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EFNS/MDS-ES GUIDELINES

Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease

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Objective: To summarize the 2010 EFNS/MDS-ES evidence-based treatment recommendations for the management of Parkinson's disease (PD). This summary includes the treatment recommendations for early and late PD.

Methods: For the 2010 publication, a literature search was undertaken for articles published up to September 2009. For this summary, an additional literature search was undertaken up to December 2010. Classification of scientific evidence and the rating of recommendations were made according to the EFNS guidance. In cases where there was insufficient scientific evidence, a consensus statement ('good practice point') is made.

Results and Conclusions:: For each clinical indication, a list of therapeutic interventions is provided, including classification of evidence.

Background

Parkinson's disease (PD) is a neurodegenerative disease that presents several challenges for the treating physicians. Treatment strategies depend on the patient's age, disease stage, most troublesome symptoms, the balance between efficacy and risk for each treatment option, and other factors. However, it is important to base treatment decisions on the best available data for each intervention. EFNS and

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Movement Disorder Society–European Section (MDS-ES) have collaborated to produce evidence-based recommendations for the treatment of PD [1,2]. The most recent recommendations are published as book chapters [3] and presented here as [4] a summary report.

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. The databases were also searched for guidelines and management reports, and requests were made to EFNS societies for their national guidelines. For the 2010 update, the MDS Evidence-Based Medicine Task Force systematically checked reference lists up to September 2009. For this summary, an additional literature search was undertaken up to December 2010.

Classification

Classification of evidence and recommendations was made according to EFNS guidance [5]. This report focuses on the highest levels of evidence available. If the available evidence is Level IV, or the rating of recommendation is below C, 'good practice point' (GPP) is recommended.

Interventions for the management of early (uncomplicated) PD (Tables 1 and 2)

Neuroprotection and disease modification

MAO-B inhibitors

Selegiline in early PD (Class I and II [6–10]) was shown to postpone the need for dopaminergic treatment by several months. Subjects whose treatment with *rasagiline* was delayed by 6 months showed greater worsening on UPDRS III (TEMPO study; Class I [11,12]).

Table 1 Levels of recommendation for the treatment of early PD

	Level of recommendation	
Therapeutic interventions	Symptomatic control of parkinsonism	Prevention of motor complications
Levodopa	Effective (level A)	Not applicable
Levodopa CR[e]	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]	Effective (level A)	Not available
Ropinirole	Effective (level A)	Effective (level A)
Ropinirole CR[e]	Effective (level A)	No recommendation[c]
Rotigotine[d]	Effective (level A)	No recommendation[c]
Selegiline	Effective (level A)	Ineffective (level A)
Rasagiline	Effective (level A)	No recommendation[c]
Entacapone[f]	No recommendation[c]	Ineffective (level A)
Tolcapone[f]	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]Ergot derivates cannot be recommended as a first-line treatment because of the risk of valvular heart disorder.
[c]No recommendation can be made because of insufficient data.
[d]Transdermal patch.
[e]Controlled release.
[f]*Entacapone* and *tolcapone* should always be given with levodopa. Because of hepatic toxicity, *tolcapone* is not recommended in early PD.

Table 2 Practical recommendations for the treatment of early untreated PD

The choice of drug depends on the impact of improving motor disability (better with levodopa) compared with the risk of motor complications (more common in younger patients, delayed by agonists) and neuropsychiatric complications (more common in older and cognitively impaired patients; greater with agonists)
Options include the following:
MAO-B inhibitor (selegiline, rasagiline) (Level A)
Oral or transdermal dopamine agonist. Pramipexole, piribedil, ropinirole and rotigotine are effective (Level A). Initial treatment with an agonist can be recommended in younger patients (GPP). Ergot derivatives are not recommended as first-line medication because of the risk of fibrotic reactions
Levodopa is the most effective symptomatic drug (Level A). Controlled-release formulations or adding entacapone is not effective in the delay of motor complications (Level A)
Amantadine or an anticholinergic (Level B)
Rehabilitation: because of the lack of evidence in early-stage disease, a recommendation cannot be made

Table 3 Practical recommendations for the adjustment of initial therapy 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, a stage will come when there is a requirement for adding levodopa or a dopamine agonist (GPP)
Patients on dopaminergic therapy
If on dopamine agonist therapy:
Increase the dose (GPP)
Switch between agonists (Level C)
Add levodopa (GPP)
If on levodopa:
Increase the dose (GPP)
Add an agonist (GPP)
Add a COMT inhibitor (GPP)
Patients with disabling tremor
If significant tremor persists:
Anticholinergics (GPP)
Clozapine (Level B)
Beta-blockers (propanolol)
Deep brain stimulation

In the ADAGIO study (Class I [13]; early versus 9 months delayed start of *rasagiline*), the primary endpoint (combined outcome targeting disease modification) was reached for 1 mg, but not for 2 mg [13]. The result is considered compatible with the concept that 1 mg/day *rasagiline* is possibly efficacious for disease modification.

Levodopa
The only placebo-controlled study is inconclusive regarding disease modification (Class I [14]). Mortality studies suggest improved survival (Class III [15]).

Dopamine agonists
There is no robust evidence of disease modification (Class I [9,16–19]).

Anticholinergics, amantadine, catechol-O-methyltransferase (COMT) inhibitors
No studies available.

Drugs without symptomatic effect
Riluzole (Class II [20]), *coenzyme Q10* (Class II [21]), *glial-derived neurotrophic factor* (Class II [22]) and *vitamin E* (Class I [6]) did not demonstrate disease-modifying effects.

