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Levodopa-induced dyskinesias and their management

Abstract This paper reviews the epidemiology, pathophysiology, clinical features and rationale for managing dyskinesias associated with Parkinson's disease. These are a common clinical problem occurring in up to 90 % of patients and more frequently affect those with early-onset. Dyskinesias have a negative impact on quality of life and are an important cause

of disability. Their precise etiology is still poorly understood, although it is recognized that dopaminergic pre-synaptic and post-synaptic mechanisms are involved together with extra-dopaminergic factors. The phenomenology of dyskinesias encompasses a variable mixture of two prevalent features: dystonia and chorea. We have studied their time course following a single acute levodopa challenge and have found that dystonia occurs throughout the duration of the on period, whereas choreiform movements occur only at the peak of therapeutic dopaminergic motor responses. This allows a schematic relationship to be drawn between a short duration motor response and the occurrence of dystonia and chorea. There is currently no satisfactory treatment for dys-

kinesias. Managing the therapeutic window does not provide an adequate solution due to the appearance of a dyskinesia threshold dose that narrows the therapeutic margin. High frequency stimulation of the subthalamic nucleus probably has some specific anti-dyskinetic action, but is limited by the small number of patients who are candidates for this treatment. Research efforts are currently focused on the development of specific anti-dyskinetic medications. Their availability will certainly change the current clinical practice and will widen again the therapeutic window of dopaminergic medications that has now become too narrow.

Key words Parkinson's disease · dyskinesias · levodopa · dopamine agonists

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Why do PD patients develop dyskinesias?

Following a period of stable response to dopaminergic medication (the “honeymoon” period), Parkinson's disease (PD) patients gradually develop two progressive clinical phenomena requiring changes in the clinical management: motor fluctuations and dyskinesias. These two phenomena are intrinsically interconnected, but often require opposite treatment attitudes, because increases of dopaminergic treatment often improve fluctuations, but worsen dyskinesias. A possible solution to this dilemma resides in the administration of additional anti-dyskinetic medication; unfortunately, how-

ever, drugs with enough anti-dyskinetic potency have not yet been developed.

Epidemiology

Dyskinesias are a central side effect of dopaminergic therapy and represent a major clinical problem in the management of patients with PD. Early studies performed before the levodopa era did not describe the presence of motor fluctuation or dyskinesias [32]. Dyskinesias were first observed following the introduction of levodopa monotherapy. In his seminal paper on levodopa treatment of PD, Cotzias [20] first observed “the

reversible induction of athetoid movements, which have been observed thus far only in patients with PD and only when the therapeutic effect was significant". Later observations clearly identified dyskinesias as a side-effect of levodopa treatment [4, 5]. It was later recognized that dyskinesias can also be caused by dopamine agonists, particularly if short-acting and of adequate potency [22, 35]. It became thus clear that any type of exogenous dopaminergic stimulation in a denervated striatum can cause dyskinesias [46], but pulsatile stimulation produced by short-acting drugs (as typically occurs with levodopa) particularly favors their occurrence [67]. The expression "levodopa-induced dyskinesias" is still currently used, although levodopa is not the only drug causing dyskinesias in PD patients [55].

Awareness of these levodopa complications has influenced treatment strategies for PD. In modern series, dyskinesias occur later than in earlier series, with an approximate risk of dyskinesias just short of 40 % following 4–6 years of levodopa monotherapy [1]. The introduction of dopamine agonists since early disease stages has further reduced and delayed the occurrence of dyskinesias [80]. Based on published series, it has been estimated that PD patients treated for less than 5 years have an 11 % risk of dyskinesias, those treated for 6–9 years have a risk of 32 %, whereas patients treated for more than 10 years have a risk of 89 % [23]. However, these figures are likely to decrease due to the widespread use of dopamine agonists, COMT and MAO inhibitors in the early disease stages.

The three most important risk factors positively associated with increased occurrence of dyskinesias are younger age at disease onset [40, 79], longer disease duration [70, 73] and longer duration of pulsatile dopaminergic treatment (typically, levodopa) [23, 80]. The first two factors are interrelated and almost all patients with early onset disease [81] develop dyskinesias, whereas they are less frequent in patients with late onset PD [43]. PD patients with early disease onset have a high probability to carry mutations for monogenic PD forms and therefore early onset and genetic predisposition are two overlapping and possibly interrelated risk factors. Other risk factors associated with increased risk of dyskinesias are female gender [50, 86] and the occurrence of spe-

cific polymorphisms for dopamine receptors or dopamine transporters [29, 36, 68].

