When Do Levodopa Motor Fluctuations First Appear in Parkinson's Disease?

Fabrizio Stocchi^a Peter Jenner^b Jose A. Obeso^c

^aInstitute of Neurology, IRCCS San Raffaele Pisana, Rome, Italy; ^bNeurodegenerative Diseases Research Centre, School of Health and Biomedical Sciences, King's College, London, UK; ^cDepartment of Neurology, Clinica Universitaria and Medical School of Navarra, Neuroscience Centre, CIMA, University of Navarra and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Instituto Carlos III, Ministerio de Investigación y Ciencias, Pamplona, Spain

Key Words

Motor fluctuations • Levodopa • Wearing-off

Abstract

Although levodopa provides therapeutic benefit over the entire course of Parkinson's disease, most patients eventually notice a decline in the duration of benefit from each dose, a phenomenon termed 'wearing-off' or 'end of dose' deterioration. This is an important indicator that the patient is entering a more complex phase of the disease. Wearing-off has been classically associated with the later stages of Parkinson's disease, but it is becoming apparent that patients with early disease, presenting as well controlled, may already be experiencing fluctuations in their response to levodopa. However, neither the pathophysiology nor the clinical relevance of the early emergence of wearing-off has been properly explored. We now review the preclinical and clinical evidence that suggests that even patients who are apparently still in the honeymoon phase of drug treatment may have early fluctuations in their motor response to dopaminergic therapy. It is important that early wearing-off is recognized as it has important consequences for the long-term outcome and for the medication regimens to be used.

Copyright © 2010 S. Karger AG, Basel

Introduction

The treatment of Parkinson's disease (PD) with dopaminergic therapy, especially in the early stages, is usually associated with significant improvements in motor disability, and the first few years of pharmacotherapy are often referred to as the 'honeymoon period' because patients generally enjoy sustained symptomatic relief with minimal side effects [1]. The trend over the last two decades has been to use a dopamine agonist as initial treatment and to subsequently introduce levodopa, although the choice of initial therapy varies depending on the age, comorbidity and circumstances of each patient. In any case, it is generally agreed that the most effective treatment for the symptoms of PD is levodopa, and virtually all patients with PD will eventually receive levodopa during the course of their illness [2–6].

Dopaminergic treatment continues to benefit patients as PD progresses [2], but within a few years of starting therapy, whether with levodopa alone or levodopa and a dopamine agonist, the majority of patients begin to notice a decline in the duration of benefit of each dose. This is referred to as 'end of dose deterioration' or 'wearing-off'. Although traditionally held to be a complication that occurs later in the disease, more recent studies have re-

Fig. 1. Mean peak (■) and baseline (○) tapping speeds to the levodopa infusion on day 1 and day 4 and over 4 years of therapy with levodopa (n = 18). The difference between peak and baseline tapping speeds is the magnitude of the SDR, which progressively increases to the levodopa infusion on day 4. Reproduced from Nutt et al. [18].

ported that up to 50% of patients show the onset of motor fluctuations within 2 years of starting conventional levodopa therapy [6], and the ELLDOPA trial reported symptom re-emergence within 5–6 months [7, 8]. Interestingly, ELLDOPA was the first study to demonstrate a dose-response relationship between improvement in motor performance and levodopa dosage. It further showed that higher dosages of levodopa are most likely to cause motor fluctuations ($p = 0.06$) [7]. By the end of the 9-month period of this trial, almost a third (29.7%) of patients receiving the highest daily dose of levodopa (600 mg/day) experienced 'wearing-off' compared with 18.2% of patients in the 300 mg/day group and 16.3% of patients in the 150 mg/day group. It is now also clear that early emergence of wearing-off is not limited to patients on levodopa, and recent studies have shown that patients with early PD receiving dopamine agonist monotherapy using either ropinirole or pramipexole experience fluctuations in their motor response within 15–21 months [6, 9]. In this paper, we review the evidence that suggests that even

patients who are apparently still in the so-called 'honeymoon period' may begin to have fluctuations in their motor response to dopaminergic therapy. Despite the availability of evidence in the literature, neither the pathophysiology nor the clinical relevance of the early emergence of wearing-off has been explored.

Clinical Features of Wearing-Off: The Short- and Long-Duration Responses to Levodopa

As soon as levodopa was introduced into clinical practice for the treatment of PD, it was recognized that the therapeutic response consists of at least two components [10]: the short-duration response (SDR), which provides an improvement in motor disability that lasts a few hours after the administration of single doses of levodopa, and the long-duration response (LDR), which is a sustained antiparkinsonian effect derived from prolonged administration of levodopa that has been shown to last for up to 2 weeks after cessation of drug treatment [7]. Importantly, both types of response are present from the initiation of therapy, although the SDR is largely unnoticed in the beginning as the LDR masks it [11, 12].

