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

M. Horstink\textsuperscript{a}, E. Tolosa\textsuperscript{b}, U. Bonuccelli\textsuperscript{c}, G. Deuschl\textsuperscript{d}, A. Friedman\textsuperscript{e}, P. Kanovsky\textsuperscript{f}, J. P. Larsen\textsuperscript{g}, A. Lees\textsuperscript{h}, W. Oertel\textsuperscript{i}, W. Poewe\textsuperscript{j}, O. Rascol\textsuperscript{k} and C. Sampao\textsuperscript{l}

\textsuperscript{a}Department of Neurology, Radboud University Medical Centre, Nijmegen, The Netherlands; \textsuperscript{b}Neurology Service, Hospital Clinic, Universitat de Barcelona, Spain; \textsuperscript{c}Department of Neurosciences, University of Pisa, Italy; \textsuperscript{d}Department of Neurology, Christian-Albrechts-University Kiel, Germany; \textsuperscript{e}Department of Neurology, Medical University of Warsaw, Poland; \textsuperscript{f}Department of Neurology, Palacky University, Olomouc, Czech Republic; \textsuperscript{g}Department of Neurology, Stavanger University Hospital, Norway; \textsuperscript{h}Reta Lila Weston Institute of Neurological Studies, London, UK; \textsuperscript{i}Philips-University of Marburg, Centre of Nervous Diseases, Marburg, Germany; \textsuperscript{j}Department of Neurology, Innsbruck Medical University, Austria; \textsuperscript{k}Clinical Investigation Centre, Departments of Clinical Pharmacology and Neurosciences, University Hospital, Toulouse, France; and \textsuperscript{l}Laboratório de Farmacologia Clínica e Terapêutica e Instituto de Medicina Molecular, Faculdade de Medicina de Lisboa, Portugal

Keywords:
management guideline, neurosurgery, Parkinson’s disease, pharmacotherapy, review.

Received 8 March 2006
Accepted 13 March 2006

Correspondence: Dr M. W. I. M. Horstink, Department of Neurology, Radboud University Medical Centre, P.O Box 9101, 6500 HB Nijmegen, The Netherlands (tel.: +31 24 361 5202; fax: +31 24 354 1122; e-mail: m.horstink@neuro.umcn.nl).

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

Methods

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

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

Interventions for the symptomatic control of motor complications

Motor complications are divided into motor fluctuations and dyskinesia. With advancing PD, patients may begin to fluctuate in motor performance, i.e. they experience a wearing-off (end-of-dose) effect because the motor improvement after a dose of levodopa becomes reduced in duration and parkinsonism reappears. However, wearing-off can also manifest in symptoms such as depression, anxiety, akathisia, unpleasant sensations and excessive sweating. Besides fluctuations, dyskinesias may occur, which are involuntary movements in response to levodopa and/or dopamine agonist intake. Most dyskinesias emerge at peak-dose levels and are typically choreiform, but may involve dystonia or myoclonus. A minority of patients may experience diphasic dyskinesia, in which they exhibit dyskinesia at the beginning of turning ON and/or at the beginning of turning OFF, but have different and less severe or absent dyskinesias at the time of peak levodopa effect. Eventually, patients may begin to experience rapid and unpredictable fluctuations between ON and OFF periods, known as the ON–OFF phenomenon.
The diagnosis and therapeutic management of motor complications depends on detecting the type of movement involved and the time of day when they occur in relation to the timing of levodopa and the resulting ON–OFF cycle. Diaries may be helpful in assessing this course over time. It must be noted that many patients prefer being ON with dyskinesia rather than OFF without dyskinesia.

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

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

During 3 weeks of steady-state infusion with amantadine, dyskinesia was reduced by 60%, with a similar effect observed at 1-year follow-up (class I: [1,3]). In patients on chronic levodopa, oral amantadine significantly reduced the dyskinetic effect of an orally administered acute levodopa/decarboxylase inhibitor challenge of 1.5 times their usual dose (class I: [4]). Similar results were found by Luginger et al. [2] (class I).

However, the antidyskinetic effect of oral amantadine may only last for 3–8 months, according to one study (class I: [5]), in which, several subjects experienced a rebound in dyskinesia severity after discontinuation.

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

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

Selegiline might increase or provoke dyskinesia in levodopa-treated patients, but this was not the primary outcome measure in the studies referred to (class I: [6,12]). Golbe et al. [8] noted that dyskinesia abated after levodopa was reduced (class I). Rasagiline increased dyskinesia in one study [11], whereas it had no significant impact in another [10]. The reason for this difference remains unknown, as levodopa dose adjustment was allowed equally in both trials.

Catechol-O-Methyltransferase (COMT) inhibitors
Because of their mechanism of action, COMT inhibitors should always be given with levodopa.