Monogenic forms of PD offer a unique viewpoint to appreciate the role played by genetic factors on the occurrence of dyskinesias. Dyskinesias occur in all patients with *parkin* disease (PARK2) [38], whereas only 84 % of patients with PINK1 disease (PARK6) present dyskinesias [2]. Parkin disease patients have an earlier mean age at disease onset (24 years, compared to 31.6) indicating that genetic make-up influences both variables. The role played by genetic factors is better highlighted in PINK1 patients by comparing those with one mutated allele to patients with two mutated alleles or with wild-type PD [52]. Heterozygous carrier PINK1 patients overlap to wild-type PD patients for age at onset and disease duration, but have a higher incidence of dyskinesias approaching that of PINK1 patients with both alleles affected [52] (Table 1).

Dyskinesias are an important cause of disability in PD and can reduce the patients' quality of life. Mild, non-disabling dyskinesias that occur in early disease stages do not impact significantly on quality of life [53]. However, in patients with advanced disease, more severe dyskinesias may cause poor quality of life, depression and increased health care costs [71]. It has been observed that peak-dose dyskinesias are better accepted by patients than off-period morning dystonia and diphasic dyskinesias [15]. Hence, the patients tolerate *on* state dyskinesias better than those occurring in the off or partial-off periods, because of the associated good motor state and lack of pain or discomfort. The quality of life of patients with advanced PD is not only limited by the occurrence of dyskinesias, but also by insufficient dopaminergic medication secondary to a low dyskinesia threshold [80] (see Fig. 6).

■ Pathophysiology

Levodopa and dopamine agonists do not induce dyskinesias in PD patients (or in experimental animals) that have never been previously treated with dopaminergic medications. The process by which the brain becomes sensitized such that each administration of dopaminer-

Table 1 Comparison of dyskinesias in wild-type PD patients (no allele affected), PINK1 single heterozygote patients (1 allele affected), and PINK1 patients carrying two mutated alleles. From [52]

Number of alleles affected	0	1	2
Number of patients (M:F)	320 (171:149)	20 (9:11)	10 (5:5)
Age at onset (years)	50.4	52.2	41*
Disease duration (years)	11.6	11.5	17.8*
Number of patients with dystonia at onset (%)	19 (6 %)	0	0
Number of patients with motor fluctuations (%)	177 (55 %)	15 (75 %)	7 (70 %)
Number of patients with dyskinesias (%)	151 (47 %)	11 (55 %)	9** (90 %)

* Significantly different from wild-type patients ($p = 0.05$) and from patients with one affected allele ($p = 0.05$),

** Significantly different from wild-type patients ($p = 0.01$)

gic therapy modifies the response to subsequent dopaminergic treatments, is called priming. In this way, with repeated treatment over time, the chance of dopaminergic stimulation eliciting dyskinesias is increased and once dyskinesias have been established, their severity increases. The priming process, which is responsible for the insidious evolution of dyskinesias over time of treatment, is associated with changes in receptors for dopamine or other neurotransmitters [27, 59].

Following priming, the development of dyskinesias largely depends on two additional factors, the pulsatile administration of levodopa (or another short-acting dopaminergic agent) and the degree of dopaminergic denervation in the striatum. The latter plays an important role in setting the threshold required for dyskinesias to develop [9]. A direct relationship between the degree of striatal denervation and the time required to develop dyskinesias has been demonstrated in monkeys rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [78]. The same observation has also been replicated in PD patients [42] and has been indirectly confirmed by the finding that patients with dopa-responsive dystonia, who have parkinsonism without nigrostriatal denervation, uncommonly develop dyskinesias [21].

Dopaminergic denervation and dopaminergic priming induce a series of anatomical and functional changes in the striatum leading to further and more persistent dysfunction. Dyskinesias are probably generated by a persistent enhancement of the responsiveness of striatal medium sized spiny neurons to dopaminergic treatment. This is an aftermath of dopamine depletion and is associated with over-expression of specific components of the signal transduction machinery. If protracted, this condition may ultimately lead to long-term changes in gene expression, which will permanently affect the function of striatal medium spiny neurons [77].

