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

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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-
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
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. 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.

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

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 post synaptic effects must contribute. We suggest that these post synaptic 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
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. 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.
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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

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**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].
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.

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