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Pharmacotherapy in Parkinson's disease: case studies

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***Abstract*:** Parkinson's disease is a common neurodegenerative disorder with the particular feature of having various available treatments with proven efficacy. However, no treatment is curative. Recent trial results provided data for the discussion about the potential disease-modifying effect of new drugs as well as of other therapeutic strategies. The changing clinical phenotype following the progression of the disease multiplies the number of treatment targets and makes the application of recommendations from guidelines or other treatment algorithms to the individual patient a complex task. In the present manuscript, we discuss the treatment management of three case studies illustrating different stages of disease with distinct phenomenology. The proposed therapeutic alternatives are discussed based on the best data available; that is, treatment guidelines, clinical trial results or observational data.

***Keywords*:** Parkinson's disease, treatment, case studies, guidelines

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease characterized by the presence of bradykinesia, rigidity, resting tremor and postural instability [Hughes *et al.* 1992]. As a progressive disease, clinical signs and symptoms change along its course and so do therapeutic targets. In early symptomatic stages, treatment decisions emphasize the objective of improving disability secondary to the initial motor signs and symptoms, the prevention of motor complications later in the disease and, ideally, slowing of its progression. At later stages, treatment objectives change and include the management of motor complications, the prevention of falls, the treatment of psychosis and dementia and lastly the delay in loss of autonomy. Additionally, the response to medication shifts from being highly effective during the first 3–5 years [Rascol *et al.* 2000] to become associated with motor complications that range from a reduction in the duration of the antiparkinsonian effect to unpredictable on–off fluctuations and dyskinesias. There is also a growing concern with the nonmotor features observed in PD such as sleep disorders, dysautonomia, pain and neuropsychiatric symptomatology such as depression, apathy, impulse-control disorders and psychosis [Chaudhuri *et al.* 2006]. Current available therapeutic options for the management of PD are not just pharmacological. Nonpharmacological interventions include speech therapy, occupational therapy, physiotherapy and psychosocial counselling. Surgical interventions have also gained a relevant role, mainly due to deep brain stimulation of the subthalamic nucleus.

This manuscript focuses on the current available evidence for the pharmacological treatment of motor symptoms in PD. Choosing the best therapeutic intervention for each individual patient is a challenge not only due to the progressive and fluctuating nature of the disease but also due to the needed appraisal of multiple sources of information with a potential application to patient management. In this article, we conduct a stepwise approach that begins by asking clinically relevant questions focused on patient-centred outcomes, followed by the appraisal of the best clinical information available. Valid and relevant summaries of research evidence such as systematic reviews and evidence-based guidelines are used to evaluate the strength of the presented evidence. In recent years, guidelines for the management of PD have been published by the Movement Disorders Society [Goetz *et al.* 2005], the National Institute for Clinical Excellence based in the United Kingdom [National Collaborating Centre for Chronic

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Conditions 2006], the European Federation of Neurological Societies [Horstink *et al.* 2006a; Horstink *et al.* 2006b] and, more recently, by the American Academy of Neurology [Montgomery 2006; Pahwa *et al.* 2006]. The dynamic nature of these sources of information should be emphasized and the reader is reminded that their validity is also dependent on when they were last updated. When required, the authors will add more recent sources of information not included in the referred management guidelines. The final step in our decisional algorithm comprehends the application of the collected information to the care of the individual patient, a process that balances benefits and harms provided by the best available data and the individual patient characteristics such as age, comorbidities and premorbid level of functioning.

Case 1

A 70-year-old male farmer was referred to a movement disorders outpatient clinic due to a 1-year nondisabling intermittent resting tremor of the left hand, that later progressed to the contralateral hand. On neurological examination the patient had normal cognition. Myerson sign was present. Oculomotor examination was normal. An intermittent mild resting tremor was observed in the left hand, as well as mild signs of asymmetrical cogwheel rigidity and bradykinesia (left > right). Gait and balance were normal as well as postural reflexes. The diagnosis of idiopathic Parkinson's disease was entertained. This case illustrates a relevant clinical landmark in the management of Parkinson's disease; that is, the decision on initiation of treatment.

