CHAPTER 15

Late (complicated) Parkinson's disease

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Methods

For background, search strategy, and method for reaching consensus, see Part I of these guidelines (Chapter 14).

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 choreatic, but may involve dystonia or – rarely – 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.

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Amantadine

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

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: [3]. Similar results were found by Luginger *et al.* [2] (Class I). During 3 weeks of stable oral amantadine, levodopa-dyskinesia was reduced by 60%, with a similar effect observed under long-term oral amantadine therapy at 1-year follow-up [4]. According to another study (Class I: [5] the antidyskinetic effect of oral amantadine may only last for 3–8 months, although several subjects experienced a rebound in dyskinesia severity after discontinuation.

Intravenous infusion of amantadine was employed for the treatment of levodopa-induced dyskinesias in one double-blind placebo-controlled [6] and two open-label trials [7], [8]. When in the later study amantadine was intravenously infused continuously for 3 days to bridge an oral levodopa 3 days withdrawal ('levodopa drug holidays'), a significant improvement of motor complications (motor fluctuations and dyskinesias) was observed for up to 4 months under reinstalled oral levodopa treatment without concomitant oral or i.v. amantadine.

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: [9–11]). Zydis selegiline, which dissolves on contact with saliva, reduces daily OFF time when used as adjunctive therapy with levodopa (Class I: [12]).

Rasagiline produced a significant reduction in OFF time in patients on levodopa (Class I: rasagiline 1 mg, −0.94 h/day [13] and rasagiline 1 mg, −0.78 h/day [14]). In the latter study, rasagiline achieved a similar magnitude of effect to the active comparator, entacapone, which reduced OFF time by 0.80 h/day (Class I: [14]).

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: [9, 15]). Golbe *et al.* noted that dyskinesia lessened after levodopa was reduced (Class I: [11]). Rasagiline increased dyskinesia in one study [13], whereas it had no significant impact in another [14]. The reason for this difference remains unknown, since levodopa dose adjustment was allowed equally in both trials.

COMT inhibitors

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

With entacapone the overall conclusion from four studies was a reduction in OFF time of 41 min/day (95% CI: 13 min, 1 h 8 min) as compared with placebo (Class I: [16]). Entacapone reduces mean daily OFF time in levodopa-treated patients by a similar extent to rasagiline (Class I: [14]). Entacapone also demonstrated long-term efficacy as shown in the meta-analysis of Class I studies and their open-label extensions [17] and was efficacious in terms of activities of daily living (ADL) in fluctuating patients (Class I: [18]). In the trials cited above, dyskinesias were more frequent with entacapone adjunct therapy than with placebo. In the majority of the trials, entacapone produced an improvement in Unified PD Rating Scale (UPDRS) motor scores.

Class I studies with tolcapone demonstrated that it was efficacious in reducing OFF time [19–22]. The effect size of tolcapone and dopamine agonists (bromocriptine, pergolide) may be similar (Class II: [23–25]), but these studies lacked the power to be fully conclusive [26].

In a double-blind 'switch study' PD patients with motor fluctuations on optimized 'levodopa plus entacapone therapy' were switched to 'levodopa plus tolcapone'. There was a tendency of tolcapone to offer enhanced efficacy, especially in PD patients with marked fluctuations [27].

Safety issue of tolcapone

Tolcapone rarely can elevate liver transaminases, and few fatal cases of liver injury have been reported. The European Agency for the Evaluation of Medicinal Products (EMEA) lifted the suspension of tolcapone for use in patients with motor fluctuations on levodopa who fail to respond to other COMT inhibitors, but imposed strict safety restrictions [26a]. Tolcapone can only be prescribed by physicians experienced in the management of advanced PD, with a recommended daily dose of 100 mg three times daily. Patients must have fortnightly blood tests for liver function in the first year, at four-weekly intervals for the next 6 months and, subsequently, every 8 weeks. Patients with abnormal liver function or a

history of neuroleptic malignant syndrome, rhabdomyolysis or hyperthermia have to be excluded.

For adverse events and further safety issues of COMT-inhibitors see Part I.

Levodopa

Immediate release (standard) levodopa is the most important component of pharmacotherapy in advanced PD. Based on its short half-life, dosing schedules may consist of up to eight, or even more, individual doses with additional dosing of immediate- or slow-release levodopa. The action of levodopa can be prolonged and enhanced when combined with a COMT-inhibitor and/or MAO-B-inhibitor. Due to its lower – compared with dopamine agonists – potency to induce hallucinations, levodopa is the drug of choice in advanced PD patients with cognitive impairment and dementia (see 'Non-motor problems, Dementia' section).

It is common practice to reduce the size of individual doses of levodopa in cases of peak-dose dyskinesia, whereas the dose interval is shortened in wearing-off ([28, 29]).

To reduce the occurrence of delayed ON, no ON, or reduced symptomatic effect due to 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: [28, 30]).

(a) Controlled-release (CR) 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 [28, 31–33]. Levodopa CR is preferably administered at bedtime or during the night to ease nocturnal akinesia (GPP).

(b) 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: [34]. A 4 weeks, double-blind, double-dummy study comparing levodopa methylester/carbidopa (melevodopa) with standard levodopa/carbidopa for the treatment of the afternoon OFF periods showed that melevodopa induced a faster ON than standard levodopa/carbidopa (Class II: [35]). Melevodopa had a similar safety profile to standard levodopa/carbidopa. A large double-blind study on 327 fluctuating patients demonstrated that etilevodopa/carbidopa, another form of soluble levodopa, did not differ from standard levodopa/carbidopa in total daily time to ON after levodopa dosing, in reducing response failures, or in decreasing total off time (Class I: [36]).

Continuous duodenal infusions of levodopa/carbidopa resulted in statistically significant increases in ON time (Class III: [37]). Continuous intrajejunal 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, or even a decrease, in dyskinesia. Median total UPDRS score also decreased (short-term, single randomised comparison to oral levodopa, Class III: [38]). Open-label trials have confirmed the beneficial effect of this therapy in very advanced PD patients in respect to reduced OFF time and – after several months – decreasing dyskinesia, but also have detailed the technical problems encountered in its long-term use in a substantial number of patients (Class III: [39]; [40]; [41]).