For many years, the development of wearing-off has been mainly attributed to a shortening of the SDR over time [13, 14] as a result of the progressive reduction in the ability of the nigrostriatal neurons to synthesize and to store dopamine formed from exogenous levodopa [15, 16]. However, a number of studies have shown that the magnitude of the SDR and modifications of the LDR during the course of PD also have a critical role in the development of symptom re-emergence [17].

Role of the LDR in the Development of Motor Fluctuations

To better understand the changes that occur in the motor response to chronic levodopa therapy and how it relates to the patients' perceptions of motor fluctuations, Nutt et al. [18] measured the magnitude of the LDR (measured as baseline tapping speed) and SDR (measured as difference between peak and baseline tapping speed) in 18 PD subjects prior to and 6, 12, 24, and 48 months after the start of levodopa therapy. The Nutt study (fig. 1) demonstrated that the magnitude of the SDR progressively increased ($p < 0.0001$) while the LDR decayed ($p < 0.0004$), and by 4 years the SDR magnitude was inversely related to the LDR magnitude ($p < 0.022$). This suggests that the

Fig. 2. Schematic depicting the decline in the LDR and its inverse relationship to the magnitude of the SDR.

LDR is a determinant of the magnitude of the SDR. A key observation made in this study was that the duration of the SDR did not differentiate between subjects with and without motor fluctuations. This indicates that the emergence of fluctuations is not simply caused by a shortening of the SDR to levodopa as previously held. In line with other studies, the rate at which the LDR decayed was related to disease severity and to the duration of therapy. Crucially, subject awareness of fluctuations generally reflected the magnitude of change in the tapping speed and subject reports of motor fluctuations tended to be associated with a large SDR ($p < 0.054$). Thus, the study clearly showed that the magnitude of the response to levodopa is a key determinant of whether a patient is aware of fluctuations related to levodopa dosing. This is supported by observations in *de novo* patients with mild general motor disability but severe focal disability (e.g. one side or body part more severely affected). These patients might show a clear SDR in the affected body parts, but they do not perceive any wearing-off of effect as their overall clinical motor state is only minimally changed. Furthermore, it is also consistent with the ELLDOPA study [7], which, as discussed earlier, showed that patients who received the highest daily levodopa dose per day (600 mg/day) showed the greatest magnitude of benefit but also the highest percentage of wearing-off.

Similar results were reported by Zappia et al. [17] who found that the duration of the SDR did not significantly change within the first year of therapy, but that 24% of patients lost the LDR to levodopa. These studies demonstrate the pivotal roles of the LDR and the magnitude

rather than duration of the SDR in the development of motor fluctuations in the early years of levodopa therapy. They further suggest that when a sustained LDR is present, the SDR is usually masked and patients may therefore be classified clinically as stable responders to levodopa therapy even though they are experiencing fluctuations. As the LDR is progressively lost, patients lose the smooth drug effect and the magnitude of the SDR increases (fig. 2). Patients are then clinically observed to become 'fluctuators' because the degree of benefit is now dependent on the magnitude of the SDR. Overall, the available evidence suggests that in the earlier stages of PD, where the difference between the ON and OFF states is less pronounced, any fluctuations in levodopa response are not noticed by the patient and therefore not reported.

The Wearing-Off Phenomenon Is More than Just the Re-Emergence of Motor Symptoms

When patients develop signs of wearing-off, rather than experiencing the consistent and sustained response to levodopa that they had previously enjoyed, they often start to notice subtle fluctuations in a variety of signs and symptoms [19]. Importantly, the first signs of symptom re-emergence are neither well established nor the same for all patients. For example, while in some patients the first signs of symptom re-emergence are characterized by a return of the classic parkinsonian motor symptoms, for others signs can also include non-motor symptoms such as pain and other sensory manifestations, anxiety, fatigue, mood changes, difficulty in thinking, restlessness, sweating or increased salivation [20]. Indeed, the re-emergence of non-motor symptoms has been suggested to precede the re-emergence of motor symptoms [21, 22]. Since non-motor symptoms can be very subtle in the beginning, it might be difficult at first for patients to link them to a change in the effect of their PD medication.