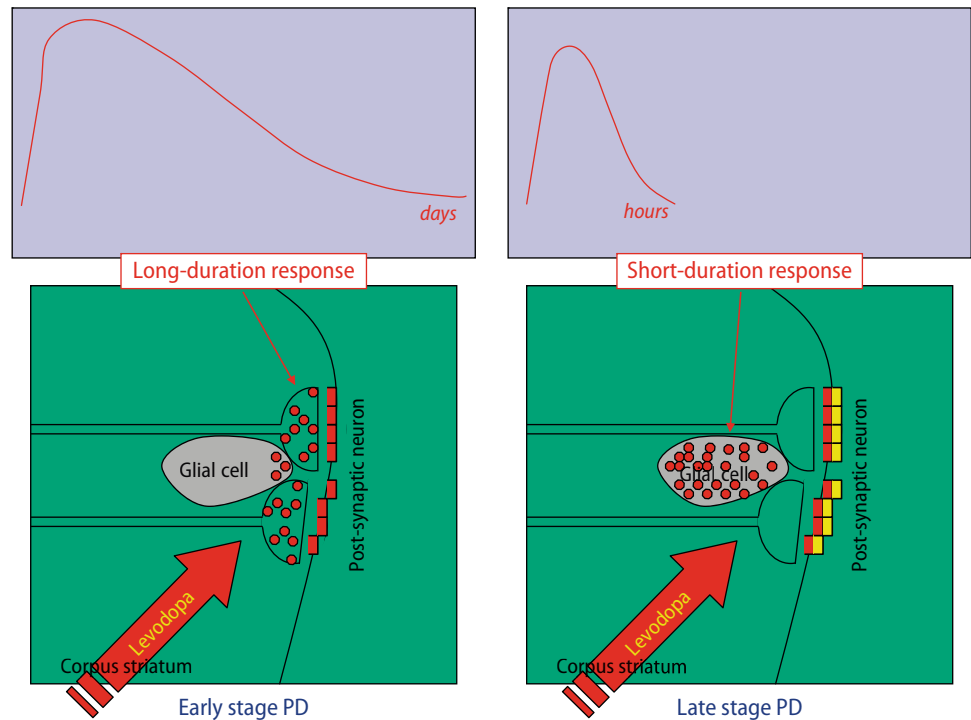
Pre-synaptic dopaminergic changes provide a first-level explanation for the occurrence of both motor complications and dyskinesias. The occurrence of severe dopaminergic denervation implies the loss of compensatory mechanism in the nigrostriatal system, and alters the routes of levodopa uptake and metabolism in the brain. When the dopaminergic system is not severely compromised, the processing of exogenous levodopa occurs primarily in nigrostriatal neurons, where levodopa is converted to dopamine, stored in synaptic vesicles, and released by physiological stimuli into the extracellular space, where clearance of dopamine is ensured from presynaptic reuptake mechanism. In the striatum of patients with mild PD, levodopa levels may be buffered by the compensatory effort of surviving nigrostriatal neurons providing more or less constant dopamine receptor activation. This is clinically evidenced by the occurrence of long-duration anti-parkinsonian responses which outlasts the half-life of levodopa, enabling a stable mo-

tor state. Studies have shown that in more advanced PD, with severe lesions of the nigrostriatal pathway, exogenous levodopa might be decarboxylated to dopamine at non-dopaminergic sites, especially serotonergic neurons, glia and endothelial cells, that are not equipped to store, release and reuptake dopamine in a controlled fashion [12, 47, 55]. As a result, intrasynaptic dopamine levels no longer remain constant, but mirror the broad fluctuation in plasma levodopa levels that occur after each dose, causing dopamine receptors to be exposed to alternating high and low concentrations of dopamine [61]. The clinical counterpart of this condition is the observation of short-duration motor responses to levodopa administration (Fig. 1). The combination of dopamine depletion and the administration of short-lived dopaminergic drugs, causing a pulsatile stimulation of striatal dopamine receptors in contrast to the tonic stimulation that occurs under physiologic circumstances, results in the development of dyskinesias.

Post-synaptic dopaminergic changes are also crucial to the development of dyskinesias in PD. Loss of dopaminergic terminals in the striatum and non-physiological dopaminergic stimulation can cause plastic changes altering the normal functioning of the striatum, further contributing to pulsatile dopamine stimulation. The development of dyskinesias is not correlated with any consistent variations in the density of dopamine receptors [8, 55], but rather to downstream signal transduction pathways causing post-synaptic changes in proteins and gene expression [7, 26, 28]. Dopaminergic priming and behavioral sensitization must cause molecular changes at the post-synaptic level in order to cause dyskinesias.