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

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

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

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

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

Alternative levodopa formulations and delivery routes
In fluctuating PD, oral dispersible levodopa/benserazide significantly shortened time to peak plasma levels compared with the standard formulation (class III: [28]).
Continuous duodenal infusions of levodopa/carbidopa resulted in statistically significant increases in ON time (class III: [29]). Continuous intraduodenal infusion of levodopa/carbidopa enteral gel resulted in a significant improvement in motor function during ON time, accompanied by a significant decrease in OFF time and no increase in dyskinesia. Median total UPDRS score also decreased (class III: [30]).

**Dopamine agonists**

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

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

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

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

**Functional neurosurgery**

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

All surgical interventions for PD involve lesioning or stimulating nuclei or fibre connections of the basal ganglia loop (direct or indirect loop) [52]. Lesioning of these nuclei destroys the circuit, and continuous electrical stimulation is probably to reversibly block the neuronal activity in the loop.

**Pallidotomy**

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

**Adjunctive therapy of parkinsonism**

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

**Symptomatic control of motor complications**

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

**Safety**

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

**Deep brain stimulation**

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

**Stimulation of the posteroverentral pallidum**

Adjunctive therapy of parkinsonism. Pallidal DBS may improve the symptoms of advanced PD, as assessed by the UPDRS-Motor score, by 33% for study periods of up to 6 and 12 months (class II: [72]). Over time, deterioration occurs in some patients who are subsequently successfully reoperated on, with implantation of electrodes into the STN (class III: [67]).
Symptomatic control of motor complications. One of the most consistent effects of DBS upon the pallidum is the reduction of dyskinesias and the reduction of OFF time. In class II and III studies, the reduction in OFF time was shown to be 35–60% [67,72]. The few long-term observations available show no loss of effect on dyskinesias [69].

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

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

Stimulation of the subthalamic nucleus

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

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

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

Safety. In general, reviews [23,81] and those studies referred to below, show that adverse effects of DBS may occur in about 50% of patients, but are permanent in about 20% only. However, the severity of adverse events seldom warrants suspension of DBS. The occurrence of adverse effects related to the procedure i.e. acute confusion, intracerebral bleeding, stroke and seizures, or to device dysfunction, i.e. infection or stimulator repositioning, causing permanent severe morbidity or death, reaches up to about 4% (review: [81]).

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

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

Surgical treatments that are rarely used in the treatment of PD

Thalamotomy

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

Stimulation of the thalamus

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

Lesioning of the subthalamic nucleus

Lesioning of the STN has only been used in experimental protocols in small patient series with a high incidence of persistent dyskinesias (class III: [104,105]).
Therefore, presently, this technique is not recommended if STN DBS is an available option.

**Foetal mesencephalic grafts**

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

**Recommendations for the symptomatic control of motor complications**

**Motor fluctuations**

**Wearing-off**

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

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

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

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

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

**Unpredictable ON–OFF**

In the large studies of wearing-off, patients with unpredictable ON–OFF were either not included or constituted <5% of the total population. Therefore, insufficient evidence exists to conclude whether the results that are valid for wearing-off are also valid for unpredictable ON–OFF. There are only a few small studies specifically including patients suffering from unpredictable ON–OFF, although studies evaluating continuous dopaminergic stimulation also include patients suffering concomitantly from wearing-off and...
unpredictable ON–OFF. The same is true for concomitant dyskinesia, which frequently occurs during the ON phase of ON–OFF. Thus, there is insufficient evidence to conclude on specific strategies for ON–OFF, although the strategies described for dyskinesia and for wearing-off should be considered for unpredictable ON–OFF (good practice point).

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

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

Dyskinesias

Peak-dose dyskinesia

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

Biphasic dyskinesia

Biphasic dyskinesias can be very difficult to treat and have not been the subject of specific and adequate class I–III studies. Usually, the strategies described for peak-dose dyskinesias can also be considered for biphasic dyskinesia (good practice point). Another option is increasing the size and frequency of levodopa dose, at the risk of inducing or increasing peak-dose dyskinesia. This latter strategy can be helpful, generally transiently, in those cases without peak-dose dyskinesia, or where they are considered less disabling than the biphasic type. A further option could be larger, less frequent doses, to give a more predictable response, which would better enable patients to plan daily activities (good practice point).

Off-period and early morning dystonias

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

Freezing

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

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

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

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

Neuropsychiatric complications

Dementia

Dementia is a late feature of PD, found in about 30–40% of patients [117–121], with reported frequencies up to 78.2% [122]. Besides abnormalities in monoaminergic functions, another neurochemical brain change associated with dementia in PD is cortical cholinergic denervation (Reviews: [120,123]).
Interventions for the treatment of dementia in PD
Several drugs, particularly anticholinergics, can impair cognitive function and considering discontinuation of such drugs is recommended. Another possible intervention is therapy with cholinesterase inhibitors (see below).

