beta-blocker therapy is effective for tremor in PD [196]. 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 (GPP, see Part II of the guidelines).

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

No later than 2013.

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## Conflicts of interest

A. Berardelli has received speaker honoraria from Allergan and Boehringer Ingelheim.

U. Bonuccelli has acted as scientific advisor for, or obtained speaker honoraria from, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, and Schwarz-Pharma. He has received departmental grants and performed clinical studies for Boehringer Ingelheim, Chiesi, Eisai, GlaxoSmithKline, Novartis, Schwarz-Pharma, and Teva.

D. Burn has served on medical advisory boards for Teva, Boehringer-Ingelheim, Archimedes, and Merck Serono. He has received honoraria to speak at meetings from Teva-Lundbeck, Orion, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Eisai, UCB, and GE Healthcare.

G. Deuschl has acted as scientific advisor for, or obtained speaker honoraria from, Orion, Novartis, Boehringer Ingelheim, and Medtronic.

E. Dietrichs has received honoraria for lecturing and/or travelling grants from GlaxoSmithKline, Lundbeck, Medtronic, Orion, Solvay, and UCB.

G. Fabbrini has received honoraria for lectures from Boehringer Ingelheim, Glaxo Pharmaceuticals, and Novartis Pharmaceuticals, and is member of an advisory board for Boehringer Ingelheim.

J. Ferreira has received honoraria for lecturing and/or consultancy from GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, and BIAL.

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V. Kostić has received honoraria for lecturing from Novartis, Boehringer Ingelheim, Merck, Lundbeck, and Glaxo-Smith-Kline, and is a member of the Regional South-Eastern European Pramipexole Advisory Board of Boehringer Ingelheim.

P. Odin has received honoraria for lectures from Boehringer Ingelheim, UCB, GSK, Solvay, and Cephalon, and participated in advisory boards for Boehringer Ingelheim, Cephalon, and Solvay.

W.H. Oertel has received honoraria for consultancy and presentations from Bayer-Schering, Boehringer Ingelheim, Cephalon, Desitin, GlaxoSmithKline, Medtronic, Merck-Serono, Neurosearch, Novartis, Orion Pharma, Schwarz-Pharma Neuroscience, Servier, Synosia, Teva, UCB, and Vifor Pharma.

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

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C. Trenkwalder has received honoraria for lectures from Boehringer Ingelheim, UCB, Glaxo Pharmaceuticals, and Astra Zeneca, and is member of advisory boards for Boehringer Ingelheim, UCB, Cephalon, Solvay, Novartis, and TEVA/Lundbeck.

## Disclosure statement

The reader's attention should be drawn to the fact that the opinions and views expressed in the paper are those of the authors and not necessarily those of the MDS or the MDS Scientific Issues Committee (SIC).

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