Clinical questions

Which treatment options should be considered to initiate treatment? In early-stage disease, the pharmacological options for the treatment of PD are multiple. These range from not initiating treatment (e.g. just scheduling a later visit) to starting treatment with one of the available efficacious symptomatic drugs: immediate-release (IR) levodopa, controlled-release (CR) levodopa, levodopa plus entacapone, dopamine agonists (immediate release, controlled release and patch), monoamine oxidase type B inhibitors (MAO-I) rasagiline and selegiline, amantadine and anticholinergics. The option of proposing the patient to enter a 'neuroprotective' or 'early symptomatic trial' also deserves consideration.

The factors that influence the decision of the clinician are related to the disease itself (rate of progression, presenting phenomenology, related physical disability), to individual characteristics of the patient (age, professional activity, expectations of benefit, fear of adverse effects) and those related to the anticipated goals of a given therapeutic intervention, namely:

(1) prevention of clinical progression;
(2) improvement of parkinsonism (mild improvement *versus* best benefit possible);
(3) delaying motor complications.

Ideally, the aim of an early therapeutic intervention in neurodegenerative diseases should be to prevent its clinical progression, defined as the delay of illness onset in presymptomatic subjects or the slowing of functional decline in patients with prodromal or early manifest illness as exemplified with this patient. Unfortunately, in clinical practice there are two major limitations when pursuing these goals for PD: (1) It is not feasible yet on an individual basis to identify subjects with presymptomatic or prodromic PD; and (2) there are no robust data to support the recommendation of any drug for the slowing of disease progression (Table 1).

Thus, in early PD, the absence of drugs with a documented disease-modifying effect does not oblige the immediate initiation of a pharmacological treatment and does not make mandatory the anticipation of a PD diagnosis in mild symptomatic subjects. Consequently, for this particular patient, the most relevant clinical information to consider is the lack of disability associated with the reported symptom, making it not clinically mandatory to initiate symptomatic treatment. However, in other cases, a similar complaint of tremor could have been judged unacceptable due to professional or social constraints, and thus prompted the initiation of treatment.

What are the pros and cons of early initiation of treatment versus *waiting for disabling symptomatology in PD?* The recently released results of the clinical trial ADAGIO [Olanow *et al.* 2008] concluded that starting rasagiline earlier when compared with its delayed start 9 months later was associated with a greater symptomatic benefit measured by the total Unified Parkinson's Disease Rating Scale (UPDRS) after 18 months of follow-up. This observation has been

Table 1. Recommendations for the treatment of early Parkinson's disease. Only the highest level of recommendation available is provided.

Recommendations	Therapeutic target		
	Prevention of clinical progression	Symptomatic control of parkinsonism	Prevention of motor complications
MDS	Insufficient data	Levodopa, levodopa CR, pergolide, pramipexole, ropinirole, DHEC, selegiline, rasagiline	Cabergoline, ropinirole, pramipexole
EFNS	No definitive evidence for pharmacological neuroprotection	Levodopa, levodopa CR, pramipexole, ropinirole, selegiline, rasagiline	Pramipexole, ropinirole
AAN	Insufficient evidence to recommend any drug for neuroprotection	No data	No data
NICE	No drug recommended	Levodopa, nonergot dopamine agonists, MAO-I	No data

MAO-I, monoamine oxidase isoenzyme type B inhibitors; CR, controlled release, DHEC, dihydroergocryptine; MDS, Movement Disorders Society; EFNS, European Federation of Neurological Societies; AAN, American Academy of Neurology; NICE, National Institute for Clinical Excellence.

suggested to be a putative disease-modifying effect that is for the first time based solely on clinical outcomes and a possible neuroprotective/disease-modifying indication is under discussion by the US and European drug regulatory agencies. However, these results deserve careful consideration and are presently being discussed by the scientific community. The short- and long-term clinical relevance of the observed benefit are not completely understood, and additionally it is not settled that the observed beneficial effect with the delayed start design is derived from a specific effect of rasagiline or simply from an earlier symptomatic treatment. A study with a similar design but using pramipexole instead has been completed recently and will add relevant information to this discussion (see identifier NCT00321854 in http://clinicaltrials.gov).

What is the best initial pharmacological intervention if the objective is improvement of parkinsonism? When the decision is to initiate a pharmacological treatment in early PD, an important step is to define the nature and magnitude of the benefit to be expected with a certain pharmacological option. It is different to consider any symptomatic improvement or maximum functional gain as therapeutic goals.