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

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

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

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

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

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

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

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

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

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

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

Interventions for the treatment of depression in PD

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

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

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

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

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

Tricyclic antidepressants. This class of agents with amongst other things an anticholinergic effect is an established treatment modality in major depression. The only randomized placebo-controlled study dates back more than 20 years and is related to nortryptiline (titrated from 25 mg/day to a maximum of 150 mg/day) (class II: [168]), which showed a significant improvement over placebo, on a depression rating scale designed by the author. Recent evidence-based reviews [22,169] found little evidence supporting the use of tricyclic antidepressants in PD.

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

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

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

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

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

Two double-blind studies have assessed repetitive transcranial magnetic stimulation (rTMS) in PD depression. There was no difference between sham and effective stimulation with respect to depression and PD measures (class I: [177]). A class I study [178] found rTMS as effective as fluoxetine in improving depression at week 2 – an effect maintained to week 8. However, interpretation of this study is hampered by lack of a placebo.
Recommendations for the treatment of depression in PD
• Optimize antiparkinsonian therapy (good practice point).
• Tricyclic antidepressants (good practice point).
• SSRIs (good practice point). SSRIs are less probably to produce adverse effects than tricyclic antidepressants (good practice point).
• ‘New’ antidepressants – reboxetine, venlafaxine (no recommendation can be made).

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

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

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

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

Recommendations for the treatment of orthostatic hypotension in PD
• General measures:
  • avoid aggravating factors such as large meals, alcohol, exposure to a warm environment and drugs known to cause orthostatic hypotension such as diuretics or antihypertensive drugs. Levodopa and dopamine agonists may also induce orthostatic hypotension.
  • increase salt intake in symptomatic orthostatic hypotension.
  • head-up tilt of the bed at night, which may be helpful.
  • wear elastic stockings.
  • highlight postprandial effects. In some patients, hypotension occurs only postprandially. Warning the patient about this effect and taking frequent small meals may be helpful.

• Drug therapy:
  • Add midodrine (level A).
  • Add fludrocortisone (good practice point: possibly effective, but note side-effects).

Urinary disturbance
Interventions for the treatment of urinary incontinence in PD
Peripherally acting anticholinergics. Drugs with anticholinergic effects (oxybutynin, amytriptyline), anti-spasmodic agents (propiverine, tolterodine) and alpha-1 agonists (prazosin and derived drugs) have not been specifically evaluated in PD [22].

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

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

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

Interventions for the treatment of gastrointestinal motility problems in PD
Cisapride has been withdrawn from the market in several European countries because of its association with cardiac arrhythmias and death [184].

Domperidone. Domperidone blocks peripheral dopamine receptors, thus increasing gastric emptying. It reduces dopaminergic drug-related gastrointestinal symptoms in patients with PD (class II–IV: [185–188]).
Metoclopramide. Metoclopramide also blocks peripheral dopamine receptors. However, in contrast to domperidone, it crosses the blood–brain barrier and reduces nausea and vomiting [186] by blocking dopamine receptors in the area postrema. However, it can also increase parkinsonism [189–191], which is considered an unacceptable risk in patients with PD.

Recommendations for the treatment of gastrointestinal motility problems in PD
- Apply general measures for treating constipation. Diet, laxatives, etc.
- Reduce or discontinue drugs with anticholinergic activity (good practice point).
- Add domperidone (level B).

Erectile dysfunction

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

Alprostadil. Insufficient evidence.

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

Recommendations for the treatment of erectile dysfunction in PD
- Add sildenafil (level A).
- Add dopamine agonists. Apomorphine and pergolide (insufficient evidence, no recommendation can be made).

Statement of the probable time when the guidelines will need to be updated
No later than 2009.

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

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

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

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

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

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

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

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

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

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

A Friedman and P Kanovsky have nothing to declare.

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

Acknowledgements
The authors thank Prof Niall Quinn for his constructive criticism and comments on this manuscript. The authors thank Juliet George for helping with the preparation of the text and Karen Henley for secretarial assistance during earlier meetings. They also acknowledge the significant contribution of Dr Yaroslau Compte to the sections on dysautonomia, amantadine and anticholinergics.
Funding sources supporting the work: Financial support from MDS-ES, EFNS and Stichting De Regenboog (the Netherlands).

References


89. Dujardin K, Defevre L, Krystkowiak P, Blond S, Destee A. Influence of chronic bilateral stimulation of the


123. Zgaljardic DJ, Foldi NS, Borod JC. Cognitive and behavioral dysfunction in Parkinson’s disease: neuro...


175. Okabe S, Ugawa Y, Kanazawa I; Effectiveness of rTMS on Parkinson’s Disease Study Group. 0.2-Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson’s disease. Movement Disorders 2003; 18: 382–388.