Dopamine agonists

Several dopamine agonists have been shown to reduce the duration of OFF episodes. There is Class I evidence for pergolide [42], pramipexole [43, 44], ropinirole [45, 46], ropinirole controlled-release [47], rotigotine transdermal patch [48, 49], and for apomorphine as intermittent subcutaneous injection (Class I: [50, 51]) or continuous infusion (Class IV: [52–54]. There is Class II evidence for bromocriptine [43, 55, 56] and cabergoline [57], and Class IV evidence for other agonists such as lisuride or piribedil ([28]).

The available comparative Class II–III trials showed no major differences between bromocriptine and other agonists such as cabergoline [58], lisuride [59], pergolide [60], and pramipexole [43]. The same was true when comparing bromocriptine [24] and pergolide [25], to the COMT inhibitor tolcapone (Class II), or cabergoline to entacapone (Class I: [61]).

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, due to their longer plasma elimination half-life and receptor occupancy. 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 [53, 62–64] or oral administration of high doses of pergolide [65] or ropinirole [66].

The continuous subcutaneous infusion of apomorphine and the intrajejunal infusion of levodopa are – as is deep brain stimulation – expensive and, to a different degree, invasive therapeutical options. Studies on a direct comparison on the efficacy and safety of apomorphine infusion, levodopa infusion, and deep brain stimulation are lacking.

For use of dopamine agonists in PD patients with dementia, see 'Non-motor problems, Dementia' section.

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 [67].

All surgical interventions for PD involve lesioning or stimulating nuclei or fibre connections of the basal ganglia loops (direct or indirect loop) [68]. Lesioning of these nuclei destroys the circuit, and continuous electrical stimulation is likely to reversibly block the neuronal activity in the loop.

In general the level I-evidence definition of the EFNS with blinded outcome assessments is difficult to achieve for surgical studies as blinding of the investigators remains often a fiction. Therefore, randomisation and adequate power of the studies are more imporant criteria.

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: [69–72]) and was found to be efficacious for the treatment of PD. According to one study (Class I: [73]) parkinsonian motor signs are more improved after 1 year with bilateral STN stimulation than with unilateral pallidotomy.

Symptomatic control of motor complications

The improvement of dyskinesia on the body side contralateral to pallidotomy is usually 50–80% (Class III: [69, 72, 74–78]).

Safety

Side effects with unilateral pallidotomy are generally limited, but the potential for severe complications due to 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: [70, 75]). Neuropsychological functioning is usually unaffected [79, 80], but frontal lobe functions and depression may show a modest deterioration (Class III: [81, 82]). Visual field defects were common in earlier series, but have decreased to <5% with modification of the surgical technique [83].

Deep brain stimulation (DBS)

Stimulation of the STN (reviews: [29, 84–87]; Class II: [88]) 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. Deep brain stimulation of the STN has been found to be superior to medical treatment in patients with advanced disease and motor fluctuations which can no longer be sufficiently treated medically in a large randomized study (Class II: [88]). STN-stimulation showed an improvement of 24% of quality of life, an improvement of motor fluctuations, and a 41% improvement of the motor score. In comparisons of STN- or GPi-DBS versus best medical treatment, DBS was found to be equally superior to medical treatment

(Class I: [89]). Both large studies compared 6 months' data. Data on long-term outcome show a slow deterioration of axial and akinesia scores with stable improvement of tremor and rigidity [90]. One small study found only a non-significant trend towards better efficacy of stimulation of STN over GPi. The trial was, however, underpowered [91]. Manual dexterity was equivalently improved by GPi and STN stimulation in a subgroup of patients of a prospective randomized trial [92]. The question wether STN or GPi-stimulation is superior is still open.

Stimulation of the posteroventral pallidum

Adjunctive therapy of parkinsonism Pallidal DBS may improve the symptoms of advanced PD, as assessed by the UPDRS-Motor score, by 33% for study periods of up to 6 and 12 months (Class II: [93]). Over time, deterioration occurs in some patients who are subsequently successfully reoperated on, with implantation of electrodes into the STN (Class III: [84]).

Symptomatic control of motor complications One of the most consistent effects of DBS on the pallidum is reduction of dyskinesias and of OFF time. In Class II and III studies, the reduction in OFF time was 35–60% ([84, 93]). The few long-term observations available show no loss of effect on dyskinesias [86].

Symptomatic control of non-motor problems Under stimulation, there is a mild but significant improvement in mood [94], 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 [84, 95–98]. A randomized comparison between stimulation of the GPi or the STN showed similar mild reductions in neuropsychological test performance for both targets, mainly for verbal fluency and working memory after unilateral and bilateral stimulation [99]. A 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 [86].

Stimulation of the subthalamic nucleus (STN)

Adjunctive therapy of parkinsonism In two large randomized trials of DBS versus medical treatment, the UPDRS-Motor score improved by 54% for STN stimulation [88] and 28% for STN- or GPi-stimulation [89], thereby confirming ealier uncontrolled data [93]. This is consistent with a meta-analysis of 20 studies, showing an average improvement of 53% [84]. Smaller controlled studies found similar results [72, 100, 101]. At the same time, the levodopa equivalence dosage could be reduced by 50–60%. UPDRS-Motor scores during stimulation were still improved by 54% after 5 years, although slightly deteriorated compared with 1 year after the operation (Class III: [90, 102]).

Quality of life is significantly better in patients undergoing DBS than medical treatment in advanced stages of the disease [89, 103].

Symptomatic control of motor complications Two Class I studies found an improvement of dyskinesias by 54% and likewise OFF-time improved from 6.2 to 2 h or 5.7 to 3.4 h respectively versus no change compared with the medically treated group [88, 89]. Similar results were obtained in uncontrolled studies [93]. Dyskinesias have been reduced by 54–75% [88, 89, 93, 104].

Two open randomized controlled studies (Class I and II: [88, 89]) have shown the superiority of STN stimulation over medical treatment for parkinsonian motor scores OFF medication. The UPDRS OFF-score was reduced by 41% or 35 %. OFF time and time in troublesome dyskinesia was reduced and sleep and ON time without troublesome dyskinesia was increased with STN stimulation after 6 months. Dyskinesia was still improved after 5 years (Class III: [90, 102]). Thus, STN stimulation is as effective in reducing dyskinesia as pallidotomy or pallidal stimulation.