Non-dopaminergic neurons are also considered to contribute to the pathophysiology of PD dyskinesias. A dysregulation of medium sized striatal spiny neurons can contribute to the pathogenesis of dyskinesias [10, 18]. Non-physiological stimulation of dopamine receptors on striatal spiny neurons leads to changes in subunit phosphorylation pattern of coexpressed ionotropic NMDA and AMPA glutamatergic receptors [17]. Resultant sensitization of these receptors augments cortical excitatory input to the spiny efferent neurons, thus altering striatal output in ways that compromise motor function [14]. Consistent with this possibility is the observation that drugs that block glutamate receptors tend to diminish motor complications in both parkinsonian models and patients [19]. In addition, enhancement of metabotropic glutamatergic receptors may also contribute to the pathogenesis of dyskinesias [76]. Other receptor types located in the basal ganglia also make an important contribution to the functional state of striatal output neurons and are targets for novel anti-dyskinetic treatments. They include: cannabinoid CB1, adenosine A_{2A}, serotonergic 5HT_{2A}, 5HT_{1A}, α -2 adrenergic and opioid receptors [11].

Fig. 1 Long-duration responses depend on the availability of functional dopaminergic nigrostriatal terminals, whereas short-duration responses are generated by levodopa produced outside nigrostriatal dopaminergic terminals, once these are degenerated. In early disease stages, long-duration responses allow for a continuous clinical benefit (“honey moon” period); later on, short-duration responses appear and long-duration responses gradually wane. Super-sensitive post-synaptic dopaminergic receptors are schematically shown in yellow



Clinical features

The perception of dyskinesias may differ between doctors and PD patients (Table 2). It is not uncommon to observe that patients stand dyskinesias in the on-period when they are mobile and try to avoid unsatisfactory partial-on periods, particularly if dystonic dyskinesias occur.

The phenomenology of dyskinesias is variable; they can occur at different times following intake of a dopaminergic medication and variably combine dystonic and choreic movements. The dystonic nature of dyskinesias in PD was recognized early, when the expressions “improvement-dystonia-improvement” (I-D-I) and “dystonia-improvement-dystonia” (D-I-D) were used [58] to describe what was otherwise called “diphasic” [6] and “peak-dose” [54] dyskinesias (Fig. 2). At the same time it

was also noted that choreic features are characteristic of dyskinesias occurring in the on-period [45]. On-period and off-period dyskinesias differ in several ways: the first are mainly choreic and dystonic whereas the latter are purely dystonic. Tremor and pain (likely related to rigidity) may be present in the off-period and decrease with improving motor condition [49, 51] (Fig. 3). This gradient provides a clinical continuum between a hyper-dopaminergic and a hypo-dopaminergic state [51].

■ Dyskinesias following acute levodopa challenge

The clinical phenomenology of dyskinesias (namely, their choreiform or dystonic appearance) has been correlated to the motor response elicited by an acute levodopa challenge.

Ten PD patients (three men and seven women) with a diagnosis according to the Queen Square Brain Bank criteria [33] were evaluated. They had disabling motor fluctuations with prolonged and, at least occasionally, unpredictable off-periods (patients spent 25 % or more of the waking day in the off-state) and on-state dyskinesias. Their Hoehn-Yahr stage was $\geq$ III in the practically defined off-condition [44].

All patients were on dopaminergic therapy with levodopa and one dopamine agonist at the moment of enrollment and gave their written informed consent. The included patients were assessed in the morning, in the practically defined off-condition [44]. The clinical eval-

Table 2 Dyskinesias: patients’ vs. doctors’ viewpoints

Doctors	
• Dyskinesias as a motor phenomenon	
• There are no tools to evaluate the impact of dyskinesias on the patients’ quality of life	
Patients	
• May not be aware of dyskinesias (particularly peak-dose dyskinesias)	
• Underestimate their actual prevalence	
• Estimate the prevalence of fluctuations and dyskinesias that are clinically significant	