As the signs of wearing-off can vary greatly among patients, they may often go unrecognized by physicians and, therefore, remain untreated until they become prominent and disabling. Patients may also be unaware that the more subtle changes they are experiencing are related to PD and thus may not discuss the full range of their symptoms with their physician, unless specifically prompted (e.g. using a questionnaire) [19]. Moreover, many physicians do not currently associate 'wearing-off' with re-emergence of non-motor symptoms, despite the fact that such symptoms can have a greater impact on the patient than motor fluctuations [20, 23]. Indeed, although

the non-motor signs associated with wearing-off have been described for more than 20 years [20, 24, 25], there have been few attempts to gauge the incidence of these features. As such, they have often been overlooked and, therefore, underestimated. However, one survey found that in a population of patients suffering from motor complications, 100% also reported the presence of non-motor symptoms (anxiety, 66%; drenching sweats, 64%; slowness of thinking, 58%; fatigue, 56%, and akathisia, 54%), with the majority experiencing a combination of symptoms [20].

Pathophysiological Mechanisms in Wearing-Off

A 'wearing-off' effect is the normal and predictable response of any sensitive pharmacological system when activated with a potent but short-acting agent. There are numerous and well-accepted examples in general pharmacology and clinical practice. For example, an SDR is expected for morphine analgesia; pilocarpine drops for mydriasis or adrenaline subcutaneous administration to increase blood pressure and heart rate. Similarly, levodopa has a plasma half-life of 60–90 min and possesses a very powerful antiparkinsonian effect. So, it is not surprising that such stimulation of the dopaminergic system in PD leads to a change in response that manifests as wearing-off and other motor complications. In this section, we review the main pathophysiological mechanisms implicated in the origin of motor fluctuations in PD.

Presynaptic Mechanisms in Wearing-Off

The finding that motor improvement following acute intravenous levodopa challenge lasts longer in de novo and stable patients than in those who are already suffering motor fluctuations was key to the development of the 'storage hypothesis', which implies that loss of presynaptic dopaminergic terminals reduces the capacity of the striatum to store dopamine and buffer the oscillations in plasma levodopa levels [16, 26]. Certainly, the pharmacokinetics of levodopa-dopamine in the brain is drastically changed after dopaminergic denervation of the striatum. In the rat with a 6-hydroxydopamine (6-OHDA) lesion of the nigrostriatal pathway, peak striatal dopamine levels and the area under the curve for synaptic dopamine availability are significantly lower in animals with larger lesions [15], which correlates with a shorter duration motor response [27]. In patients, the availability of dopamine

in the synapse has been measured by PET using the D-2 receptor antagonist raclopride as the radioligand. Raclopride was administered before and after levodopa intake in patients with and without motor fluctuations, with the result that patients with motor fluctuations demonstrated a greater decrease in raclopride binding than stable patients. Because raclopride competes with dopamine for binding to D2 receptors, reduced raclopride uptake is an index of higher synaptic dopamine levels and, therefore, reduced numbers of dopaminergic terminals [28].

These data have been taken to suggest that the wearing-off phenomenon can be explained on the basis of reduced presynaptic dopamine availability. However, we would argue that reduced pre-synaptic storage of dopamine is not the only major factor that determines the onset of motor fluctuations in PD. In the 6-OHDA rat model – where a full and stable lesion of the nigrostriatal pathway results within less than 3 days – twice daily administration of levodopa is associated with a progressive shortening in the duration of the motor response [29] but, importantly, in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-treated monkeys, repeated administration of short-acting dopamine agonists, such as apomorphine or (+)-PHNO, also results in a shortening of the duration of response [30]. Moreover, the duration of the motor response to short-acting apomorphine is longer in de novo and stable patients with PD than in those with motor fluctuations [31, 32]. So, both levodopa and short-acting dopamine agonists lead to wearing-off. It might be argued that the effects of apomorphine are due to its actions on presynaptic dopamine autoreceptors that result in reduced synaptic release of dopamine [33]. However, this is unlikely to occur in 6-OHDA- and MPTP-lesioned animals and in patients with advanced PD where there is a greater than 90% loss of nigrostriatal terminals. Thus, reduced presynaptic dopamine storage capacity cannot be the only mechanism explaining wearing-off and a role for postsynaptic mechanisms in the origin of motor fluctuations must be considered.

Postsynaptic Mechanisms in Wearing-Off

To evaluate the relevance of postsynaptic mechanisms, it is necessary to break down the wearing-off into its LDR and SDR components. Strong support for the involvement of postsynaptic mechanisms comes from the slow decay of the LDR on withdrawing dopamine agonist treatment in patients with de novo PD. For example, the time taken for motor symptoms to deteriorate back to

baseline after stopping treatment with ropinirole (9–21 mg daily) was 6.2 ± 1.7 days [34] and 9.0 ± 1.9 days with the short-acting agonist lisuride [35]. Interestingly, similar studies in de novo PD patients with the very long-acting dopamine agonist cabergoline showed a shorter LDR compared to short-acting lisuride. From these results, it can be concluded that dopamine agonists have LDR effects that are similar to levodopa and that postsynaptic effects must contribute. We suggest that these postsynaptic changes include complex alterations in genes and protein at the striatal level mediating receptor and intracellular activity and also functional abnormalities in basal ganglia output pathways [36].