A pilot study in 20 patients with earlier disease (mean disease duration 7 years) comparing STN-DBS and best medical treatment showed similar results as in the two large randomized studies [105].

Symptomatic control of non-motor problems Depression and anxiety scores improve at 6 and 12 months after the operation in a controlled study against medical treatment [106] as well as in open studies [90, 107–110]. However, verbal fluency and the Stroop test were found to be significantly worse in the DBS group versus the medically treated group [106]. See also safety section, below.

Disease-related quality of life was the primary or secondary outcome in large studies on advanced complicated PD over 6 months (Class I: [88, 89]) and in a small pilot trial on early complicated PD over 18 months (Class I: [105]). In all these studies quality of life was improved by 20–24% by stimulation and remained unchanged in the medical control group.

Safety In general, reviews [29, 104] and those studies referred to below, show that adverse effects of DBS may occur in about 50% of patients, but are permanent only in about 20%. 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: [104]). In a large observational study of more than 1,100 patients the mortality was found to be 0.4% and the permanent morbidity was 1% [111]. The major risk factor is age.

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 particularly verbal fluency and stroop test [80, 106, 108, 112–119]. Older patients or patients with moderate cognitive impairment prior to surgery may be at greater risk of cognitive deterioration [97, 114–116, 120]. Apathy, hypomania, psychosis, depression, anxiety, and emotional lability occur in up to 10% of patients [84, 90, 118, 121, 122], although many of these might instead be caused by a reduction in dopaminergic therapy.

Suicide has been reported in 0.45%, and suicide attempts in 0.9% of patients with STN stimulation. The risk of suicide is over 15-fold increased in the first postoperative year after STN surgery and tapers down to the risk in the general population within 3 years [123]. 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% [103]. 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 [90, 122], but could in part result from disease progression or a reduction in levodopa dose.

Surgical treatments that are now rarely used in the treatment of PD

Thalamotomy

Thalamotomy has been performed for many years 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: [124]). Unilateral thalamotomy, as assessed in historical case series, has a permanent morbidity rate of 4–47%, and bilateral thalamotomy is associated with a 30% chance of developing serious dysarthria [125].

Stimulation of the thalamus

Stimulation of the thalamus is frequently used for the treatment of tremors, especially essential tremor [126, 127] and, unlike thalamotomy, can be relatively safely applied bilaterally. Stimulation of the thalamus improves tremor (and rigidity) in PD, but not akinesia [127, 128], and is therefore rarely employed. Thalamotomy and stimulation of the thalamus were found to be equally efficient after 6 months, but DBS had fewer side effects (Class I: [129]). An open-label 5-year follow-up suggests that thalamic stimulation may be preferable over unilateral thalamotomy to improve functional abilities (Class III: [130]).

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 after surgery (Class III: [131, 132]). Therefore, presently, this technique is not recommended if STN DBS is an available option.

Fetal mesencephalic grafts

Two Class I studies found that the symptoms of parkinsonism were not improved by fetal mesencephalic grafts, and some patients developed serious dyskinesias [133, 134]. However, in the study by Freed *et al.*, 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%, while 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 [135–137]. 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.

Non-pharmacological, non-surgical management of motor symptoms

Despite optimal medical and/or neurosurgical treatment, the clinical picture of PD becomes progressively complicated by an increased risk of falling, marked mobility problems (e.g. freezing of gait or difficulty rising from a chair), disabling communication and swallowing problems, and a variety of non-motor symptoms. These motor symptoms and signs generally respond poorly to dopaminergic treatment, and this underscores the importance of non-pharmacological treatment approaches. As in early stage PD, this includes a broad range of disciplines, among others rehabilitation specialists, allied health professionals (physiotherapy, occupational therapy, speech-language therapy), PD nurse specialists, and social workers.

Sufficient PD-specific expertise is required to strike a balance between promoting mobility and maintaining optimal levels of physical activity on the one hand, versus the need for safety and prevention of falls and injuries on the other hand [138, 139].

Specifically, the evidence-based guideline of physiotherapy in PD recommends training of transfer difficulties using compensatory cognitive strategies and cueing.

- The effectiveness of cued training of sitting to standing transfers is supported by recent evidence (Class II: [140]).
- Cognitive movement strategy training for ADL functions and transfer movements probably improves functional performance and quality of life, when embedded in a 2-week inpatient rehabilitation period (Class II: [141]). However, effects of strategy training were similar to musculoskeletal exercises of the same duration and intensity. Benefits of training declined after 3 months follow-up without training.

Recent evidence has emerged that physiotherapy intervention improves freezing of gait and balance.

- Cued gait training in the home is probably effective in reducing the severity of freezing of gait (Class II: [142]). The combination of 4 weeks of treadmill training and cueing induces even greater benefits for freezing of gait than cueing alone (Class II: [143, 332]).
- Physical activity and exercise are probably effective in improving postural instability and balance task performance (Class II: [144]). Also, treadmill training is beneficial for balance measures (Class II: [145]). Furthermore, physical activity likely reduces the risk of sustaining near-falls (Class II: [146]) and possibly the risk of actual falls (some Class III studies, in a systematic review [144]).

Three reviews found insufficient evidence for the efficacy of speech and language therapy for dysarthria [147–149]. Lee Silverman Voice Therapy (LSVT) improves vocal intensity and phonation (Class II: [150–152]). The Pitch Limiting Voice Treatment (PLVT) produces the same increase in loudness, but limits an increase in vocal pitch and prevents a strained voicing (Class IV) [153]. No scientific evidence supports or refutes the efficacy of non-pharmacological swallowing therapy for dysphagia in PD [154, 155].

One Cochrane review concluded that there is insufficient evidence to support or refute the efficacy of occupational therapy for PD, in light of the substantial methodological drawbacks in the studies, the small number of patients examined, and the possibility of publication bias [156].

Clinical experience suggests that PD nurse specialists are beneficial for patients with PD, for example by providing information to patients and their families, or by acting as a liaison within a multidisciplinary team, or by enabling the application of complex treatments such as apomorphine, intrajejunal levodopa-carbidopa, and DBS. However, a systematic review did not support the clinical and cost effectiveness of specialized PD nurses in the management of PD [157].