Presently, no single first-choice drug exists for the management of early PD. According to the available recommendations the treatments with higher level of evidence are levodopa, the dopamine agonists dihydroergocryptine, pergolide, pramipexole and ropinirole, and the MAO-Is selegiline and rasagiline (Table 1). More recently, the new nonergolinic dopamine agonist rotigotine with a transdermal delivery system was licensed for early PD (http://www.emea.europa.eu/humandocs/PDFs/EPAR/neupro). Nevertheless, special care must be exerted regarding the storage conditions of rotigotine since crystallization of the active substance has been observed under heat conditions. These findings have limited its prescription to patients already on the medication, a restriction only recently lifted by regulatory authorities (http://www.emea.europa.eu/humandocs/PDFs/EPAR/neupro).

Among these drugs, levodopa continues to be the drug with best efficacy for the control of parkinsonian symptoms [Oertel *et al.* 2006; Fahn *et al.* 2004; Parkinson Study Group, 2000; Rascol *et al.* 2000], namely rigidity and bradykinesia but at the expense of a higher risk of motor complications in the first 3–5 years of disease, a factor that should also be incorporated into a decision algorithm for early PD. Due to the reported risk of cardiac valvular fibrosis, the use of ergot-derived dopamine agonist is now less recommended [Horstink *et al.* 2006a].

Concerning anticholinergics, their use as monotherapy or as an add-on option may be considered to improve motor function but with the major limitation of neuropsychiatric and cognitive adverse events [Katzenschlager *et al.* 2003]. Although frequently suggested in the literature,

an evidence-based analysis does not convincingly support a specific antitremor effect of anticholinergic drugs over other motor parkinsonian symptoms [Katzenschlager *et al.* 2003]. Concerning amantadine, although its antiparkinsonian effect is recognized, no clinical studies have methodologically evaluated its benefit for the treatment of early PD [Crosby *et al.* 2003].

What should be the first pharmacological option if one of the main concerns is to delay motor fluctuations and dyskinesias? The use of dopamine agonists (pramipexole, ropinirole, pergolide, cabergoline) has consistently proved to delay the onset of motor complications when compared with levodopa as the first option for the treatment of Parkinson's disease (Table 1). However, single clinical trials comparing levodopa with each one of these dopamine agonists reveal that this delaying effect is obtained at the expense of a poorer control of motor symptoms, and a higher incidence of dopaminergic adverse events, namely somnolence, hallucinations and peripheral edema [Clarke and Guttman, 2002]. Additionally, in one study comparing pramipexole and levodopa, the occurrences of dyskinesias and motor fluctuations have been shown to have no significant impact in quality of life during the first 4 years of treatment [Marras *et al.* 2004].

Is there a benefit of CR levodopa over IR levodopa for the prevention of motor complications? Both IR and CR levodopa formulations (Sinemet CR® or Madopar HBS®) have demonstrated a symptomatic effect. However, modified-release levodopa preparations have not demonstrated the ability to delay the onset of motor complications in patients with early PD [Block *et al.* 1997; Dupont *et al.* 1996].

Is there a benefit in initiating levodopa associated with entacapone over levodopa/carbidopa alone as monotherapy once it has been decided to initiate levodopa in patients without motor fluctuations? The recent presentation of the results of two trials comparing Levodopa + carbidopa + entacapone (Stalevo®) *versus* levodopa + carbidopa alone (Sinemet®) in early PD brought an important insight to this relevant question. In the First Step trial, which compared Stalevo® with Sinemet®, a mild symptomatic benefit (UPDRS part II + III) with Stalevo® was observed with Stalevo, with no difference found in motor benefit [Hauser *et al.* 2008]. The incidence of dyskinesias was found not to be higher in the Stalevo® group. However, in a second study (the STRIDE-PD trial), which compared both interventions in a larger sample of PD patients, the protective effect of Stalevo® for onset of dyskinesias was not observed and, in fact, it seems to be associated with an increased risk of early dyskinesias (http://www.orion.fi/en/News-and-media/Stock-exchange-releases/Archive/1/11/).