Dopamine Depletion, the Basal Ganglia and Motor Fluctuations

The overall determinant of the motor features in PD is the physiological state of basal ganglia output activity. Dopamine depletion can be very severe but motor features of PD can be controlled or prevented if subthalamic nucleus (STN) and globus pallidus pars interna neuronal firing stays within normal levels. Accordingly, therapeutic interventions aimed at reducing the abnormal and excessive activity of basal ganglia output neurons in PD should improve the SDR to levodopa. This is precisely what has been found in the 6-OHDA rat model [37, 38] where lesions of the STN ameliorated wearing-off and, more importantly, are a characteristic effect of functional neurosurgery for PD. Thus, modulation of basal ganglia output activity, without changing striatal dopamine availability, modifies the SDR. This has led to the suggestion that alterations of compensatory mechanisms involved in maintaining basal ganglia homeostasis in PD are compromised by the deleterious effects of ‘pulsatile’ dopaminergic stimulation caused by the use of short-acting drug treatments [39, 40].

Role of Pulsatile Dopaminergic Stimulation in Motor Fluctuations

The role of the nigrostriatal dopaminergic system is primarily to exert a modulatory effect on basal ganglia circuitry, particularly the striatum, but also on other nuclei of the basal ganglia and on thalamic and brain stem regions (fig. 3a). Phasic release of dopamine occurs in response to the firing of dopaminergic neurons, and this is mediated by spike-dependent release of dopamine into

the synaptic cleft resulting in potent but brief activation of postsynaptic dopamine receptors [41, 42]. Under normal circumstances, neuronal activity adapts quickly to phasic release and firing stops when events lose novelty or relevance [43]. However, the loss of phasic dopamine release is important and it is likely to be responsible for some specific motor and non-motor problems in PD, such as learning deficits, anodynia and, more relevantly in the context of this review, levodopa-induced motor complications.

However, the majority of striatal dopaminergic terminals make ‘open’ contact with their target cells, delivering dopamine outside the typical synaptic cleft and beyond the reach of classical release and reuptake mechanisms [44]. This is the basis for ‘volume transmission’ in the striatum that gives rise to tonic dopaminergic stimulation of postsynaptic receptors. Through volume transmission, the effects of tonic release of dopamine extend widely over the striatum [41, 42] and exert effects on medium spiny neurons that make up the striatal output pathways [45]. The normal functioning of the nigrostriatal dopaminergic system and the basal ganglia mainly depends on tonic dopaminergic activity and it forms one of the main mechanisms underlying functional compensation for the effects of dopaminergic cell degeneration in the early stages of PD. Accordingly, dopaminergic activity during the initial period of nigrostriatal terminal loss (i.e. up to 50–60% neuronal loss) may be maintained by tonic dopamine release through a mechanism termed ‘passive stabilization’ [46]. The preservation of tonic stimulation when using dopaminergic replacement therapies in early PD is therefore key to restoring the normal physiological function of the basal ganglia and in the prevention of the onset of ‘wearing-off’ and other motor complications.

Non-Motor Features of Wearing-Off

By contrast with the plethora of studies examining typical motor wearing-off, the pathophysiological mechanisms underlying non-motor features have received less attention. However, the temporal relationship of non-motor fluctuations to dopaminergic therapy is indicative of a role for the dopaminergic system probably similar to the one explaining motor fluctuations. To date, there have been little or no studies that report on mechanisms associated with non-motor fluctuations. One of the major hurdles to this important area of research is the lack of a reliable model for non-motor fluctuations, and even

Fig. 3. Diagram of the main pathways of the basal ganglia in different functional states. Black arrows indicate dopaminergic connections, dark grey arrows indicate GABAergic connections and light grey arrows indicate glutamatergic connections. SN = Substantia nigra; GPe = globus pallidus pars externa; GPi = globus pallidus pars interna. **a** Normal basal ganglia highlighting that dopaminergic innervation is not limited to the striatum and the various 'internal' loops, which appear designed to maintain activity of basal ganglia nuclei within normal range. **b** Modifications induced by dopaminergic depletion in early PD. Hyperactivity of the STN precedes significant dopamine putaminal depletion. Thus, the GPe is still functionally operative and overstimulated by the STN. This leads to increased inhibition from the GPe to the GPi, which partially compensates for the augmented excitation from the STN and reduced inhibition in the 'direct' pathway.

the classical models of PD produced by using MPTP or 6-OHDA to destroy the nigrostriatal pathway have not been utilized to study non-motor fluctuations. In PD, the subjective nature of these manifestations means that they are often only detected by speaking to patients or carers and not on examination.