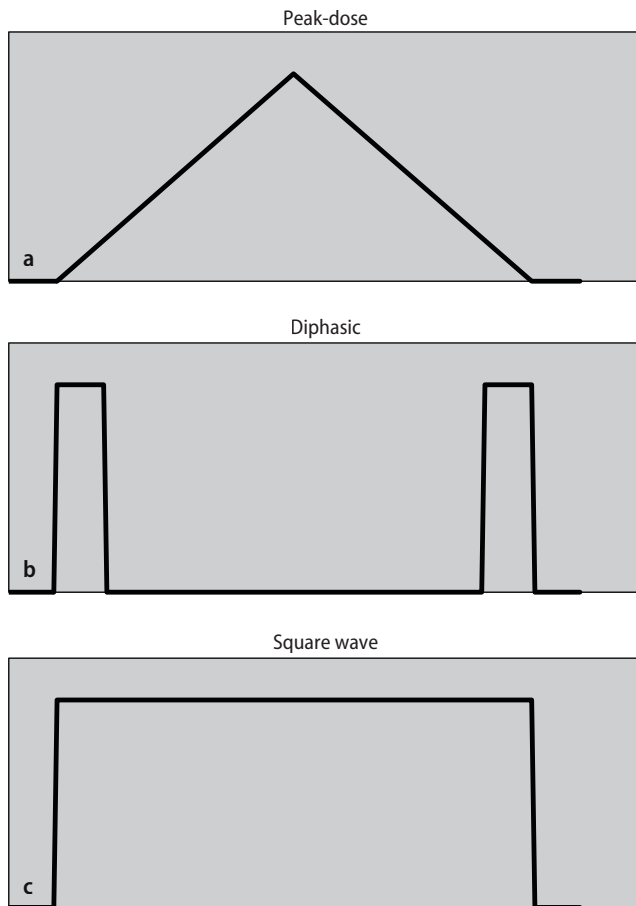


Fig. 2 Peak-dose dyskinesias (corresponding to I-D-I) are the typical on-period dyskinesias observed in PD (A); diphasic dyskinesias (corresponding to D-I-D) occur when patients are in the transitional state from the off- to the on-period (B); square-wave dyskinesias encompass a combination of both types (C)

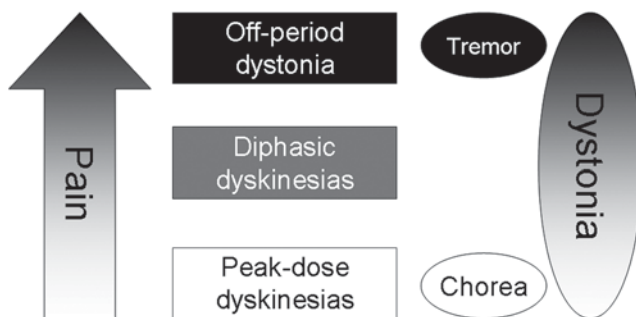


Fig. 3 The transition from peak-dose to diphasic dyskinesias and off-period dystonia is associated with increasing pain and dystonia and the occurrence of tremor. This phenomenological gradient appears as a clinical continuum between a hyperdopaminergic and a hypo-dopaminergic state in patients with complicated PD

uation of each patient was carried out using the following outcome measures: parkinsonian motor disability was assessed using the Unified Parkinson's Disease Rating Scale motor score (UPDRS) [24], upper limb speed

as an index of bradikinesia was assessed by the tapping test (TT) [62]; the evaluation of topography, type and severity of dyskinesias was performed while the patient was sitting, walking and performing TT, by using items 11 and 12 of the Unified Huntington's Rating Scale [34], applied to face, mouth, trunk, upper and lower limbs. Following baseline assessment of all the measured variables, the patients received an acute levodopa/carbidopa (250/25 mg) challenge followed by TT and dyskinesias rating every 15 min and by UPDRS motor assessment every 75 min. The complete clinical evaluation was carried out until the TT score returned $< 15\%$ better than baseline TT score.

The patients had a mean age of $61.2 (\pm 10.4)$ years and a disease duration of $12.3 (\pm 5)$ years. They had been treated with levodopa for $10.6 (\pm 5.1)$ years, had motor fluctuations for the last $4.1 (\pm 2.3)$ years and dyskinesias for $3.9 (\pm 2.5)$ years. At the time of evaluation the total levodopa equivalent dose was $1,086.5 (\pm 529)$ mg. All the patients had an excellent response to levodopa with an average improvement of 53.4% following the acute challenge.

The drug challenge produced appreciable short-duration motor responses in every patient, as shown by the time-dependent decrease of UPDRS motor score and increase of TT scores (Fig. 4A). Onset of motor improvement occurred between 15 and 45 min following the levodopa challenge and averaged 28.5 ± 8.5 min. The on-period lasted for a minimum of 130 and a maximum of 240 min (on average 179.5 ± 41.3 min). Dyskinesias occurred in all patients during the on-period, with dystonic, choreic or combined features (Fig. 4B).