Symptomatic pharmacotherapy of parkinsonism (Table 3)

Anticholinergics
Anticholinergics were the first drugs for the treatment of PD.

Monotherapy. Three Class II trials found anticholinergic monotherapy more effective than placebo in improving motor function (*bornaprine* [23] and *benzhexol* [24,25]). *Biperiden* was as effective as *apomorphine* for parkinsonian tremor (Class III [26]). Two systematic reviews concluded that anticholinergics have a small motor effect, but that evidence for a specific effect on tremor is inconclusive [27,28].

Adjunctive therapy. Class II studies of *trihexyphenidyl* [29], *benzotropine* [30] and *bornaprine* [31] in *levodopa*-treated patients and two systematic reviews conclude that there is a minor effect on PD symptoms and that tremor-specific data are inconclusive [27,28].

Prevention of motor complications. No studies available.

Safety. The clinical use of anticholinergics is limited by cognitive and neuropsychiatric side effects (Class IV [32]).

Amantadine
Amantadine blocks NMDA glutamate receptors and may have an anticholinergic effect and release presynaptic dopamine stores.

Monotherapy. Class II studies [24,33–35] and systematic reviews [28,36] concluded that there is an improvement of parkinsonism.

Adjunctive therapy. Addition of *amantadine* to anticholinergics was superior to placebo (Class II [37,38]). *Amantadine* was beneficial as an adjunct to *levodopa* (Class II [39,40]). Two systematic reviews [28,36] also suggest that *amantadine* is probably effective.

Prevention of motor complications. No studies available.
Safety. Side effects include dizziness, anxiety, insomnia, vomiting, oedema, headache, nightmares, ataxia,

confusion/agitation, constipation/diarrhoea, anorexia, xerostomia and livedo reticularis [<5%; 28].

Levodopa

Levodopa acts through conversion to dopamine and is routinely combined with a decarboxylase inhibitor (benserazide/carbidopa).

Standard levodopa formulation

Monotherapy. The efficacy of *levodopa* is well accepted [28,41]. A Class I trial confirmed a dose-dependent significant reduction in UPDRS scores versus placebo [14]. Its symptomatic effect proved better than *ropinirole* (Class I [18]), *pramipexole* (Class I [42]), *pergolide* (Class I [19,43]), *lisuride* (Class III [44]) and *cabergoline* (Class I [45]).

Adjunctive therapy. Supplementation of *levodopa* to other antiparkinsonian medications in stable PD is common clinical practice to improve symptomatic control (GPP).

Prevention of motor complications. Shortening of dose intervals and reducing individual doses may postpone the emergence of motor complications (GPP).

Safety. Adverse effects include motor complications; risk factors include younger age, disease duration and *levodopa* dose [41,46,47]. Neuropsychiatric complications are rare in *de novo* patients [41,46]. Gastrointestinal and cardiovascular dysfunction may occur [28,41,46–48].

Controlled-release (CR) levodopa formulations

Monotherapy. *Standard* and *CR levodopa* induce similar motor control in patients with *de novo* PD (Class I [49]) and in more advanced patients without motor fluctuations (Class I [50]).

Prevention of motor complications. *CR levodopa* does not delay motor complications compared with *standard levodopa* (Class I [49,51,52]).

MAO-B inhibitors

Selegiline and *rasagiline* inhibit monoamine oxidase isoenzyme type B, preventing the breakdown of dopamine [53]. Unlike oral *selegiline*, buccal selegiline and *rasagiline* are not metabolized to amphetamine.

Monotherapy. Five of six studies (Class I and II [6,8,10,54–56]) and a meta-analysis [57] concluded that there is a small symptomatic effect of *selegiline*.

Two large placebo-controlled trials with *rasagiline* in early PD (Class I [11–13]) showed a modest benefit.

Adjunctive therapy. No consistent beneficial effect was demonstrated in studies (Class I [58–62]) for the addition of *selegiline* to other antiparkinsonian therapies in non-fluctuating patients. There are no studies with *rasagiline*.

Prevention of motor complications. *Selegiline* has shown no effect in preventing motor complications (Class I [63]; Class II [64,65]). No studies are available with *rasagiline*.

Safety. Dopaminergic adverse reactions may occur. The risk of tyramine-induced hypertension ('cheese effect') is low [66]. MAO-B inhibitors carry a small risk of serotonine syndrome, particularly when combined with other serotonergic agents.

COMT inhibitors

Catechol-O-methyltransferase inhibitors reduce the metabolism of *levodopa*, extending its plasma half-life and prolonging its action.

Monotherapy. Not applicable (COMT inhibitors are always given with *levodopa*).

Adjunctive therapy. Trials (Class I and II) with *tolcapone* [67,68] and *entacapone* [69,70] showed a small benefit, mostly in UPDRS part II (activities of daily living), but the results were not consistent across endpoints.

Levodopa/carbidopa/entacapone showed borderline significance when compared with *levodopa*/*carbidopa* alone in UPDRS parts II and III in patients with no or minimal fluctuations [71]. In the FIRST-STEP study [72], *levodopa*/*carbidopa*/*entacapone* was compared with *levodopa*/*carbidopa* in patients *with de novo* PD. A significant difference was present in combined UPDRS II and III, but not in UPDRS III (Class I [72]).