For example, sensory symptoms (such as pain, tingling, burning) occur in about 43% of PD patients in the

OFF state [47]. These symptoms are typically focal and somatotopically distributed, suggesting somehow a primary disorder in the processing of somatosensory signals. However, clinical examination and neurophysiological evaluation fail to reveal any primary defect of sensation. A link between pain, which is the most common and disabling sensory complaint in PD patients, and the basal ganglia is clearly demonstrated by its partial reversal

Fig. 3. Diagram of the main pathways of the basal ganglia in different functional states. Black arrows indicate dopaminergic connections, dark grey arrows indicate GABAergic connections and light grey arrows indicate glutamatergic connections. SN = Substantia nigra; GPe = globus pallidus pars externa; GPi = globus pallidus pars interna. **c** Changes associated with advanced PD and the effects of levodopa. At this stage, striatal depletion has progressed and both striatopallidal projections are altered. There is increased inhibition from the GABA-enkephalin projection to the GPe that is hypoactive and no longer compensates for STN hyperactivity. This results in overactivity of GPi output and abnormal inhibition of motor areas. In this state, levodopa does not restore the normal physiology of the basal ganglia. Adapted from Obeso et al. [36].

following a single administration of levodopa or apomorphine. A direct relationship is demonstrated in patients with unilateral pain, without associated dystonic features, in whom pallidotomy or subthalamotomy completely abolishes the pain [Obeso, unpubl. obs.]. Dopaminergic depletion in PD could therefore alter the mechanisms of sensory processing, provoking the spontaneous onset of sensory symptoms. So, once again, the need to target dopaminergic therapy in early PD towards restoring normal physiological function seems highly important in preventing non-motor components of ‘wearing-off’ from appearing.

Clinical Relevance of Early Recognition of Wearing-Off

In clinical practice, treatment is initiated once the compensatory mechanisms operative in early stages of the loss of the nigrostriatal pathway have failed. As a result, there is already a reduced capacity at the presynaptic dopamine terminal level to compensate for changes in dopamine availability associated with fluctuations in plasma and brain levodopa levels after oral administration. Therefore, the output of basal ganglia motor oscillates precariously between various abnormal states. The critical and therapeutically relevant point is that standard short-acting levodopa formulations lead to levels of

striatal dopamine and dopamine receptor stimulation different from those prevailing under normal conditions and oscillating between subphysiological and supraphysiological levels. This being a reflection of the ‘peaks’ and ‘troughs’ associated with changes in plasma levodopa concentrations that characterize the use of standard levodopa preparations. Thus, standard levodopa administration does not restore the normal physiology of the basal ganglia (fig. 3c), but induces, through ‘pulsatile’ stimulation, molecular abnormalities such as phosphorylation of NMDA subunits and upregulation of AMPA receptors in medium spiny striatal neurons that underlie wearing-off [48, 49].

The mechanisms underlying ‘wearing-off’ and dyskinesia also appear closely interrelated. For example, in a post-hoc analysis of the CALM-PD study, Hauser et al. [50] found that motor fluctuations (wearing-off) are often the first motor complication to occur and that the presence of motor fluctuations is a significant predictor of earlier dyskinesia and vice versa. This feeds into the suggestion that the emergence of wearing-off is one of the first clinical signs that the patient is entering a more complex phase of the disease.

Strategies to extend the plasma and striatal half-life of levodopa and thereby avoid such pulsatile stimulation are therefore of considerable interest. For example, administration of levodopa/carbidopa with a COMT inhibitor, such as entacapone, extends its elimination half-life of

levodopa and leads to more stable and predictable plasma levels of the drug that remain in the therapeutic range for longer periods of time [51]. In the early stages of PD, this pharmacokinetic and pharmacodynamic effect of entacapone on levodopa levels may permit treatment with more continuous dopaminergic stimulation and partially restore the normal physiological functioning of the motor system in conjunction with those basal ganglia compensatory mechanisms that are still operative. This is to some extent supported by experiments in the 6-OHDA rat model where treatment with the combination of levodopa, carbidopa and entacapone was shown to significantly attenuate the induction of the SDR and potentiate the LDR [52], although it did not normalize changes in basal ganglia activity induced by the loss of the nigrostriatal pathway. The latter may be related to the fact that in these experiments levodopa/carbidopa/entacapone was given twice a day, when it is believed that stable levodopa delivery requires a higher number of doses, i.e. at least four times per day in humans. Indeed, in related studies, the administration of levodopa/carbidopa and entacapone four times daily to MPTP-treated primates resulted in continuous improvement in motor function, and reduced dyskinesia induction compared to levodopa administered alone, which induced pulsatile motor function, and compared to twice daily levodopa treatment that was even more pulsatile in nature [53]. However, the results of a clinical trial (STRIDE-PD) designed to test this hypothesis in early PD patients have been recently reported as negative, as four times daily dosing with levodopa/carbidopa/entacapone resulted in a shorter time to dyskinesias compared with four times daily dosing with traditional levodopa/carbidopa [reported in 54]. Factors such as compliance and time interval between doses may have in practice reduced the theoretical aim of achieving stable levodopa plasma levels. Thus, while the negative results of this trial go against the early use of levodopa in PD, they should not negate the wealth of experimental and clinical data indicating that sustained dopaminergic stimulation reduces the likelihood of motor complications and is the best pharmacological approach to treat them once developed.