Is it clinically relevant to delay the onset of dyskinesias up to 5 years of treatment? The delayed onset of motor complications *per se* must be weighed against other aspects such as the associated disability due to poorer motor improvement and the long-term outcome after 5 years of dopaminergic treatment. For this decision, it is relevant to consider that after 5 years of treatment more than 80% of patients will need levodopa for the control of the parkinsonian symptoms [Rascol *et al.* 2006]. In fact, long-term studies comparing the early use of levodopa *versus* dopamine agonists have shown that motor complications are inevitable after 10–15 years of treatment, regardless of the initial treatment option [Katzenschlager *et al.* 2008; Constantinescu *et al.* 2007; Hely *et al.* 2005] and can be nontroublesome for most of the patients [Hely *et al.* 2005]. Additionally, for more severe and disabling motor complications, the loss of the 'protective' effect provided by dopamine agonists is observed earlier [Lees *et al.* 2001]. The results from the open long-term extension of the ropinirole *versus* levodopa trial concluded that the effect of delaying the onset of dyskinesias declines with the use of levodopa as adjuvant and, after 10 years of treatment, there is no significant difference in the prevalence of moderately disabling dyskinesias [Hauser *et al.* 2007]. The long-term results of the trial comparing pramipexole with levodopa also show that the effect of delaying the onset of dyskinesias disappears with adjuvant levodopa treatment [Constantinescu *et al.* 2007]. Other studies comparing levodopa with the dopamine agonist bromocriptine with longer follow-ups give further clues into this topic: the PDRG-UK trial comparing bromocriptine with levodopa concluded that the benefit of bromocriptine monotherapy in reducing motor complications at 5 years, diminishes by 10 years and disappears at 14 years of follow-up [Katzenschlager *et al.* 2008]. The Sydney Multicenter Study of Parkinson's Disease concluded that, although in the bromocriptine group the onset of dyskinesias was delayed, no significant difference for predictable offs, unpredictable offs, sudden-offs and off duration was

observed between groups after 15 years of treatment [Hely *et al.* 2005].

Comments

- The best data available support the options of delaying treatment onset or initiating treatment with levodopa, nonergot dopamine agonists or MAO-I.
- The option of levodopa guarantees the best symptomatic treatment but with a dose-dependent risk of inducing dyskinesias after some months of treatment.
- Treatment with pramipexole or ropinirole translates into a relevant symptomatic treatment with a significant percentage of patients being kept on monotherapy for years and delaying the onset of motor complications when compared with levodopa. The clinical relevance of this delaying effect is not universally accepted and the protective effect declines with the initiation of adjuvant levodopa and treatment duration.
- There are no supportive data to initiate treatment with the association of levodopa and entacapone, or with amantadine or anticholinergics.
- The evidence associating anticholinergics with a higher risk of cognitive deterioration [Katzenschlager *et al.* 2003] recommends these drugs to be avoided.

Case 2

A 75 year-old male with a history of 14 years of PD was referred to the movement disorders outpatient clinic due to deterioration of parkinsonism and frequent falls. Falls occurred more frequently in the early afternoon when the patient felt he was more parkinsonian and that was his main concern. The occurrence of wearing-off and unpredictable dose failure after lunch was also mentioned. His daughter clearly mentioned the presence of occasional mild dyskinesias of which the patient was unaware. He was being treated with levodopa-carbidopa 100/25 mg one and a half pills q.i.d., and ropinirole 2 mg t.i.d. This case illustrates later-stage PD defined by the presence of motor complications that significantly compromise the patient's health condition and shape as new therapeutic goals.

Clinical questions

Which therapeutic goals would the reader prioritize? In the clinical follow-up of a PD patient, the occurrence of falls is a potential alert sign of disease aggravation and of increasing difficulty to effectively treat the symptoms of the disease. Beside falls, at this stage of the disease manageable therapeutic goals may also include:

(1) improvement of parkinsonism;
(2) reduction of off time;
(3) increase of on time;
(4) reduction of the intensity and frequency of dyskinesias;
(5) improvement of postural instability/freezing.