Prevention of motor complications. FIRST STEP (Class I [72]) assessed as secondary endpoints the occurrence of motor complications, and no difference was found between two arms [72]. STRIDE-PD (Class I [73]) compared *levodopa*/*carbidopa*/*entacapone* and *levodopa*/*carbidopa,* using the same levodopa target dose (100 mg four times daily) in both arms. Time to onset of dyskinesia was significantly shorter in the *levodopa*/*carbidopa*/*entacapone* group. There was no difference in wearing-off [73].

Safety. COMT inhibitors induce dopaminergic reactions. Diarrhoea occurs in 3–5% of patients 2–3 months after initiation and may require discontinuation. *Tolcapone* can rarely increase liver enzymes, and postmarketing surveillance reported a few cases of fatal hepatotoxicity. The European Medicines Agency lifted the suspension of *tolcapone* for patients who fail to respond to other COMT inhibitors, but imposed strict liver function tests [74].

Dopamine agonists

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

Apart from *apomorphine* and *rotigotine*, which are used via the subcutaneous or transdermal routes, respectively [75,76], all other agonists are used orally. Once-daily controlled-release formulations of *pramipexole* and *ropinirole* are now available [77,78].

Monotherapy. *Agonists versus placebo*. *Dihydroergocryptine* [79], *pergolide* [80], *pramipexole* [81,82], *ropinirole* [83], *piribedil* [84] and *rotigotine* [85–87] are effective in early PD (Class I). *Bromocriptine* and *cabergoline* are probably effective (Class II and III [45,88]) [89,90]. *Lisuride* is possibly effective (Class IV [44]).

A randomized study of *pramipexole prolonged-release* once-daily versus *standard pramipexole* and placebo showed similar efficacy and tolerability in the two *pramipexole* arms [78].

Agonists versus levodopa. *Levodopa* is more efficacious than any oral dopamine agonist. The proportion of patients able to remain on agonist monotherapy falls progressively to < 20% after 5 years (Class I: *bromocriptine* [65,89]), *cabergoline* [90], *pergolide* [19], *pramipexole* [91]) and *ropinirole* [17]) [92].

There are no studies assessing whether the strategy to start with an agonist and to add *levodopa* later (Class II: *bromocriptine* [93], *lisuride* [94]) or to combine an agonist with *levodopa* within the first months of treatment is preferable.

Agonists versus agonists. From the limited data available (Class II: *bromocriptine* versus *ropinirole* [95,96]; Class III: *bromocriptine* versus *pergolide* [97]), the clinical relevance of any reported differences between agonists remains questionable. *Ropinirole prolonged release* was shown to be non-inferior to *ropinirole immediate release* [77], whilst this was not demonstrated for *rotigotine* versus *ropinirole* (Class I [85]).

Agonists versus other antiparkinsonian medications. No studies available.

Adjunctive therapy. *Agonists versus placebo*. Most agonists are effective in improving parkinsonism in patients already treated with *levodopa* (*apomorphine* [98], *bromocriptine* [99,100], *cabergoline* [101], *pergolide* [102], *piribedil* [103], *pramipexole* [104–106], *ropinirole* [107] and *rotigotine* [108]) (Class I). Class II evidence is available for *dihydroergocryptine* [109] and *lisuride* [94].

Agonists versus agonists. Several Class I and II studies have compared the symptomatic effect of two different dopamine agonists (*bromocriptine* as comparator) on parkinsonism when given as an adjunct to *levodopa* (*cabergoline* [110], *lisuride* [111,112], *pergolide* [97,113,114], *pramipexole* [100], *piribedil* [115], *rotigotine* [116] and *ropinirole* [117]). Methodological factors limit the conclusions from these studies.

An overnight switch from one agonist to another is sometimes considered in clinical practice (Class IV [118–126]). *Ropinirole* and *pramipexole* can be switched overnight from immediate- to prolonged-release formulation (Class I [77]) [127].

Agonists versus other antiparkinsonian drugs. *Bromocriptine* [128] and *pergolide* [129] have been compared with *tolcapone* (Class II), without significant difference in motor improvement.

Prevention of motor complications. *Agonists versus levodopa*. Class I trials demonstrate that early agonist use can reduce the incidence of motor complications versus *levodopa* (*cabergoline* [90,130], *pramipexole* [91], *pergolide* [19], *ropinirole* [17,18]). Similar conclusions were reported with *bromocriptine* (Class II [65]) [89,131]. Conflicting results have been reported with *lisuride* [44,94]. Long follow-up (6–15 years) suggests little difference in outcome between patients initially randomized to an agonist (*bromocriptine*, *pramipexole*, *ropinirole*) as opposed to *levodopa* [92,132].

A randomized study compared the addition of *ropinirole prolonged release* to increased doses of *levodopa* in patients not optimally controlled with *levodopa* to evaluate time to onset of dyskinesia (Class I [133]). Three per cent of the *ropinirole prolonged-release* group and 17% of the *levodopa* group developed dyskinesia. The time to onset of dyskinesia was significantly delayed in the *ropinirole* group.

Agonists versus agonists. There is no available indication that one agonist might be more efficacious than another in delaying time to motor complications. The only published Class II comparison (*ropinirole* versus *bromocriptine* [96]) did not show any difference in dyskinesia at 3 years.

Agonists versus other antiparkinsonian drugs. No studies available.