At baseline evaluation, fixed dystonia was present in five patients. In two of them it exclusively involved the trunk, whereas in the other three the distribution was generalized. All patients had on-period dystonia with the features of mobile or fixed dystonia. Two patients presented chorea and dystonia in combination during the entire on-period. Dystonia was more commonly detected in the mouth (9 patients), in the upper limbs (9 patients), in the lower limbs (9 patients), in the trunk (8 patients) and in the face (5 patients). Dystonia severity was ranked in decreasing order from the trunk (mean score 2.0 ± 1.6 , legs 1.5 ± 1.5 , arms 1.4 ± 1.3 , mouth 0.8 ± 1.0 and to the face 0.6 ± 1.0).

Chorea was not observed at baseline and only occurred in the on-period. It was detected in nine patients starting 41.7 ± 26.8 min following levodopa challenge. In three patients, limb chorea preceded the observable on state by an average of 13.5 ± 9.5 min. On-period chorea occurred in decreasing frequency from the upper limbs (8 patients), to the lower limbs (7 patients), the trunk (2 patients), and the mouth or face (1 patient). Chorea severity was maximal in the trunk (0.6 ± 1.1), and milder in the legs and arms (0.4 ± 0.7), or face and mouth (0.1 ± 0.2).

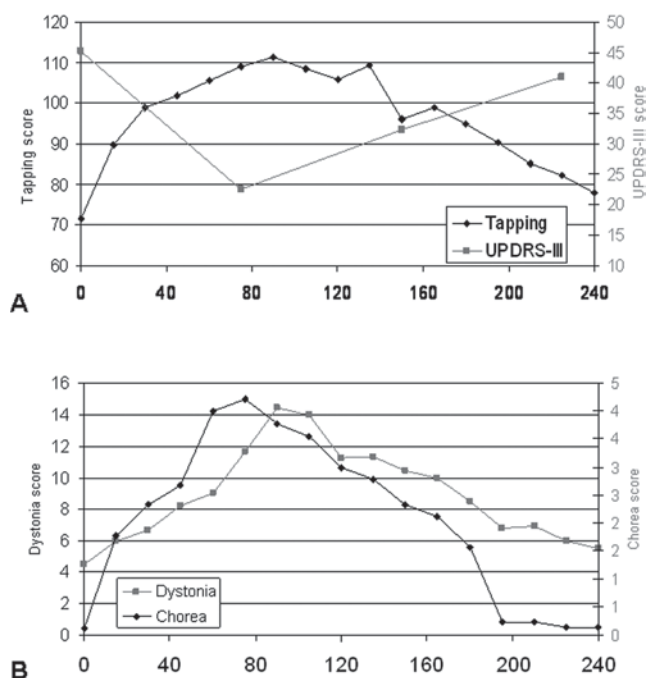
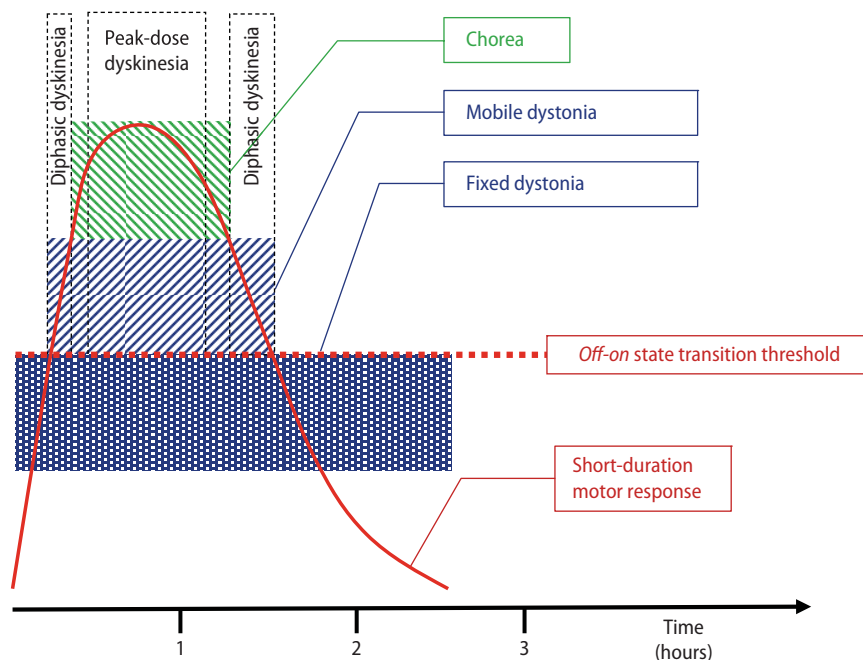