In summary, compensatory mechanisms in the basal ganglia allow dopaminergic striatal depletion to be asymptomatic until relatively high deficits are reached. At this stage, the basal ganglia becomes dysfunctional and clinical features become severe enough to allow the diagnosis of PD. Disease progression is associated with further nigral cell loss, augmented dopamine depletion and marked physiological changes in the output nuclei of

the basal ganglia which lose their capacity to compensate. As a consequence, restoring dopaminergic deficit with short-acting drugs will soon be associated with an SDR and the induction of 'wearing-off', as pulsatile dopaminergic stimulation fails to provide a physiological restoration of striatal dopaminergic activity.

Conclusions and Implications for Treatment

By the time patients are diagnosed with PD, they have already suffered a significant loss of dopaminergic neurons and therefore are already susceptible to the effects of pulsatile dopaminergic stimulation. The wearing-off phenomenon may be one of the most important indicators that the patient is entering the more complex phase of the disease; but because the awareness of motor fluctuations appears to be dependent on the magnitude of the SDR which is often masked by the LDR, it is highly likely that many patients who are apparently 'doing fine' are actually experiencing fluctuations.

If pulsatile treatment continues at this stage, it can only lead to an even more nonphysiologic situation in the basal ganglia. Thus, the earlier fluctuations are managed, the better chance the patient has of improved long-term outcomes.

It is therefore logical that treatment should be optimized from the very beginning. Recent advances in the development of once-daily formulations of pramipexole and ropinirole are a step in the right direction, but could be improved upon. We propose that when levodopa is initiated, either alone or added to previous treatment with a dopamine agonist, it should be optimized to have as long a half-life as possible and given frequently enough to avoid drastic differences in plasma levels.

References

- 1 Olanow CW, Watts RL, Koller WC: An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. *Neurology* 2001;56:S1-S88.
- 2 Olanow CW, Agid Y, Mizuno Y, Albanese A, Bonucelli U, Damier P, De Yebenes J, Gershnik O, Guttman M, Grandas F, Hallett M, Hornykiewicz O, Jenner P, Katzenschlager R, Langston WJ, LeWitt P, Melamed E, Mena MA, Michel PP, Mytilineou C, Obeso JA, Poewe W, Quinn N, Raisman-Vozari R, Rajput AH, Rascol O, Sampaio C, Stocchi F: Levodopa in the treatment of Parkinson's disease: current controversies. *Mov Disord* 2004;19:997.