Safety. Hallucinations, somnolence and leg oedema are more frequent with some agonists than with *levodopa* (Class I [17,42,130,134,135]). The risk of pleuropulmonary/retroperitoneal and heart valve fibrosis is greater with ergot agonists [136,137]. Impulse control disorders have recently been identified as an adverse

Table 4 Recommendations for the treatment of motor complications in PD

Motor fluctuations
Wearing-off (end-of-dose akinesia, predictable ON–OFF)
Adjust levodopa dosing: adjustments in the frequency of dosing may attenuate wearing-off (GPP)
Add COMT or MAO-B inhibitors: no recommendations can be made on which should be chosen first – all reduce OFF time by about 1–1.5 h/day. The only direct comparison (Level A) showed no difference between entacapone and rasagiline. *Tolcapone*, although more effective than entacapone, is potentially hepatotoxic and only recommended in patients failing on other medications
Add dopamine agonists: non-ergot dopamine agonists are first-line compounds. Dopamine agonists reduce OFF time. None has proven superior, but switching from one agonist to another can be helpful (Level B/C)
CR levodopa: may improve wearing-off (Level C) and night-time akinesia (GPP)
Add amantadine or an anticholinergic: the addition of an anticholinergic (in younger patients) or amantadine may improve symptoms (GPP)
Severe motor fluctuations
Deep brain stimulation of the STN or the GPi is effective against motor fluctuations and dyskinesia (Level A), but because of risk for adverse events, the procedure is only recommended for patients below the age of 70 without major psychiatric or cognitive problems
Subcutaneous apomorphine as penject (Level A) or pump (Level C)
Intrajejunal levodopa/carbidopa enteric gel administered through percutaneous gastrostomy (Level C)
Unpredictable ON–OFF
DBS of the STN is effective (Level A)
In studies of treatment for wearing-off, patients with unpredictable ON–OFF were either not included or uncommon. Therefore, insufficient evidence exists to conclude whether the results are valid for unpredictable ON–OFF
The strategies described for dyskinesia and wearing-off should be considered (GPP)
For delayed ON, dispersible levodopa and subcutaneous injections of apomorphine have some value (Level C)
Reduction or redistribution of dietary proteins may be helpful, more practical approach is to take levodopa on an empty stomach about 1 h before, or at least 1 h after, each meal (Class IV)
Freezing
Options for OFF freezing are the same as for wearing-off
Freezing during ON often does not respond to dopaminergic strategies
Visual or auditory cues are empirically useful for facilitating the start of motor acts (Level C)
Dyskinesias
Reduce levodopa dose, at the risk of increasing OFF. The latter can be compensated for by increasing the number of doses or a dopamine agonist (Level C)
Discontinue/reduce MAO-B or COMT inhibitors (GPP), at the risk of worsening wearing-off
Amantadine (Level A) (200–400 mg/day)
DBS of the STN allows reduction in dopaminergic treatment (Level A). *GPi stimulation* may reduce severe dyskinesia (Level A)
Add atypical antipsychotics, *clozapine* (Level C) or quetiapine (Level C). C*lozapine* is associated with potential serious adverse events (agranulocytosis, myocarditis) (GPP)
Apomorphine continuous subcutaneous infusion allows reduction of levodopa (Level C)
Intrajejunal levodopa infusion (Level C)
Biphasic dyskinesia
Biphasic dyskinesias can be very difficult to treat and have not been studied in specific Class I–III studies
STN-DBS is effective (Level A)
The strategies described for peak-dose dyskinesias can be considered (GPP)
Another option is increasing the size and frequency of levodopa doses, at the risk of increasing peak-dose dyskinesia
Larger, less frequent doses may give more predictable responses (GPP)
Apomorphine and intrajejunal levodopa infusion can be tried (Level C)
Off-period and early-morning dystonias
Strategies for wearing-off can be applied (GPP)
Additional doses of levodopa or dopamine agonist at night may be effective (GPP)
DBS of STN or GPi (Level A)
Botulinum toxin can be employed in OFF-period and early-morning dystonia (GPP)

reaction to dopamine agonists (5–15%) [138]. Risk factors include personality traits and younger age [138,139].

Interventions for the symptomatic control of motor complications (Table 4)

Pharmacological interventions

Levodopa

Controlled-release levodopa has prolonged daily ON time in a minority of studies [140,141], but the improvement is often only minor. No Class I study shows long-lasting improvement.

Alternative formulations and delivery routes

Dispersible levodopa significantly shortens time to peak plasma levels compared with *standard levodopa* (Class III [142]).

A randomized study showed that *levodopa methylester/carbidopa* induced a faster ON than *standard levodopa* (Class II [143]), with similar safety profiles. A large double-blind study found no differences between *etilevodopa/carbidopa* and *standard levodopa* (Class I [144]).

Continuous duodenal levodopa infusions significantly increased ON time (Class III [145]). *Continuous intrajejunal infusion of levodopa/carbidopa gel* resulted in significant motor improvement during ON and decreases in OFF time, dyskinesia and median total UPDRS score (Class III [145,146]), but technical problems are frequently encountered (Class III [147,148]).

Dopamine agonists

Most dopamine agonists have been shown to reduce OFF time, including *pergolide* [102], *pramipexole* [99,100], *ropinirole* [149,150], *ropinirole prolonged release* [151], *rotigotine* [116,152] and *apomorphine* as intermittent subcutaneous injection (Class I [98,153]) and continuous infusion (Class IV [75,154,155]), *bromocriptine* [99,156,157], *cabergoline* (Class II [101]), *lisuride* and *piribedil* (Class IV). Class II–III trials showed no major differences amongst agonists [99,110,112]. The same was true when comparing *bromocriptine* [128] or *pergolide* [129] to *tolcapone* (Class II), or *cabergoline* to *entacapone* (Class I).