Fig. 4 Mean motor improvement demonstrated by TT and UPDRS motor score (A), compared to the mean chorea and dystonia scores (B) following an acute challenge with levodopa/carbidopa (250/25 mg). X-axes show time in minutes following the acute administration; Y-axes show mean scores, as outlined in the text

When patients returned to the *off* state, off-period dystonia recurred at the same degree and characteristics in all of five patients who had it at baseline, whereas it was not observed in the remaining patients. No choreic movements were detected in the off-period.

Fig. 5 Schematic representation of dyskinesias occurring in relation with a short-duration motor response (red line) elicited by levodopa. Dystonia is indicated in blue, chorea in green. Fixed dystonia occurs throughout the duration of motor response, prevalently in the *off* state. When the patient turns *on* (crossing the dotted red threshold), mobile dystonia (hatched blue area) occurs during the on-period; chorea (hatched green area) can additionally be observed at peak dose. This schematic drawing also indicates that peak-dose dyskinesias are choreic and dystonic, whereas diphasic dyskinesias are dystonic, but not choreic



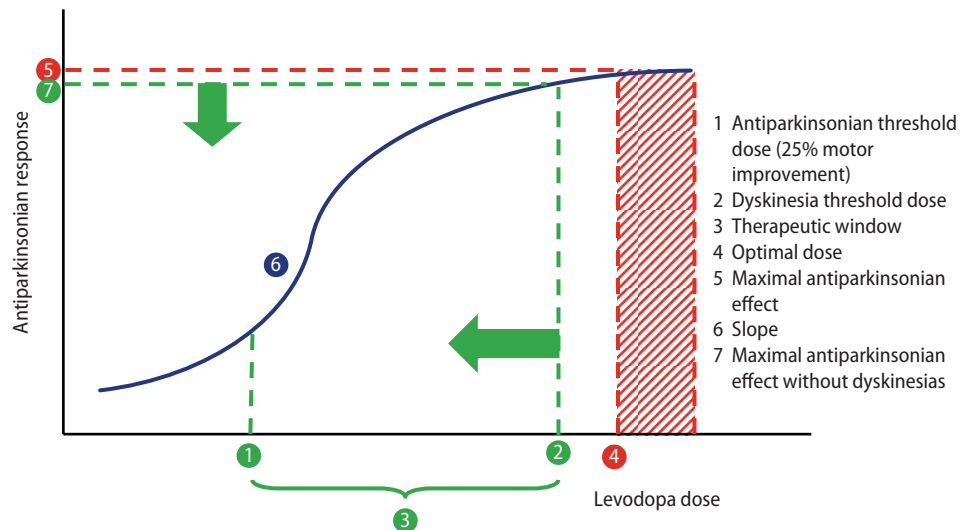
This observational study following acute levodopa challenge was designed to evaluate in a controlled setting the onset and presentation of dyskinesias, from the *off* motor condition preceding the acute challenge through the complete duration of the *on* state, until the end of short-duration motor response. This allowed the comparative features of choreic and dystonic dyskinesias to be observed through the off and on-periods, and to recognize that chorea is only present during the peak of motor effect. Dystonia, instead, was observed throughout the observation period and increased during the duration of motor response. Diphasic dyskinesias, which occurred at the beginning and end of motor response, were mainly dystonic, whereas peak-dose dyskinesias were mixed, choreic and dystonic (Fig. 5). These data extend and complete previous suggestions that dyskinesias constitute a continuum with changing phenomenology [51] and better specify how PD motor response is associated to chorea and dystonia.

It has been already observed that dystonia can also occur in the off motor state [49, 51, 85]. Off-period dystonia is mainly fixed and turns into a mobile form during the on-period. As the motor response induced by acute challenge vanishes, dystonia turns back again to a fixed form.