- 3 Rascol O, Goetz C, Koller W, Poewe W, Sampaio C: Treatment interventions for Parkinson's disease: an evidence based assessment. *Lancet* 2002;359:1589–1598.
- 4 Goetz CG, Poewe W, Rascol O, Sampaio C: Evidence-based medical review update: pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. *Mov Disord* 2005;20:523–539.
- 5 Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE: A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. *N Engl J Med* 2000;342:1484–1491.
- 6 Parkinson Study Group: Pramipexole vs. levodopa as initial treatment for Parkinson disease: a randomized controlled trial. *JAMA* 2000;284:1931–1938.
- 7 Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, Olanow CW, Tanner C, Marek K: Levodopa and the progression of Parkinson's disease. *N Engl J Med* 2004;351:2498–2508.
- 8 Fahn S: Does levodopa slow or hasten the rate of progression of Parkinson's disease? *J Neurol* 2005;252(suppl 4):IV37–IV42.
- 9 Thomas A, Bonanni L, Di Iorio A, Varanese S, Anzellotti F, D'Andreagiovanni A, Stocchi F, Onofri M: End-of-dose deterioration in non ergolinic dopamine agonist monotherapy of Parkinson's disease. *J Neurol* 2006;253:1633–1639.
- 10 Muentert MD, Tyce GM: L-dopa therapy of Parkinson's disease: plasma L-dopa concentration, therapeutic response, and side effects. *Mayo Clin Proc* 1971;46:231–239.
- 11 Nutt JG, Woodward WR, Carter JH, Gancher ST: Effect of long-term therapy on the pharmacodynamics of levodopa. Relation to on-off phenomenon. *Arch Neurol* 1992;49:1123–1130.
- 12 Nutt JG, Holford NH: The response to levodopa in Parkinson's disease: imposing pharmacological law and order. *Ann Neurol* 1996;39:561–573.
- 13 Hughes AJ, Frankel JP, Kempster PA, Stern GM, Lees AJ: Motor response to levodopa in patients with parkinsonian motor fluctuations: a follow-up study over three years. *J Neurol Neurosurg Psychiatry* 1994;57:430–434.
- 14 Contin M, Riva R, Martinelli P, Cortelli P, Albani F, Baruzzi A: Longitudinal monitoring of the levodopa concentration-effect relationship in Parkinson's disease. *Neurology* 1994;44:1287–1292.
- 15 Spencer SE, Wooten GF: Altered pharmacokinetics of L-dopa metabolism in rat striatum deprived of dopaminergic innervation. *Neurology* 1984;34:1105–1108.
- 16 Fabbrini G, Mouradian MM, Juncos JL, Schlegel J, Mohr E, Chase TN: Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms. I. *Ann Neurol* 1988;24:366–371.
- 17 Zappia M, Oliveri RL, Montesanti R, Rizzo M, Bosco D, Plastino M, Crescibene L, Bastone L, Aguglia U, Gambardella A, Quattrone A: Loss of long-duration response to levodopa over time in PD: implications for wearing-off. *Neurology* 1999;52:763–767.
- 18 Nutt JG, Carter JH, Lea ES, Sexton GJ: Evolution of the response to levodopa during the first 4 years of therapy. *Ann Neurol* 2002;51:686–693.
- 19 Stacy M, Bowron A, Guttman M, Hauser R, Hughes K, Larsen JP, LeWitt P, Oertel W, Quinn N, Sethi K, Stocchi F: Identification of motor and nonmotor wearing-off in Parkinson's disease: comparison of a patient questionnaire versus a clinician assessment. *Mov Disord* 2005;20:726–733.
- 20 Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, Poncet M, Cherif AA: Nonmotor fluctuations in Parkinson's disease: frequent and disabling. *Neurology* 2002;59:408–413.
- 21 Chaudhuri KR, Yates L, Martinez-Martin P: The non-motor symptom complex of Parkinson's disease: a comprehensive assessment is essential. *Curr Neurol Neurosci Rep* 2005;5:275–283.
- 22 Isaacson SH: Non-motor symptoms frequently herald end-of-dose wearing off in Parkinson's disease. *Mov Disord* 2005;20:S52.
- 23 Thanvi BR, Munshi SK, Vijaykumar N, Lo TC: Neuropsychiatric non-motor aspects of Parkinson's disease. *Postgrad Med J* 2003;79:561–565.
- 24 Hillen ME, Sage JJ: Nonmotor fluctuations in patients with Parkinson's disease. *Neurology* 1996;47:1180–1183.
- 25 Raudino F: Non motor off in Parkinson's disease. *Acta Neurol Scand* 2001;104:312–315.
- 26 Chase TN, Baronti F, Fabbrini G, Heuser IJ, Juncos JL, Mouradian MM: Rationale for continuous dopaminomimetic therapy of Parkinson's disease. *Neurology* 1989;39:7–10; discussion 9.
- 27 Papa SM, Engber TM, Kask AM, Chase TN: Motor fluctuations in levodopa treated parkinsonian rats: relation to lesion extent and treatment duration. *Brain Res* 1994;662:69–74.
- 28 de la Fuente-Fernandez R, Lu JQ, Sossi V, Jivan S, Schulzer M, Holden JE, Lee CS, Ruth TJ, Calne DB, Stoessl AJ: Biochemical variations in the synaptic level of dopamine precede motor fluctuations in Parkinson's disease: PET evidence of increased dopamine turnover. *Ann Neurol* 2001;49:298–303.
- 29 Engber TM, Papa SM, Boldry RC, Chase TN: NMDA receptor blockade reverses motor response alterations induced by levodopa. *Neuroreport* 1994;5:2586–2588.
- 30 Luquin MR, Laguna J, Herrero MT, Obeso JA: Behavioral tolerance to repeated apomorphine administration in parkinsonian monkeys. *J Neurol Sci* 1993;114:40–44.
- 31 Grandas F, Obeso JA: Motor response following repeated apomorphine administration is reduced in Parkinson's disease. *Clin Neuropharmacol* 1989;12:14–22.
- 32 Grandas F, Gancher ST, Rodriguez M, Lera G, Nutt JG, Obeso JA: Differences in the motor response to apomorphine between untreated and fluctuating patients with Parkinson's disease. *Clin Neuropharmacol* 1992;15:13–18.
- 33 de la Fuente-Fernandez R, Sossi V, Huang Z, Furtado S, Lu JQ, Calne DB, Ruth TJ, Stoessl AJ: Levodopa-induced changes in synaptic dopamine levels increase with progression of Parkinson's disease: implications for dyskinesias. *Brain* 2004;127:2747–2754.
- 34 Barbato L, Stocchi F, Monge A, Vacca L, Ruggieri S, Nordera G, Marsden CD: The long-duration action of levodopa may be due to a postsynaptic effect. *Clin Neuropharmacol* 1997;20:394–401.
- 35 Stocchi F, Vacca L, Berardelli A, De Pandis F, Ruggieri S: Long-duration effect and the postsynaptic compartment: study using a dopamine agonist with a short half-life. *Mov Disord* 2001;16:301–305.
- 36 Obeso JA, Rodriguez-Oroz M, Marin C, Alonso F, Zamarbide I, Lanciego JL, Rodriguez-Diaz M: The origin of motor fluctuations in Parkinson's disease: importance of dopaminergic innervation and basal ganglia circuits. *Neurology* 2004;62:S17–S30.
- 37 Marin C, Jimenez A, Tolosa E, Bonastre M, Bove J: Bilateral subthalamic nucleus lesion reverses L-dopa-induced motor fluctuations and facilitates dyskinetic movements in hemiparkinsonian rats. *Synapse* 2004;51:140–150.
- 38 Perier C, Marin C, Jimenez A, Bonastre M, Tolosa E, Hirsch EC: Effect of subthalamic nucleus or entopeduncular nucleus lesion on levodopa-induced neurochemical changes within the basal ganglia and on levodopa-induced motor alterations in 6-hydroxydopamine-lesioned rats. *J Neurochem* 2003;86:1328–1337.
- 39 Olanow CW, Obeso JA, Stocchi F: Drug insight: continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Nat Clin Pract Neurol* 2006;2:382–392.
- 40 Olanow CW, Obeso JA, Stocchi F: Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. *Lancet Neurol* 2006;5:677–687.
- 41 Grace AA: Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience* 1991;41:1–24.
- 42 Onn SP, West AR, Grace AA: Dopamine-mediated regulation of striatal neuronal and network interactions. *Trends Neurosci* 2000;23:S48–S56.
- 43 Schultz W: Predictive reward signal of dopamine neurons. *J Neurophysiol* 1998;80:1–27.