High doses of dopamine agonists might allow a reduction in *levodopa*; consequently, it might lessen dyskinesias (Class IV [75,158–162]).

There are no randomized studies comparing *apomorphine* infusion, *levodopa* infusion and deep brain stimulation (DBS).

COMT inhibitors

For *entacapone,* the conclusion from four studies was an OFF time reduction of 41 min/day (95% CI 13 min, 1 h 8 min) compared with placebo (Class I [163]), which is similar to *rasagiline* (Class I [164]). *Entacapone* demonstrated long-term efficacy [165] and improved ADL in fluctuating patients (Class I [166]). Most trials showed improved UPDRS motor scores. Dyskinesias occurred more frequently with *entacapone* than with placebo.

Class I studies with *tolcapone* demonstrated reduced OFF time [167–170]. The effect size of tolcapone and dopamine agonists appears similar (Class II [128,129,171]), but these studies lacked the power for definite conclusions [172].

In a double-blind study, patients with motor fluctuations on 'optimized' *levodopa*/*entacapone* were switched to *levodopa*/*tolcapone*. There was a tendency for enhanced efficacy, especially in marked fluctuations [173].

Amantadine

One study found that *amantadine* significantly decreased OFF time (Class I [174]), whereas another small study found no significant differences (Class I [175]). Two studies showed that *amantadine* significantly reduced dyskinesias during a *levodopa* challenge test (Class I [175,176]).

During 3 weeks of *amantadine*, dyskinesia was reduced by 60%, with a similar effect at 1 year [177]. A randomized withdrawal study in patients who had been on *amantadine* for at least 1 year showed significant dyskinesia worsening only in the patients switched to placebo (Class I [178]).

Intravenous *amantadine* improved dyskinesias in an open-label [179] and one placebo-controlled trial [180].

MAO-B inhibitors

Short-duration studies showed motor improvement with *selegiline* but no consistent effect on OFF time (Class I, II [181–183]). Orally soluble *selegiline* may reduce OFF time, although evidence is not consistent (Class I [184,185]). *Rasagiline* significantly reduces OFF time by 0.8–0.9 h/day (Class I [164,186]), a magnitude similar to *entacapone* [164].

MAO inhibitors may increase or provoke dyskinesia [64,164,181,186], which may be counteracted by decreasing *levodopa*.

Functional neurosurgery

Parkinson's disease surgery involves lesioning or stimulating nuclei or fibre connections of the basal ganglia loops.

Pallidotomy

Unilateral pallidotomy is efficacious (Class I [187], Class II [188–191]). Improvement at 1 year is greater with bilateral STN stimulation than with unilateral pallidotomy. Contralateral dyskinesia reduction is 50–80% (Class III [188,191]). Symptomatic infarction occurred in 3.9%, and mortality was 1.2%. Frontal lobe functions, speech and depression may deteriorate (Class III [192,193]).

Bilateral pallidotomy is rarely performed, and there is insufficient evidence on safety.

Thalamotomy

Thalamotomy improves tremor and rigidity but has no consistent effect on akinesia (Class IV [194]). Bilateral thalamotomy causes serious dysarthria in 30% [195].

DBS

BS Stimulation of the subthalamic nucleus (STN). In two large randomized 6-month trials versus best medical treatment, UPDRS motor scores improved by 54% for STN [196] and 28% for STN or pallidal stimulation [197]. A meta-analysis showed an average improvement of 53% [198]. *Levodopa*-equivalent dosage could be reduced by 50–60%. UPDRS motor scores were still improved after 5 years, although deteriorated compared with 1 year after surgery (Class III [199,200]). Dyskinesias were reduced by 54%. OFF time improved from 6.2 to 2 h or 5.7 to 3.4 h versus no change in the medical group [196,197]. Similar results were reported in a small study in patients with shorter disease duration [201]. These studies found improvements in quality of life of 20–24% in the DBS but not in the medical arms.

Uncontrolled studies reported dyskinesia reductions of 54–75% [196,197,202], maintained for up to 5 years (Class III [199,200]).

Long-term data show a slow deterioration of axial and akinesia scores [199].

Safety. Adverse effects occur in about 50% and are permanent in about 20%, and include confusion, intracerebral bleeding, stroke, seizures, infection and stimulator repositioning. Permanent severe morbidity or death reaches up to 4% [203]. In a study of 1100 patients, mortality was 0.4% and permanent morbidity was 1% [204]. The major risk factor is age. Neuropsychological tests were unchanged or deteriorated slightly, particularly verbal fluency and Stroop test [205–212]. Older or cognitively impaired patients are at greater risk [210–217]. Apathy, hypomania, psychosis, depression and anxiety occur in up to 10% [198,199,216,218,219]. Suicide was reported in 0.5% and suicide attempts in 0.9% [220]. Weight gain is found in 13%, speech and swallowing disturbances in 7.1%, and apraxia of eyelid opening in 1.5% [221]. Gait and balance disorder [199,219] may occur.

Stimulation of the posteroventral pallidum (GPi). Stimulation of the GPi may improve UPDRS motor score by 33% (Class II [202]). In Class II/III studies, OFF time reduction was 35–60% [198,202]. Long-term observations show no loss of effect on dyskinesias [222].