Falls represent an important cause of significant morbidity and dependence in PD [Schrag *et al.* 2006]. To approach this problem properly, there is a need to rigorously characterize the presented phenomenology. For this patient, it is crucial to determine the time of occurrence of falls, putative triggering factors and associated symptoms. Additionally, the determination of wearing-off and off episodes and their association with the intake of medication will help to determine if falls are happening during on- or off-time. For this purpose, clinical data may be gathered by direct patient interview or abstracted from patient-filled diaries [Hauser *et al.* 2006]. Falls in PD may have different causes like freezing of gait (whether an off- or on-phenomenon), postural instability and orthostatic hypotension. For this patient, the analysis of on and off-periods (Figure 1) allowed the identification of freezing during off-periods in the context of dose failure as the most probable cause of falls. Thus, the need to decrease off-periods by optimizing treatment is the most suitable treatment option.

What is the best pharmacological intervention to decrease off-time? Assuming the reduction of off-time as a primary goal, several pharmacological options can be considered:

(1) increase the dose of ropinirole;
(2) switch to another dopamine agonist;
(3) increase levodopa/carbidopa dose;
(4) change the regimen of levodopa/carbidopa (increase frequency of intakes and not with high-protein food intake);
(5) switch to an extended-release formulation of dopamine agonists (oral or transdermal route);
(6) switch to equivalent dose of controlled-release levodopa/carbidopa;
(7) add a catechol-O-methyl transferase (COMT) inhibitor (entacapone);
(8) switch to the combination of levodopa/carbidopa + entacapone;
(9) add an MAO-I (rasagiline or selegiline).

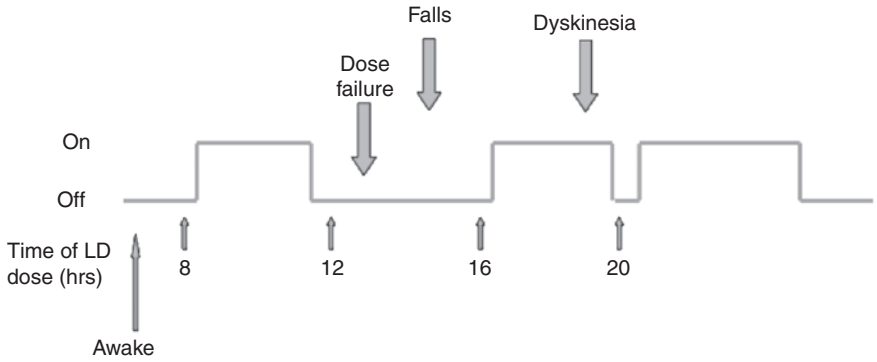

Figure 1. Example of a patient diary (case 2) with on- and off-states, falls and dyskinesias. Small upward vertical arrows indicate medication intake. LD, levodopa.

Table 2. Recommendations for the symptomatic control of motor complications in PD. Only the highest level of recommendation available is provided.

Recommendations	Type of motor complicatons		
	Wearing-off	Peak-dose dyskinesias	Unpredictable on–off
MDS	Pergolide, pramipexole, ropinirole, apomorphine, selegiline, rasagiline, entacapone, tolcapone	Amantadine	No data
EFNS	Entacapone, selegiline, rasagiline, pramipexole, ropinirole, subcutaneous apomorphine	Amantadine, clozapine	Oral dispersible levodopa formulations for delayed on (low level)
AAN	Entacapone, rasagiline	Amantadine	No data
NICE	Levodopa, nonergot dopamine agonists, entacapone, MAO-I	Amantadine, continuous subcutaneous apomorphine	Intermittent apomorphine

MAO-I, monoamine oxidase isoenzyme type B inhibitors; MDS, Movement Disorders Society; EFNS, European Federation of Neurological Societies; AAN, American Academy of Neurology; NICE, National Institute for Clinical Excellence.