Recommendations for the symptomatic control of motor complications

Recommendations

Motor fluctuations

Wearing-off (end of dose akinesia, predictable ON-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 4–6 daily doses, may attenuate wearing-off (GPP).
- *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, although more effective than entacapone, 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.* Non-ergot dopamine agonists are first-line compounds. Pergolide and other ergot agonists are reserved for second-line treatment, due to their association with lung, retroperitoneal, and heart valve fibrosis. 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).
- *Switch from standard levodopa to CR formulation.* CR formulations of levodopa can also improve wearing-off (Level C). This formulation is useful for the treatment of night-time akinesia (nocturnal end of dose akinesia) (GPP).
- *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 (GPP).

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, ease of use, experience of the treating physician, and patient preference. 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 mainly to one meal a day may facilitate better motor responses to levodopa following other 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: [158, 159]).

Oral dispersible levodopa can be useful for delayed ON (Level B).

Severe motor fluctuations

Try oral therapy, as outlined above. If oral therapy fails to improve (marked to) severe predictable motor fluctuations, the following strategies can be recommended.

• *Deep brain stimulation of the STN* 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 problems or cognitive decline. Stimulation of other targets may also be effective, but results are less well documented.

• *Subcutaneous apomorphine* as penject (Level A) or pump (Level C).

• *Intrajejunal levodopa/carbidopa enteric gel* administered through percutaneous gastrostomy (PEG) can also help to stabilize patients with refractory motor fluctuations and dyskinesia (Level C).

Unpredictable ON–OFF

Deep brain stimulation of the STN is effective for unpredictable ON-OFF fluctuations (Level A). In the large studies of oral medical treatment for 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 only 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 oral medical strategies for ON–OFF, although the strategies described for dyskinesia and for wearing-off should be considered for unpredictable ON–OFF (GPP).

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, and reducing the size of individual doses, 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.

Recommendations

Dyskinesias

Peak-dose dyskinesia

- *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* (GPP), at the risk of worsening wearing-off.
- Add amantadine (Level A) – most studies use oral 200–400 mg/day. The benefit may last <8 months. The use of other antiglutamatergic drugs is investigational. In some cases discontinuation of oral levodopa for a short period of time (3 days) with simultaneous continuous intravenous infusion of amantadine may temporarily improve dyskinesia (GPP).
- *Deep brain stimulation of the STN*, which allows reduction of dopaminergic treatment (Level A). Effective inhibition of severe dyskinesia may also be obtained by GPi stimulation (Level C).
- *Add atypical antipsychotics*, clozapine (Level C: [160, 161]), in dosages ranging between 12.5–75 mg/day up to 200 mg/day, or quetiapine (Level C: [162, 163]). However, clozapine is associated with potential serious adverse events (agranulocytosis and myocarditis), which limits its use (GPP).
- *Apomorphine continuous subcutaneous infusion*, which allows reduction of levodopa therapy (Level C).
- *Intrajejunal levodopa infusion* in patients with marked peak dose dyskinesia and motor fluctuations (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. Deep brain stimulation of the STN is effective (Level A) and the strategies described for peak-dose dyskinesias can also be considered for biphasic dyskinesia (GPP). 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 (GPP). Finally apomorphine- and intrajejunal levodopa-infusion can be tried (Level C).

Recommendations

Off-period and early morning dystonias

- *Usual strategies for wearing-off* can be applied in cases of off-period dystonia (GPP).
- *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 (GPP).
- *Deep brain stimulation of the STN* (Level A) or GPi (Level C).
- *Botulinum toxin* can be employed in both off-period and early morning dystonia (GPP).

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, a reduction in dopaminergic therapy can be tried, although this may result in worsening of wearing-off.

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

Neuropsychiatric complications

Dementia

The prevalence of dementia in PD is 30–40% [164], although the cumulative incidence is closer to 80% [165]. Current age, rather than disease duration, is the highest risk factor for development of dementia associated with PD [166]. The pathological and neurochemical substrates underpinning cognitive decline in PD are heterogeneous, although a profound cortical cholinergic deficiency is characteristic [167, 168].

Interventions for the treatment of dementia in PD

Several drugs, particularly anticholinergics, can impair cognitive function and a gradual, graded discontinuation

of such drugs is recommended. Other possible interventions are therapy with cholinesterase inhibitors or the N-methly D-aspartate receptor antagonist memantine (see below).

Cholinesterase inhibitors Several reports on cognitive dysfunction in patients with dementia in PD have claimed beneficial treatment effects with donepezil (Class I: [169–171]), rivastigmine (Class I: [172]), galantamine (Class III: [173]), and tacrine (Class IV: [174, 175]). A Cochrane review concluded that cholinesterase inhibitors lead to a clinically significant benefit in 15% of cases, but that further studies were required to better ascertain impact on quality of life, as well as health economic measures [176].

For the effect of cholinesterase inhibitors on neuropsychiatric symptoms (including hallucinations) see below.

Increased tremor is an uncommon reason for discontinuation of cholinesterase inhibitors [177], while nausea and vomiting can also result in discontinuation of therapy in a minority of patients. These drugs may also be associated with a modest increase in risk for syncope, need for pacemaker insertion and hip fracture [178]. They may also worsen urinary frequency, urgency, and urge incontinence.

Memantine Two relatively small randomized trials in patients with either dementia associated with PD (PDD) or the closely related dementia with Lewy bodies (DLB) demonstrated benefit for memantine, although the effects were very modest (Class I: [179, 180]). In both studies the drug was well tolerated.

Recommendations

Treatment of dementia in PD

Most of the recommendations are off-label recommendations.

- *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), galantamine (Level C). Given the hepatotoxicity of tacrine, its use is not recommended (GPP). There may be idiosyncrasy in clinical response and side effects with these agents so it may be worth trying an alternative agent before abandoning (GPP).
- *Add or substitute with memantine if cholinesterase inhibitors not tolerated or lacking efficacy* (Level C).

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 [181].

Interventions for the treatment of psychosis in PD

Due to the prominent role of dopaminergic treatment in inducing 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.

Visual hallucinations often preceed or accompany cognitive decline and should be considered as a warning sign for developing dementia in PD.