- 44 Moss J, Bolam JP: A dopaminergic axon lattice in the striatum and its relationship with cortical and thalamic terminals. *J Neurosci* 2008;28:11221–11230.
- 45 Wilson CJ, Kawaguchi Y: The origins of two-state spontaneous membrane potential fluctuations of neostriatal spiny neurons. *J Neurosci* 1996;16:2397–2410.
- 46 Bergstrom BP, Garriss PA: 'Passive stabilization' of striatal extracellular dopamine across the lesion spectrum encompassing the presymptomatic phase of Parkinson's disease: a voltammetric study in the 6-OHDA-lesioned rat. *J Neurochem* 2003;87:1224–1236.
- 47 Snider SR, Fahn S, Isgreen WP, Cote LJ: Primary sensory symptoms in parkinsonism. *Neurology* 1976;26:423–429.
- 48 Obeso JA, Grandas F, Herrero MT, Horowski R: The role of pulsatile versus continuous dopamine receptor stimulation for functional recovery in Parkinson's disease. *Eur J Neurosci* 1994;6:889–897.
- 49 Chase TN, Oh JD: Striatal dopamine- and glutamate-mediated dysregulation in experimental parkinsonism. *Trends Neurosci* 2000;23:S86–91.
- 50 Hauser RA, McDermott MP, Messing S: Factors associated with the development of motor fluctuations and dyskinesias in Parkinson disease. *Arch Neurol* 2006;63:1756–1760.
- 51 Gordin A, Kaakkola S, Teravainen H: Clinical advantages of COMT inhibition with entacapone – a review. *J Neural Transm* 2004;111:1343–1363.
- 52 Marin C, Aguilar E, Mengod G, Cortes R, Rodriguez-Oroz M, Obeso J: Entacapone potentiates the long-duration response to levodopa but does not normalize levodopa-induced molecular changes. *Neurobiol Dis* 2008;32:340–348.
- 53 Smith LA, Jackson MJ, Al-Barghouthy G, Rose S, Kuoppamaki M, Olanow W, Jenner P: Multiple small doses of levodopa plus entacapone produce continuous dopaminergic stimulation and reduce dyskinesia induction in MPTP-treated drug-naïve primates. *Mov Disord* 2005;20:306–314.
- 54 Olanow CW, Stern MB, Sethi K: The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology* 2009;72:S1–S136.