Overall, current guidelines support the use of dopamine agonists, MAO-I, levodopa/carbidopa and COMT-inhibitors as options for the management of wearing-off (Table 2). The combination of these different treatments will eventually occur, since a single treatment fails to provide adequate symptomatic motor control. There is insufficient evidence about the best strategy to combine more than two drugs and the choice of drugs is mainly dependent on data generated from trials that have studied single adjuvant interventions. In recent years, the use of extended release forms (ropinirole prolonged-release and rotigotine transdermal system) has provided additional resources to the clinician. Ropinirole extended-release was shown to be better tolerated than ropinirole immediate-release: using higher doses of the extended-release formulation it was possible to reach higher doses of ropinirole and consequently a greater reduction of off time [Stocchi *et al.* 2008]. Also, some patients appreciate the ease of single daily administration. Rotigotine has also been found to reduce off-time in PD patients with wearing-off [Poewe *et al.* 2007] although this is not an approved indication. Most of the available data about treatment of motor fluctuation deal with wearing-off phenomena or predictable on–off. Whatever the pharmacological option, off-time reduction ranges from 40 min (entacapone [Deane *et al.* 2004] and ropinirole [Clarke and Deane, 2001]) to 95 min with rotigotine [Poewe *et al.* 2007] and 2 h with pramipexole [Clarke *et al.* 2000].

Regarding on–off phenomena in which delayed-on is included, there is insufficient evidence to determine specific strategies for these phenomena, since in the vast majority of trials that included patients with motor fluctuations,

unpredictable on–off phenomena was considered exclusion criterion or constituted <5% of the participants [Horstink *et al.* 2006b]. Nevertheless, it is good practice to apply the management strategies described for wearing-off [Horstink *et al.* 2006b].

For this patient, it was decided to increase the daily dosage of ropinirole to 9 mg and to have an earlier second intake of levodopa/carbidopa to prevent the erroneous absorption of levodopa when taken concurrently with a high-content protein meal. After adjusting the treatment regimen, there was an increase of dyskinesias in between intakes of medication, as well as the appearance of troublesome dyskinesias.

What is the best pharmacological intervention to treat dyskinesias? In this patient the increase of dyskinesias and the appearance of troublesome dyskinesias was a direct effect of increasing the dose of ropinirole. It is worth mentioning that all dopaminergic drugs have the risk of inducing or worsening dyskinesias, including the combination of levodopa with a dopamine agonist or a COMT inhibitor, or adding a MAO-I.

A meta-analysis individually comparing two dopamine agonists (pramipexole [Clarke *et al.* 2000] and ropinirole [Clarke and Deane, 2001]) with levodopa shows that both cause dyskinesias. However, treating troublesome dyskinesias should not be achieved at the cost of increasing parkinsonian symptoms. The available guidelines unanimously present amantadine 200–400 mg/day as the antidyskinetic drug of choice (Table 2). Clozapine may also be considered [Horstink *et al.* 2006b] but potentially serious adverse events (agranulocytosis and myocarditis) make it a good practice point to limit its use and warrant regular laboratorial monitoring during the full extension of its use. Other possible strategies are fractioning the daily dose of the IR levodopa throughout but with the limitation of potentially aggravating parkinsonian disability, and changing the IR levodopa to the CR levodopa (but this is not recommended due to a less predictable response to levodopa).

Comments. Multiple options could be applied in this patient: to increase total levodopa dose and fractionate levodopa intake, to increase dopamine agonist dose and to add an MAO-I or COMT-inhibitor. All of these strategies have proved efficacious in the reduction of off time but the concomitant increase of on time may be associated with an increase of dyskinesias and even troublesome dyskinesias.

Case 3

A 70-year-old female with a 15-year history of Parkinson's disease that began with resting tremor of the left arm was referred to a movement disorder clinic. During the first years, the patient had a good and maintained response to levodopa treatment. At age 64, the patient began having leg dyskinesias, followed 1 year later by the onset of wearing-off. At age 67, the patient reported falls and gait disturbance. The referral to a movement disorders outpatient clinic was made due to falls and worsening of motor fluctuations, namely wearing-off (~5 h of daily off) and on–off fluctuations. No cognitive or behavioural complaints were recorded. The patient was medicated with levodopa/carbidopa, 100/25 mg one and a half pill t.i.d. plus one pill t.i.d., ropinirole 5 mg t.i.d., amantadine 100 mg b.i.d. and domperidone 10 mg, two pills t.i.d. The clinical observation documented a severe off and on freezing as the major cause for falls. The patient did not present postural instability as documented by a good performance in the pull test. Gait disturbance and the risk of falls was her major complaint.