Two large randomized studies compared DBS of STN and GPi. Similar improvement compared with medical treatment was found following either surgery, although medication could be reduced to a greater extent with STN stimulation (Class I [197,223]).

Safety. A large randomized study found similar adverse events as with STN stimulation, although depression improved with GPi and worsened with STN stimulation, and visuomotor processing worsened with STN stimulation ([Class I [223]).

Stimulation of the thalamus. Stimulation of the thalamus improves tremor but not akinesia [224].

Foetal mesencephalic grafts

Despite encouraging Class IV reports [225,226], two Class I studies found no motor improvement, and serious dyskinesias occurred [227,228]. The procedure must, at present, be considered ineffective (Level A), but further investigation is probably warranted.

Non-pharmacological and non-surgical treatments

Cued training of sitting to standing transfers is effective (Class II [229]).

Cued gait training is probably effective for freezing of gait (Class II [230]). The combination with treadmill training induces greater benefits than cueing alone (Class II [231,232]).

A randomized study reported improvements with treatments aiming at large amplitude movements [233]. Another showed improved quality of life following a 6-week rehabilitation programme involving strategies such as exercise, speech therapy and gait training [234]. Physical activity likely reduces the risk of near-falls (Class II [235]). Several other recent randomized studies of physical therapy approaches have involved: treadmill training, downhill walking, qi gong, muscle exercises and specific sensory attention-focused exercises. Whilst these studies were mostly small, of short duration and lacked blinding, they consistently showed improvements in the treatment groups, suggesting that physical therapy is probably effective for motor function in PD (Class II [236–247]).

Reviews found insufficient evidence for the efficacy of speech and language therapy for dysarthria [248,249]. Lee Silverman Voice Therapy improves vocal intensity and phonation (Class II [250–252]). Pitch Limiting Voice Treatment also increases loudness, but limits vocal pitch and prevents strained voicing (Class IV [253]). Insufficient evidence exists for non-pharmacological therapy for dysphagia in PD [254,255].

Table 5 Recommendations for the treatment of neuropsychiatric problems in PD

Dementia
Discontinue potential aggravators: anticholinergics (Level B), amantadine (Level C), tricyclic antidepressants (Level C), tolterodine and oxybutynin (Level C) and benzodiazepines (Level C)
Add cholinesterase inhibitors: rivastigmine (Level A), donepezil (Level A) and galantamine (Level C). There may be idiosyncrasy in clinical response and side effects, so it is worth trying an alternative agent (GPP)
Add/substitute with memantine if cholinesterase inhibitors not tolerated or lacking efficacy (Level C)
Psychosis
Control triggering factors (GPP): treat infection and metabolic disorders, fluid/electrolyte balance and sleep disorder
Reduce polypharmacy (GPP): reduce/stop anticholinergic antidepressants and reduce/stop anxiolytics/sedatives
Reduce antiparkinsonian drugs (GPP): stop anticholinergics, stop amantadine, reduce/stop dopamine agonists, reduce/stop MAO-B and COMT inhibitors and lastly, reduce levodopa (GPP)
Add atypical antipsychotics: *clozapine* (Level A) (requires monitoring). Quetiapine is possibly useful (GPP). Olanzapine (Level A), risperidone (Level C) and aripripazole (GPP) can worsen parkinsonism (harmful)
Typical antipsychotics should not be used because they worsen parkinsonism
Add cholinesterase inhibitors rivastigmine (Level B) and donepezil (Level C)

There is insufficient evidence for the efficacy of occupational therapy in PD.

Interventions for the symptomatic control of non-motor problems (Table 5)

Neuropsychiatric complications

Dementia

The prevalence of dementia in PD (PDD) is 30–40% [256], although the cumulative incidence may reach 80% [257]. Several drugs, particularly anticholinergics, can impair cognition.

Cholinesterase inhibitors. Beneficial cognitive effects were reported with rivastigmine (Class I [258]), and – with less robust findings – donepezil (Class I [259–261]) and galantamine (Class III [262]). Adverse effects include nausea, tremor and urinary dysfunction.

Memantine. Two small randomized trials in patients with PDD or the closely related dementia with Lewy bodies (DLB) demonstrated (modest) benefit and good tolerability for memantine (Class I [263,264]). A randomized trial comparing memantine with placebo showed improvement in global clinical status and behavioural symptoms in patients with mild to moderate DLB but not PDD (Class I [265]).

Psychosis

Visual hallucinations occur in up to 40% of patients [266] and may precede dementia.

Interventions include withdrawal of offending drugs and treatment of infections or metabolic disorders.

Atypical antipsychotics. *Clozapine*. The efficacy of clozapine was documented in several placebo-controlled trials (Class I [267,268]). There was no motor worsening, and one study [267] found significant tremor improvement. Myocarditis is a rare but serious adverse event [170], as is leucopaenia (0.4%), which makes regular blood count checks mandatory. Side effects include sedation, dizziness, drooling and orthostatic hypotension.

Olanzapine. In two Class I studies, olanzapine was demonstrated to be ineffective for psychosis in PD [269,270] and to induce unacceptable motor worsening.

Quetiapine. Two randomized trials found no significant antipsychotic effect versus placebo (Class I [271]) [272]. These studies contradict results from another randomized [283] and several Class III studies and two randomized studies (Class II [273,274]) that found no difference between quetiapine and clozapine.

Risperidone improves psychosis (Class IV [275–278]) but is not recommended because of frequent motor worsening [279].