Atypical antipsychotics

Clozapine The efficacy of clozapine was documented in two 4-week trials (Class I: [182, 183]). There was no worsening of UPDRS-Motor scores, and one study [182] 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 [184]. Leucopenia is a rare (0.4%) but serious adverse event with clozapine as is myocarditis [185]. 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 [186, 187]. Both studies also found significant motor worsening with olanzapine, as did Goetz *et al.* [188] (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 [189]. However, a relationship between olanzapine and stroke has been denied by others [190].

Quetiapine A recent trial found no significant improvement in psychosis rating with quetiapine versus placebo (Class I: [331]). This study contradicts previous encouraging results from several Class III studies [191–197], and a study by Morgante *et al.* [162] (Class II), which found no difference between quetiapine and clozapine.

Risperidone Risperidone improves hallucinations and psychosis in PD (Class IV: [198–201]). However, motor worsening was observed in most of these reports and, therefore, risperidone is not recommended in patients with PD [202].

Cholinesterase inhibitors

Rivastigmine (Class III: [202a, 203] and donepezil (Class IV: [204, 205]) 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: [172, 206]). 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

Treatment of psychosis in PD

- *Control triggering factors* (GPP). Treat infection and metabolic disorders, rectify fluid/electrolyte balance, treat sleep disorder.
- *Reduce polypharmacy* (GPP). Reduce/stop anticholinergic antidepressants, reduce/stop anxiolytics/sedatives.
- *Reduce antiparkinsonian drugs* (GPP). 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. As a rule dopamine agonists have a higher psychosis-inducing potential than levodopa (GPP).
- *Add atypical antipsychotics*. Clozapine (Level A) – although it can be associated with serious haematological adverse events, requiring monitoring. There is insufficient data on quetiapine, and it is possibly useful (GPP). Quetiapine is thought to be relatively safe and does not require blood monitoring. Olanzapine (Level A), risperidone (Level C), and aripripazole (GPP) are not recommended, but can induce – sometimes with a delay – parkinsonism (harmful).
- *Typical antipsychotics* (e.g. phenothiazines, butyrophenones) should not be used because they worsen parkinsonism.
- *Add cholinesterase inhibitors*. Rivastigmine (Level B), donepezil (Level C).

Depression

Depression is one of the most common non-motor symptoms of PD and, overall, available studies suggest that it may be found in about 40% of patients [207, 208]. Depressive episodes and panic attacks may occur before the onset of overt motor symptoms [209, 210] and, in established PD, depression is a major determinant of quality of life [211, 212].

There is consensus that PD-specific neurobiological changes also play a key role [213–215].

Interventions for the treatment of depression in PD

Despite its clinical importance, relatively few pharmacological intervention studies on how to treat PD-associated depression have been reported and ony recently Class I trials have been published and initiated.

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: [216]). 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: [217]). A meta-analysis of seven randomized controlled trials of the effect of the non-ergot dopamine agonist pramipexole on depression in PD suggests that this compound has a beneficial effect on mood and motivational symptoms in PD patients, who do not suffer from major depressive disorder [218].

MAO inhibitors In a study of the effects of selegiline on motor fluctuations, Lees et al. [9] (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: [219]). However, this study was confounded by motor improvement in the combined treatment group.

Tricyclic antidepressants This class of agents features among others an anticholinergic effect and is an

established treatment modality in major depression. One randomised placebo-controlled study in 19 patients (all on levodopa 7 of whom also were on anticholinergics) dates back more than 20 years and is related to nortriptyline (titrated from 25 mg/day to a maximum of 150 mg/day) (Class II: [220]), which showed a significant improvement over placebo, on a depression rating scale designed by the author. Although evidence-based reviews ([28, 221]) found little evidence supporting the use of tricyclic antidepressants in PD, a randomized controlled trial of paroxetine CR versus nortriptyline versus placebo in 52 patients with PD and depression showed that nortriptyline was efficacious but paroxetine CR was not. The primary endpoint in this study was the Hamilton Depression Scale and the percentage of depression responders at 8 weeks [222, 223].

Selective serotonin reuptake inhibitors (SSRIs) 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 [224] for review). 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: [225]).

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: [226, 227]). 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. Avila *et al.* [228] (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 treatments in PD, but with no difference between the active and placebo groups [224]. The controlled, although small study by Menza *et al.* [222] also failed to demonstrate a beneficial effect of an SSRI, i.e. paroxetine CR, on depression in PD (see above) – in contrast to nortriptyline.

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: [229]) and venlafaxine (Class III: [230]) 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 [28]. 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: [231]. A Class I study [232] 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

Treatment of depression in PD

- *Optimize antiparkinsonian therapy* (GPP).
- *Tricyclic antidepressants* (Level B).
- *SSRIs* (GPP). SSRIs are less likely to produce adverse effects than tricyclic antidepressants (GPP).
- *'New' antidepressants (mirtazapine, 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 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 adverse effects on cardiac function. Two Class II studies of midodrine that included PD and other causes of neurogenic orthostatic hypotension revealed a significant increase in standing blood pressure [233,

234]. Such effect lasts only a few hours, which may be an advantage in some cases since patients can take it only when the effects are needed. The main side effects are supine hypertension (4% of patients) [234], paresthesias, and goose bumps.

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 [235]. In a more recent, small (17 patients with PD) crossover clinical trial (Class III; [236]*) with four dropouts, both fludrocortisone and domperidone improved scores on two clinical scales used as outcome measures (CGI and COMPASS-OD), with only a trend towards reduced blood pressure drop on tilt table testing (domperidone > fludrocortisone). Hypertension, hypokalaemia, and ankle oedema [237] are the main side effects of fludrocortisone. Other studies have found fludrocortisone effective in various other causes of orthostatic hypotension. At least 4-5 days of treatment are necessary before therapeutic response is observed and full benefit requires a high dietary salt and adequate fluid intake.