Clinical questions

Which therapeutic goals would you want to treat? The present case illustrates an advanced-staged PD with an increased burden of motor complications including dopaminergic non-responsive features like on freezing. Although being treated with a combination of several anti-parkinsonian drugs in medium to high therapeutic doses, motor fluctuations including unpredictable on–off phenomena, troublesome dyskinesias and severe freezing imposed a severe functional limitation.

After listing the identified clinical problems (wearing-off, on–off fluctuations, freezing, postural instability and dyskinesias), freezing was considered as the primary cause of disability and a treatment priority. Clinical observation was made during on and off periods thus enabling the characterization of freezing, its severity and the assessment of the risk of falls, that was considered identical for both periods.

What are the best pharmacological interventions to improve freezing of gait? Freezing, particularly freezing of gait, is one symptom of PD that is most difficult to treat. It is more frequent in off periods but may also occur during on periods. Considering the current evidence, no therapeutic intervention has demonstrated a specific benefit. Options for off freezing are the same as those described for wearing-off. Although evidence is low, the use of visual or auditory cues may be used to facilitate the ignition of the motor action once freezing has occurred. For on freezing, the reduction in dopaminergic therapy is recommended, although this may result in increased off time.

If the patient presented freezing during off-time what should be the best pharmacological intervention to improve freezing of gait? In the case of freezing of gait that occurs predominantly during off time, the most logical therapeutic strategy is to reduce off time. However, patients frequently present additional motor complications like biphasic dyskinesias and unpredictable on–off fluctuations that warrant specific strategies and are difficult to manage.

At this stage, other strategies may be considered to deal with a more advanced disease stage taking in account the broad range of motor complications. These include:

(1) increase daily dose of IR levodopa (intake frequency or the dose intake);
(2) switch to CR levodopa;
(3) increase dose of dopamine agonist;
(4) start an MAO-I: rasagiline or selegiline;
(5) start entacapone alone or in combination pills with levodopa/carbidopa;
(6) subcutaneous apomorphine;
(7) levodopa/carbidopa enteric gel.

As with other clinical problems present in the advanced stage, freezing and postural instability do not respond significantly to dopaminergic treatments. Very limited evidence suggests that low-frequency stimulation of the subthalamic nucleus in advanced PD patients may have a beneficial effect on freezing episodes [Moreau *et al.* 2008]. Thus, freezing may be considered as an orphan problem and is frequently excluded from clinical studies in PD. The same applies to unpredictable on–off phenomena. When oral therapy fails, other more invasive but efficacious strategies can be recommended. Subcutaneous apomorphine as a penject and levodopa/carbidopa enteric gel administered through percutaneous gastrostomy (PEG) are options in patients with refractory motor fluctuations (Table 2). These formulations allow a stable and continuous supply of dopaminergic drugs avoiding trough low levels thus avoiding off-time, on–off phenomena and biphasic dyskinesias.

Comments. In advanced stage PD, clinically relevant problems are often not responsive to dopaminergic treatments. Additionally, for the enumerated hypothesis the available evidence is low, due to the lack of clinical studies looking specifically at late-stage complications of PD.

Conclusions

PD is a neurodegenerative movement disorder with a long duration and changing phenomenology that makes its management challenging, even in the strict motor perspective. During its course, different clinical problems emerge as potential therapeutic goals. Applying the available evidence concerning treatment options in PD to the individual patient is the key to a successful management of patients. In early PD, multiple options exist ranging from no treatment to different pharmacological agents such as levodopa, dopamine agonists, and even MAO-I. All have their advantages and drawbacks. The appearance of motor complications defines a new stage of the disease where the control of motor symptoms is more delicate and difficult to achieve. The advanced stage of PD is marked by clinical problems that are often dopamine nonresponsive, more difficult to manage, and for which the few available options lack the support of a good-quality body of evidence. These remain orphan therapeutic goals.

Conflict of interest statement

JJF acted as independent consultant for different pharmaceutical companies involved in the marketing and development of antiparkinsonian medications and received honoraria from them. He has been involved as investigator in multiple clinical trials testing antiparkinsonic drugs. He has no other kind of financial or personal relationships that could influence this work, including stock ownership, paid expert testimony or patent applications.

TM has been involved as investigator in clinical trials testing antiparkinsonic drugs. He has no

other kind of financial or personal relationships that could influence this work, including stock ownership, paid expert testimony or patent applications.

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