Rationale for management

The observation that dyskinesias increase in the *on* state has prompted attempts to identify perfectly titrated individual doses for continuous infusions of levodopa [72, 74] or dopamine agonists [65, 66]. This was supposed

Fig. 6 Sigmoid dose-effect curve for anti-parkinsonian response to the administration of increasing doses of levodopa (blue). Motor-related thresholds are red, dyskinesia-related thresholds are green. See text for an explanation



to avoid the occurrence of severe on-state dyskinesias, yet providing an adequate motor condition for the duration of infusion. This historical approach was based on the observation that motor fluctuations and dyskinesias coexisted in patients with complicated PD. It seemed therefore reasonable to address both phenomena using a unique treatment strategy [16]. Unfortunately, attempts to ameliorate dyskinesias in advanced PD patients by giving smaller, more frequent doses of levodopa or a continuous infusion turned out to be counter-productive [56]. Attempts to manage the therapeutic window by changing the pharmacokinetics of levodopa or of dopamine agonists were not efficacious in controlling on-period dyskinesias. The reason why this option does not provide an efficient solution is highlighted in Fig. 6 which schematically shows a typical sigmoid dose-effect curve for anti-parkinsonian response to levodopa (or dopamine agonists). In order to elicit maximal antiparkinsonian effect ⑤ an optimal dose ④ of levodopa (or dopamine agonist) must be given. There is no advantage of further increasing the medication, as this would provide no additional anti-parkinsonian effect (dashed red area). This is a very efficacious treatment in early disease stages, when dyskinesias are not present. However, after dyskinesias are established, a threshold medication dose for dyskinesias becomes apparent ②. Once the dyskinesia threshold ② moves to the left of the maximal antiparkinsonian dose line ④, dyskinesias become inevitably associated with the maximal anti-parkinsonian effect. In practical terms, it becomes necessary to provide suboptimal treatment to keep the patient free from dyskinesias ⑦. As PD treatment and disease progress, the dyskinesia threshold moves further to the left and the therapeutic window ③ narrows, making the threshold of maximal anti-parkinsonian effect without dyskinesias move further down.

Continuous levodopa infusion corrects the phar-

macokinetic causes leading to dyskinesias, as it allows avoiding the peaks and troughs of repeated oral administration [63]; however, the pharmacodynamic causes of dyskinesias illustrated by Fig. 6 remain. This explains why dyskinesias are still observed when the patients are treated enough to reach an adequate *on* state [3, 60, 64]. Similarly, dyskinesias do not disappear when patients are treated with continuous infusions of dopamine agonists [37, 82].

High frequency stimulation of the subthalamic nucleus or the globus pallidum provide an alternative approach to the treatment of dyskinesias in PD [83]. The two targets are considered to reduce dyskinesias by means of different anatomofunctional mechanisms [13]. Globus pallidum stimulation probably has a direct anti-dyskinetic effect by interfering with pallidal outflow, whereas subthalamic nucleus stimulation reduces medication requirements (thus changing the pharmacodynamic dose-effect curve) [57] and in addition may also affect pallidal outflow at the level of the ansa lenticularis, situated just below the subthalamic nucleus. Deep brain stimulation of the subthalamic nucleus has striking ameliorative effects on off-period dystonia [41], yielding an average reduction in dyskinesias of approximately 70 % [39]. It must be remembered that the number of candidate patients for deep brain stimulation represent a minority of the PD population, because strict selection criteria are usually implemented in most centers [75].

A third line of treatment is based on the administration of specific antidyskinetic drugs capable to move to the right the dyskinesia threshold ② depicted in Fig. 6. Novel potential therapeutic strategies attempt to act on non-dopaminergic neurotransmitter systems and reduce the expression of dyskinesias, once they are established, without interfering with the anti-parkinsonian activity of dopaminergic drugs [7, 25]. The first (and

still only) drug with proven anti-dyskinetic efficacy is amantadine, a glutamate antagonist active on NMDA receptors, whose activity lends further support to the glutamatergic hypothesis on the pathogenesis of dyskinesias [31, 69]. The improvement of dyskinesias is around 50 % without concomitant worsening of parkinsonian symptoms [48, 84].

Other potential anti-dyskinetic candidates have been excluded or are still under scrutiny. Sarizotan demonstrated potential efficacy in an open label trial, but subsequently proved to be ineffective in two double blind

placebo-controlled studies [30]. Atypical neuroleptics (particularly clozapine) have also been considered, but presently there is insufficient evidence to support the efficacy of clozapine in reducing dyskinesias [69]. Other promising anti-dyskinetic drugs act on glutamate (NMDA, AMPA or mGluR), serotonin (5HT_{1A}, 5HT_{1B/D}, 5HT_{2A-2C}), adenosine (A₂), opiate or other receptors. Their potential efficacy is currently under scrutiny.

■ **Conflict of interest** The authors have no conflict of interest to declare.

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