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

Recommendations

Treatment of orthostatic hypotension in PD

General measures

- *Avoid aggravating factors* such as large meals, alcohol, caffeine at night, exposure to a warm environment, volume depletion, and drugs known to cause orthostatic hypotension, such as diuretics or antihypertensive drugs, tricyclic antidepressants, nitrates, alpha-blockers used to treat urinary disturbances related to prostatic hypertrophy. Levodopa, dopamine agonists, and MAO-B inhibitors may also induce orthostatic hypotension.
- *Increase salt intake (1g per meal)* in symptomatic orthostatic hypotension.
- *Head-up tilt of the bed at night (30–40°)*, which may be helpful.
- *Wear waist-high elastic stockings and/or abdominal binders.*
- *Exercise as tolerated.*
- *Introduce counter-manoeuvres to prolong the time for which the patient can be upright* (leg crossing, toe raising, thigh contraction, bending at the waist).
- *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* (GPP: possibly effective, but note side effects).

Urinary disturbance

Interventions for the treatment of urinary disturbance in PD

Dopaminergic drugs There are indications that dopaminergic therapy (apomorphine, L-dopa) can improve storage urodynamic properties in patients with PD, at least in *de novo* patients (Class IV: [238]). In non-*de novo* patients the results of different studies are partly conflicting and variable concerning effects of dopaminergic therapy (Class III: [239–246]). With subcutaneous apomorphine a reduction of bladder outflow resistance and improved voiding was demonstrated (Class III: [242]).

Peripherally acting anticholinergics Neurogenic bladder problems with overactive bladder in general improve with anticholinergics [247, 248] but there are no placebo-controlled double-blind/randomized studies on this treatment in patients with PD. It is important to balance the therapeutic benefits with the adverse effects of these drugs. Dry mouth, constipation, and cognitive adverse events are a concern. It has been suggested that anticholinergic drugs that do not pass the blood–brain barrier so readily should have priority because of their lower risk of cognitive side effects, but there are no studies addressing this issue.

Intranasal desmopressin spray Intranasal desmopressin spray showed a good response in PD patients with nocturia (Class IV: [249]).

Deep brain stimulation Deep brain stimulation might have benefitial effects with improved bladder capacity, and increased voiding volumes, but does not influence bladder emptying (Class III: [250, 251]).

Recommendations

Treatment of urinary disturbance in PD

Most PD patients develop bladder problems. The symptoms include urgency, frequency, nocturia, and sometimes urge incontinence. The most common bladder disturbance is detrusor hyperactivity. Detrusor hypoactivity is uncommon, and usually caused by anticholinergic and tricyclic antidepressive drugs. Pronounced incontinence is relatively uncommon and when it occurs it mostly relates to late stage disease or akinesia. PD patients with bladder problems should be referred to a urologist, at least if response to anticholinergic therapy is insufficient or if incontinence is present. Further management includes the following.

- *When symptoms appear suddenly*: exclude urinary tract infection.
- *When frequency and polyuria dominate*: exclude diabetes mellitus.
- *Nocturia*: reduce intake of fluid after 6pm. Sleep with head-up tilt of bed to reduce urine production.
- *Night-time dopaminergic therapy should be optimized* (GPP). Apomorphine injections can be considered if outflow obstruction is the dominating problem (GPP).
- *Use anticholinergic drugs* (GPP): drugs that do not pass the blood–brain barrier should have priority (since those that pass the blood–brain barrier tend to cause cognitive side effects in this patient category (GPP)). Substances: trospium chloride (10–20 mg two to three times per day), tolterodine (2 mg twice per day), oxybutynin (2.5–5 mg twice per day). Compared to other alternatives trospium is less apt to penetrate the blood–brain barrier. In case of cognitive side effects the advantage of better control of the urine must be balanced against the cognitive drawbacks. Postmicturation residual urine should be measured before and especially after start of anticholinergic therapy.
- A recent pilot study showed that botulinum toxin type A injected in the detrusor muscle under cystostopic guidance ameliorated clinical symptoms and urodynamic variables in a small sample of PD patients with overactive bladder. [252].

Gastrointestinal motility problems

Dysphagia: therapeutic interventions

The literature on treatment of dysphagia in Parkinson's disease is limited. Several studies have methodological problems and results are difficult to compare because of heterogeneous methods and outcome measures. Levodopa and apomorphine can improve the early phases (oral and pharyngeal) of swallowing, resulting in a shorter swallowing time, but do not affect all patients and might reduce swallowing efficiency (Class III: [253–259]). Percutaneous injection of botulinum toxin can be considered in selected patients (Class III: [260]). The effects of cricopharyngeal myotomy have not been fully evaluated (Class IV: [261, 262]). The effect of different rehabilitative treatments and modification of food/drink could be effective in some patients (Class III: [263–267]).

Recommendations

Dysphagia

Dysphagia difficulties in PD usually relate to disease severity and are rare in early PD. They are connected to a risk for asphyxia, aspiration pneumonia, malnutrition, and dehydration. There is a high risk of silent aspiration in PD. Pneumonia is a leading cause of death in later disease stages. The following recommendations can be given (GPP).

- Optimization of motor symptom control should be given priority3. Levodopa and apomorphine can improve dysphagia at least in some patients.
- Early referral to speech therapist for assessment, swallowing advice, and further instrumental investigations if needed.
- Videofluoroscopy in selected cases to exclude silent aspiration.
- Enteral feeding options may need to be considered (short-term nasogastric tube feeding or longer-term feeding systems (percutaneous endoscopic gastrostomy)).

Concerning surgical therapies, rehabilitative treatments, and botulinum toxin therapies there is still very limited experience and these treatments can not be generally recommended.

Gastric dysfunction: therapeutic interventions

Domperidone has been reported to accelerate gastric emptying and reduces dopaminergic drug-related gastrointestinal symptoms in patients with PD (Class II–IV: [268–271]). Mosapride, a selective 5-hydroxytryptamine

type 4 (5HT4) agonist drug, improved gastric emptying in PD patients with motor fluctuations (Class III: [272]*)

Metoclopramide also blocks peripheral dopamine receptors and reduces nausea and vomiting [269] by blocking dopamine receptors in the area postrema. However, in contrast to domperidone, it also crosses the blood–brain barrier, thus can also worsen or induce parkinsonism [273–275], which is considered an unacceptable risk in patients with PD.