Cholinesterase inhibitors. In Class III/IV studies, rivastigmine [280,281] and donepezil [282,283] were suggested to improve psychosis. In a placebo-controlled PD dementia study, rivastigmine improved hallucinations (Class III [258,284]).

Depression

Depression occurs in about 40% of patients [285,286] and is a major determinant of quality of life [287,288].

Levodopa. There are no studies on the effects of chronic levodopa on depression in PD.

Dopamine agonists. A small 8-month study found improvement with *pergolide* and *pramipexole* (Class III [289]). A meta-analysis had suggested an antidepressant effect of *pramipexole* in PD, which was confirmed in a placebo-controlled study, where most of the improvement was attributable to a direct antidepressant rather than a motor effect (Class I [290]).

Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). Most studies were small and short term and preclude definite conclusions. SSRIs were suggested to be beneficial in uncontrolled studies (Class II–IV). However, in placebo-controlled studies, no SSRIs (paroxetine, citalopram, sertraline and fluoxetine) were clearly demonstrated to be effective, which may be owing to study design and large effect sizes on placebo [291].

One placebo-controlled study (Class II [292]) showed improvement on *nortriptyline*, and another found improvement with *desipramine* and *citalopram* (Class II [293]). A placebo-controlled trial in 52 patients found *nortriptyline* but not paroxetine to be efficacious [294]. A small, single-blind study found improvement with *sertraline* but not amitryptiline [295].

Newer antidepressants. A Class II study [296] found improvements with fluoxetine. There is insufficient evidence from a small study of *atomoxetine* [297].

Non-pharmacological interventions. There is insufficient data for electroconvulsive therapy [28], repetitive transcranial magnetic stimulation [298] and psychotherapy [299] in PD.

Autonomic dysfunction (Table 6)

Autonomic dysfunction is a common complication of PD but may also occur as a side effect of medication.

Table 6 Recommendations for the treatment of autonomic and sleep disorders in PD

Constipation
Increased intake of fluid and fibre is recommended (GPP)
Increased physical activity can be beneficial (GPP)
Polyethylene glycol solution (macrogol) is recommended (Level A)
Fibre supplements such as psyllium (Level B) or *methylcellulose* and osmotic laxatives (e.g. lactulose) (GPP)
Short-term irritant laxatives for selected patients
Dysphagia
Optimization of motor control
Speech therapy for assessment, swallowing advice and instrumental investigations if needed
Videofluoroscopy in selected cases to exclude silent aspiration
Enteral feeding options (short-term nasogastric tube or percutaneous endoscopic gastrostomy)
Daytime somnolence and sudden onset of sleep
Assessment of nocturnal sleep disturbances (GPP)
Improve nocturnal sleep by reducing akinesia, tremor and urinary frequency (GPP)
Recommendation to stop driving (GPP)
Reduce/discontinue sedative drugs (GPP)
Decrease dopaminergic drugs (mainly dopamine agonists; GPP)
All dopaminergic drugs may induce daytime somnolence
Switch to other dopamine agonist (GPP)
Add modafinil (Level B)
Add other wake-promoting agents like methylphenidate (GPP)
Orthostatic hypotension
Avoid aggravating factors such as large meals, alcohol, warm environment, volume depletion, diuretics, antihypertensive drugs, tricyclic antidepressants, nitrates and alpha-blockers used to treat prostatic hypertrophy. Dopaminergic drugs may induce orthostatic hypotension
Increase salt intake
Head-up tilt of the bed at night (30–40°) may be helpful
Wear waist-high elastic stockings and/or abdominal binders
Exercise as tolerated
Introduce counter manoeuvres (leg crossing, toe raising, thigh contraction)
Add midodrine (Level A)
Add fludrocortisone (GPP: possibly effective, but note side effects)
Urinary disturbance
When symptoms appear suddenly: exclude urinary tract infection
Nocturia: reduce intake of fluid after 6 pm. Sleep with head-up tilt of bed to reduce urine production
Night-time dopaminergic therapy should be optimized (GPP)
Use anticholinergic drugs (GPP): trospium chloride (10–20 mg 2–3 times daily) and tolterodine (2 mg twice daily). Trospium is less apt to penetrate the blood–brain barrier. Cognition may worsen
Botulinum toxin type A injected in the detrusor muscle

Orthostatic hypotension

Midodrine is a peripheral alpha-adrenergic agonist. Two Class II studies that included PD and other causes of neurogenic orthostatic hypotension revealed a significant increase in standing blood pressure [300,301]. Side effects include supine hypertension (4%) and paraesthesias [301].

Fludrocortisone enhances renal sodium reabsorption and potassium excretion and increases blood volume and cardiac output. A Class IV study in patients with PD showed increased systolic pressure upon standing and disappearance of orthostatic symptoms [302]. In a small trial (Class III [303]), fludrocortisone and domperidone improved scores. Hypertension, hypokalaemia and ankle oedema are side effects.

Dihydroergotamine, etilefrine, indomethacin, yohimbine, L-DOPS (L-threo 3,4-dihydroxyphenylserine), desmopressin, pyridostigmine and erythropoietin. Insufficient evidence is available in orthostatic hypotension in PD.

Urinary disturbance

Most patients with PD develop urinary problems, including urgency, frequency and nocturia. The most common disturbance is detrusor hyperactivity. Pronounced incontinence is related to late-stage disease. Urology referral is recommended, at least in cases of incontinence or lacking treatment response (GPP).