Recommendations

Gastric dysfunction

- Gastric emptying is often delayed in PD, both in early and advanced patients. In addition to nausea and vomiting, symptoms may include early satiety, postprandial fullness, and abdominal pain. Through delayed absorption of medication motor fluctuations such as 'delayed on' can result. Domperidone can be considered to accelerate gastric emptying (GPP).
- Parenteral treatment such as transdermal patches can be considered for patients with severe fluctuations due to erratic gastric emptying (GPP). In cases with gastroparesis a PEG often becomes necessary.

Nausea and vomiting: therapeutic interventions

These symptoms often occur as adverse events in the initiation of dopaminergic therapy (see Part I) or when dopaminergic therapy is increased. To block or reduce nausea (and vomiting) and improve compliance to the symptomatic therapy, antiemetics can be used as concomitant therapy.

Recommendations

Nausea and vomiting

Domperidone (30–60 mg/daily) reduces dopaminergic drug-related gastrointestinal symptoms in patients with PD (Class II–IV: [268–271]). Ondansetron may be used as second-line drug. No other antiemetic is recommended. In fact, metoclopramide, cinnarizine, and prochlorperazine must be avoided (GPP) (see above).

Constipation: therapeutic interventions

Psyllium was reported to increase stool frequency (Class II: [276]). A placebo-controlled study showed Macrogol to be effective in the treatment of chronic constipation in 57 patients with PD (Class I: [277]). Also tagaserode (a 5-HT4 partial agonist) has proven to be an efficacious and safe therapy (Class II: [278]).

Recommendations

Constipation

- Constipation is the most commonly reported gastrointestinal symptom in PD patients. It can occur in both clinical and preclinical stages of the disease and worsens with disease progression. Anticholinergic drugs can worsen constipation and should be removed (GPP).
- Among non-pharmacological therapies, increased intake of fluid and fibre are recommended (GPP).
- Increased physical activity can be beneficial (GPP).
- As medication polyethylene glycol solution (Macrogol) is recommended (Level A).
- Alternative treatments are fibre supplements such as psyllium (Level B) or methylcellulose and osmotic laxatives (e.g. lactulose) (GPP).
- Irritant laxatives should be reserved for selected patients and short treatment duration.

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: [279]; Class IV: [280, 281]). 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: [282, 283]).

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: [284]).

Recommendations

Treatment of erectile dysfunction in PD

Erectile dysfunction is more common in PD patients compared with age matched controls. Urological investigation should be considered. Comorbidities, such as endocrine abnormalities (e.g. hypothyroidism, hyperprolactinemia, low testosterone) and depression should be considered and treated. Drugs associated with erectile dysfunction (e.g. alpha-blockers) or anorgasmia (e.g. SSRIs) should be discontinued. Dopaminergic therapy can have both negative and positive effects on this symptom. Sildenafil (50–100 mg, 1 h before sex) can be tried in PD patients with these problems (Level B). Other drugs of this class, like tadalafil (10 mg, 30 min–12 h before sex) or vardenafil (10 mg, 1 h before sex) can be alternative choices (GPP; no published experience in PD). In some patients apomorphine injections (5–10 min before sex) can also be an alternative treatment (GPP). Intracavernous injections of papaverine or alprostadil can be considered in selected patients (GPP; no published experience in PD).

Sleep disorders

Clinically significant sleep disorders are common in PD. It is estimated that 60–90% of patients complain of difficulties associated with sleep [285]. These disorders can be classified into those that involve nocturnal sleep (insomnia), daytime manifestations such as excessive daytime sleepiness, and those that involve specific nocturnal motor problems such as akinesia, dystonia, periodic limb movements, and restless legs syndrome. The causes of sleep disorders are related to the disease itself, to comorbidity or ageing, or linked to the effects of medications. There are a limited number of controlled clinical trials specifically on sleep problems associated with PD. There are also data on sleep outcomes generated in trials that selected patients who were not specifically recruited because of their sleep problems.

Daytime somnolence

There is huge variability in the frequency of daytime sleepiness depending on the population investigated and the tools used [286, 287]. Using the Epworth Sleepiness Scale (ESS) to define daytime somnolence, the frequency reaches 33% of patients as compared to 11–16% in a population of non-PD controls [288–290].

Interventions for the treatment of daytime somnolence in PD

Modafinil Modafinil is an orally administered wake-promoting agent, indicated to improve wakefulness in adults with excessive sleepiness associated with obstructive sleep apnoea, shift work disorder, and narcolepsy. Three small Class II, short-term, placebo-controlled, randomized, double-blinded trials evaluated the effect of oral modafinil on daytime sleepiness in PD [291, 292, 293]. The two trials with a crossover design [291, 292] found a small improvement in the ESS, while in the parallel trial [293] modafinil failed to significantly improve ESS. There was no benefit documented in other secondary sleep related outcomes [291–293].

Other pharmacological treatments An open-label study (Class III: [294]) on STN-stimulated patients with advanced PD with severe gait disorders, treated with high doses of methylphenidate, reported an improvement in the ESS.

Recommendations

Treatment of daytime somnolence in PD

General measures

- Assessment of nocturnal sleep disturbances (GPP).
- Optimize improvement of nocturnal sleep by reducing disturbing factors, such as akinesia, tremor, urinary frequency, etc. (GPP).
- Recommendation to stop driving (GPP).

Drug therapy

- Decrease dose or discontinue sedative drugs prescribed for another medical condition (GPP).
- Decrease dose of 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).

Sudden-onset sleep episodes

Sudden-onset sleep episodes ('sleep attacks') were originally described as 'sudden, irresistible, and overwhelming sleepiness without awareness of falling asleep'. The percentage of PD patients complaining of sleep episodes varies greatly in different reports between 3.8 and 20.8% [288, 295–300].

Recommendations

Treatment of sudden onset sleep in PD

There are no studies that specifically addressed the treatment or prevention of sudden-onset sleep in PD.

Recommendations are similar to the ones proposed for excessive daytime somnolence (GPP).

Nocturnal sleep problems

Nocturnal sleep disorders may not be a major clinical problem in the early stages of the disease, although changes of motor events, REM sleep behaviour disorder (RBD), and sleep fragmentation are recognized in untreated PD [301]. However, with disease progression there are specific symptoms of PD that may interfere with global sleep quality. The most frequent sleep problems include sleep fragmentation and nocturia. Other problems include difficulty in turning over in bed, a restless legs-like syndrome, vivid dreams, hallucinations, dyskinesias, pain, dystonia, and others [302]. All these phenomena result in worse quality of sleep when compared with a control group without PD [290]. Another frequent sleep disorder both in early and late stage PD is RBD.

REM sleep behaviour disorder

REM sleep behaviour disorder is a parasomnia characterized by the occurrence of muscle activity enabling dream enactment during REM sleep [303]. Patients may present complex, vigorous, and sometimes violent behaviours [304]. RBD is present in 25–50% of PD patients [304, 305] and may precede the onset of clinical symptoms of parkinsonism by many years [306].

Interventions for the treatment of RBD

There are no controlled trials that specifically addressed the treatment of RBD in Parkinson's disease or any parkinsonian syndrome.

Clonazepam Two case series (Class IV: [307, 308]) that have included patients with PD concluded that small doses of clonazepam (0.5–2 mg) are efficacious for the treatment of RBD. Clonazepam may induce daytime sedation and exacerbate underlying obstructive breathing in sleep and increase the risk of nocturnal falling in the elderly.

Dopamine agonists Three small open-label studies (Class III: [309–311] reported contradictory results on the efficacy of pramipexole for the treatment of RBD in PD patients.

Antidepressants Most antidepressants, especially serotonin reuptake inhibitors and mirtazapine, may carry a risk of worsening pre-existing RLS, periodic leg movements and RBD (Class IV: [312]).

Recommendations

Treatment of RBD in PD

General measures

- Protective measures to prevent sleep related injuries (safeguard bedroom environment) (GPP).
- Reduce or withdraw antidepressants, primarily SSRIs (GPP).

Drug therapy

- Add clonazepam at bedtime (0.5–2 mg) (Level C).

Other sleep disorders

In the available studies, the translation of the concept of night-time sleep disorders to the inclusion criteria of the different trials is very heterogeneous. The applied criteria varied from sleep fragmentation (frequency of nocturnal awakenings) to subjective complaint of unsatisfactory night-time sleep with nocturnal akinesia as a frequent and clinically relevant complaint.

Interventions for the treatment of other night-time sleep disorders in PD

Levodopa Two randomized, crossover placebo controlled trials (Class II: [313]; [314]) suggested that a bedtime intake of a standard or slow release dose of L-dopa may improve nocturnal and early morning disabilities. A small trial (Class II: [313]) comparing three different night-time doses (100 mg levodopa/25 mg carbidopa) found an increased sleep quality, decreased number of spontaneous moves in bed, and improved walking time in the morning. A placebo-controlled trial (Class II: [314]) reported an improvement in nocturnal akinesia and sleeping time with a bedtime single dose of slow-release levodopa/carbidopa. In a crossover double-blind trial, both levodopa/benserazide formulations (controlled release vs standard release) reduced nocturnal and early-morning disability scores (compared with baseline) [315].

Dopamine agonists A Class II [316] randomized, double-blind, placebo-controlled trial demonstrated that a

night-time dose of 1 mg pergolide worsened sleep (sleep efficiency, movement, and fragmentation index) in PD patients with fragmented sleep. A small open-label trial that evaluated the effect of nocturnal continuous subcutaneous overnight apomorphine infusion (Class III: [317]) documented a reduction of nocturnal awakenings and off periods and improvement of nocturia and nocturnal and early-morning akinesia in PD patients with nocturnal disabilities.

Nocturnal disturbances were measured with the Parkinson's Disease Sleep Scale (PDSS) – as secondary outcome criteria and not as an eligibility criteria in two Class I trials [47, 49]. It was concluded that transdermal rotigotine, pramipexole, and ropinirole prolonged release improved most aspects of sleep and night quality (PDSS) in advanced PD.

Two small open-label studies (Class III: [318, 319]) evaluated the benefit of a single evening intake of cabergoline. In the first trial, cabergoline improved early morning motor function, did not change sleep efficiency, and aggravated fragmented sleep. In the second trial, there was significant increase of sleep efficiency and sleep quality (PDSS).

Melatonin An improvement in night sleep outcomes was reported in two randomized placebo-controlled studies (Class II: [320, 321]) with two completely different doses of melatonin (50 mg and 3 mg). There were no reports of relevant adverse events.

Other pharmacological treatments Two case series with zolpidem (Class IV: [322]), an imidazopyrimidine short-acting hypnotic, and quetiapine (Class IV: [323]), an atypical antipsychotic with sedative properties, suggested an improvement of insomnia. Low doses of clozapine (mean dose 26 mg at bedtime) were reported to improve nocturnal akathisia and rest tremor with no serious side effects observed (Class IV: [324]).

An open-label study (Class III: [249]) showed a reduction in the frequency of nocturnal voids with bedtime desmopressin (nasal spray) in PD patients with nocturia. However, desmopressin treatment is not advised in the elderly.

Deep brain surgery Several open-label studies (Class III: [325–330]) concluded that subthalamic nucleus stimulation consistently improves sleep duration and reduces nigh time akinesia, sleep fragmentation, and early morning dystonia. There were also consistent reports of no improvement on periodic leg movements, restless legs symptoms, RBD. and excessive daytime sleepiness.

Recommendations

Treatment of sleep problems in PD

- Add a bed-time intake of a standard or slow-release dose of levodopa (Level B).
- Transdermal rotigotine, pramipexole, and prolonged-release ropinirole improve sleep quality in advanced PD patients with motor fluctuations (Level A).
- Subthalamic nucleus deep brain stimulation improves sleep quality in advanced PD patients except for nocturnal motor phenomena of sleep disorders (Level B).

Need of update

No later than 2013.

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Conflicts of interest

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

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

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

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

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

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

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

Andrzej Friedman received honoraria for presentations at educational conferences from Roche Poland, MSD Poland, and Allergan Poland.

P. Kanovsky has received honoraria for lectures from Ipsen and GSK, and received a research grant from Novartis.

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

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

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

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

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M. Schüpbach has received speaker's honoraria and travel reimbursement from Medtronic.

E. Tolosa has received honoraria for lectures from Boehringer Ingelheim, Novartis, UCB, GlaxoSmithKline, Solvay, Teva, and Lundbeck, and participated in advisory boards for Boehringer Ingelheim, Novartis, Teva, and Solvay.

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

Disclosure statement

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

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