Dopaminergic drugs (*apomorphine*, *levodopa*) may improve urodynamic properties, at least in de novo PD (Class IV [304], Class III [305–309]). *Apomorphine* reduced bladder outflow resistance (Class III [306]).

Peripherally acting anticholinergics improve overactive bladder [231], but there are no placebo-controlled studies. Dry mouth, constipation and cognitive adverse events are a concern.

Intranasal desmopressin spray improved nocturia in PD (Class IV [310]).

DBS may improve bladder capacity and voiding volumes, but does not influence bladder emptying (Class III [311,312]).

Intradetrusor injection of botulinum toxin type A induced clinical and urodynamic improvement in overactive bladder lasting several months, but there are no placebo-controlled studies (Class IV [312,313]).

Gastrointestinal motility

Dysphagia. Dysphagia relates to disease severity and may cause silent aspiration, asphyxia, aspiration pneumonia, malnutrition and dehydration. *Levodopa* and *apomorphine* can improve early phases of swallowing but might reduce swallowing efficiency (Class III [314–317]). Rehabilitative treatments and food/drink modifications can be effective in some patients (Class III [318–321]). A percutaneous gastrostomy may become necessary.

Gastric dysfunction. Gastric emptying is often delayed and may cause nausea, vomiting, postprandial fullness and pain. Delayed drug absorption may lead to 'delayed' or 'no ON'. Domperidone accelerates gastric emptying and reduces dopaminergic gastrointestinal symptoms (Class II–IV [322–325]). Mosapride, a 5-hydroxytryptamine type 4 (5-HT4) agonist, improved gastric emptying (Class III [326]). Ondansetrone may be used; metoclopramide, cinnarizine and prochlorperazine can worsen parkinsonism and should be avoided (GPP).

Constipation. Constipation is the most common gastrointestinal symptom in PD. Anticholinergics can worsen constipation (GPP).

Psyllium increased stool frequency (Class II [327]). A placebo-controlled study showed *macrogol* to be effective (Class I [328]).

Erectile dysfunction (ED)

Erectile dysfunction is more common in patients with PD compared with controls. Drugs associated with ED (e.g. alpha-blockers) or anorgasmia (e.g. SSRIs) should be discontinued. Dopaminergic therapy can have negative and positive effects.

Sildenafil was found to be efficacious (Class I [329]). Side effects may be transitory (headache, visual effects, flushing) or, occasionally, severe (hypotension, priapism, cardiac arrest).

Dopamine agonists. In some patients *apomorphine* injections (GPP) can improve ED (Class IV [330,331]). Nausea, yawning and hypotension may occur.

Intracavernous injections of *papaverine* or *alprostadil* can be considered in selected patients (GPP).

Sleep disorders

Sixty–90% of patients complain of difficulties associated with sleep [332].

Daytime somnolence [333]. Using the Epworth Sleepiness Scale (ESS), the frequency reaches 33%, compared with 11–16% in a non-PD population [334]. Sudden-onset sleep episodes ('sleep attacks') occur in 3.8–20.8% [335,336].

Modafinil. Two of three small placebo-controlled Class II trials in PD [337–339] found small improvements in ESS [339], without benefit in other sleep-related outcomes [337–339].

Methylphenidate. An open-label study (Class III [340]) reported an improvement in the ESS.

REM sleep behaviour disorder (RBD). RBD is characterized by muscle activity during REM sleep enabling dream enactment, sometimes resulting in violent behaviours. RBD occurs in 25–50% of patients with PD. Two case series (Class IV [341,342]) suggested that *clonazepam* (0.5–2 mg) is efficacious. Clonazepam may lead to sedation, exacerbated obstructive breathing and increased risk of falling. Two open-label studies (Class III [343,344]) reported conflicting results with *pramipexole* for RBD in PD. Most antidepressants, especially *SSRIs* and *mirtazapine*, may worsen restless legs syndrome (RLS), PLM and RBD (Class IV [295]).

Nocturnal sleep problems. Nocturnal sleep problems include sleep fragmentation, nocturia, difficulty in turning over in bed, RLS, vivid dreams, hallucinations and dystonia [345–347].

Levodopa. Two placebo-controlled trials (Class II [348,349]) showed that *standard-* or *CR levodopa* at bedtime may improve akinesia, sleeping time and early-morning disability.

Dopamine agonists. A Class II [350] placebo-controlled trial demonstrated that *pergolide* worsened sleep efficiency and fragmentation. A small open-label trial showed that nocturnal *apomorphine* infusion (Class III [351]) reduced awakenings and improved nocturia and akinesia [116,151]. *Rotigotine, pramipexole* and *ropinirole* prolonged-release formulations improved sleep quality. Two small open-label studies (Class III [352,353]) reported improvements in early-morning mobility and sleep quality but aggravated fragmentation with *cabergoline* at bedtime.

Other pharmacological treatments. Improved sleep was reported in two Class II placebo-controlled studies [354,355]) with *melatonin* (50 and 3 mg), without relevant adverse events. Case series with *zolpidem* (Class IV [356]), a short-acting hypnotic, and *quetiapine* (Class IV [357]) suggested improved insomnia. Low-dose *clozapine* improved nocturnal akathisia and tremor (Class IV [358]). An open-label study (Class III [310]) reported fewer nocturnal voids with bedtime *desmopressin* (nasal spray). However, desmopressin is not advised in the elderly.

DBS. Open-label studies (Class III [358–363]) concluded that STN-DBS improves sleep duration and reduces akinesia, sleep fragmentation and early-morning dystonia.

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