

Review

Levodopa-Induced-Dyskinesias Clinical Features, Incidence, Risk Factors, Management and Impact on Quality of Life

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Abstract. Levodopa-induced dyskinesias (LID) belong to the most common dose-limiting adverse effects of levodopa therapy. “Peak-dose” LID occur with the maximum effect of medication, ‘diphasic dyskinesias’ have a “beginning- and end-of-dose” pattern, and the, “off-period dyskinesia” occur during off-periods, most frequently in the early mornings and are typically dystonic in nature.

The majority of patients will have developed dyskinesias after 10 years of treatment, and about 40–50% after 5 years. Occurrence of LID appears to be related to dose and duration of treatment with levodopa and severity and duration of disease. In addition, patients with younger age of onset have been reported to have an earlier onset and higher rate of LID. The important aetiological role of non-physiological pulsatile stimulation of dopaminergic receptors is increasingly recognized and more continuous dopaminergic stimulation with the longer acting dopamine agonists has been shown to reduce and delay the onset of dyskinesias. LID may not have a significant effect on quality of life in patients with early disease or in very advanced disease stages. when often other problems arise, but in other patients they may be severely disabling. Treatment strategies to overcome LID include adjustment of timing, type and amount of dopaminergic medication, treatment with amantadine and, in treatment resistant cases, stereotactic surgery involving deep brain stimulation or lesioning procedures. A number of other pharmacological options are also being explored. Several methods for the assessment of LID are available to attempt accurate assessment of efficacy, although all of these have limitations, and further evidence on their utility if needed.

Keywords: Dyskinesia, clinical features, epidemiology, treatment

PHENOMENOLOGY

Soon after the introduction of levodopa for the treatment of Parkinson's disease (PD) [1], it was noted that this treatment could be associated with undesirable, involuntary movements or ‘dyskinesia’ (derived from ‘dys’ difficult and ‘kinesis’ movement).

The most commonly recognized pattern of dyskinesia [2–4], are the *peak-dose* dyskinesias. Muenter

et al. termed this pattern of dyskinesia the ‘improvement – dystonia – improvement’ or ‘IDI’ response, and established that it occurred around the time of peak plasma levels of medication [5], even though the severity of ‘peak-dose’ dyskinesias does not correspond well to plasma levels, suggesting a more complex mechanism to be involved in their generation [3, 6]. Indeed, LID often occurs as a patient-specific ‘all or nothing’ response to adequate levodopa-dosing, and whilst their duration may be dose-responsive, it is also other factors such as emotional stress that affect severity [3, 7–9]. Peak dose LID are typified by usually generalized, choreiform type movements: i.e.: fleeting,

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non-rhythmic, purposeless fidgety-type movements. Often these are exaggerated by stress or activity and are typically asymmetric, being most prominent in the most affected side by the underlying disease [3, 9–11]. In addition to chorea, several other manifestations of peak-dose LID are seen: namely ballism (wild, proximal, flinging movements of the limbs), choreoathetoid (writhing-type) movements and more dystonic posturing (which will often begin in the lower limb or foot and herald the onset of the LID). Pure dystonic movements, although occasionally occurring as peak-dose phenomena, are more often seen in the ‘wearing-on’ or ‘-off’ phase or as an ‘off’-period manifestation.

As well as the ‘IDI’ response, Muentner et al. also described a ‘DID’ (dystonia-improvement-dystonia) response, whereby patients would experience drug-induced dyskinesia as the effects of levodopa were wearing on and off [12]. They noted that these dyskinesias affected predominantly younger patients and occurred when the concentration of levodopa in plasma passed through a critical but relatively low level, whereas it remained absent as long as the concentration remained above that level. As noted above, this type of dyskinesia is predominantly dystonic in character and, due to its occurrence at the onset and/or end of action of levodopa, is now more commonly referred to as ‘*diphasic*’ or ‘*biphasic*’ dyskinesia.

The third pattern of dyskinesia in levodopa treated patients with PD is that of ‘*off*’-period dystonia. This is a recognized complication of drug therapy and is separate from the dystonia of untreated Parkinsonism: it commonly occurs early in the morning, and is often painful, distressing and disabling. It frequently affects the lower limbs but can involve any region such as facial, oral, lingual and even the laryngeal, respiratory and extra-ocular muscles [4, 9, 13].

INCIDENCE

Estimation of rate of LID occurrence as a function of disease duration is difficult, partly due to the uncertainty of establishing the exact time of disease onset; in addition, dyskinesias only occur after antiparkinsonian treatment is started, with the exception of dystonia, which can occasionally occur in untreated PD [14]. Therefore latency from onset of treatment to onset of dyskinesias often provides a more useful measure. The frequency of LID in parkinsonian patients has been reported in several studies but the reported incidence varies greatly between them. Such differences may partly depend on different study methods, different selections of patients [15] and different patient

populations (community-based or clinic-based) [2, 16], but partly also reflect differences in ascertainment if dyskinesias are not reported by patients, who are often unaware especially of mild dyskinesias [2, 17], and if dyskinesias are not present during a consultation.

It is widely accepted that it is rare (<10%) to develop LID within the first year of treatment with levodopa, but reports vary from 0% [18] to 50% [15, 19] of patients with dyskinesia in the first year of treatment.

In retrospective analyses in clinic-based samples dyskinesias were reported between 54% of patients at 6 years of levodopa therapy in one study [20] and in 56% after a mean duration of 3 years [21]. In prospective randomized controlled trials (RCTs) approximately 40–50% of patients are found to develop LID after 5 years of treatment with levodopa [15, 22, 23].

In long term follow-up studies, the incidence of LID at 10 years of treatment with levodopa treatment was found in 52–78% at 10 years [24, 25], and after 15 years 94% of survivors in the Sydney Multicentre study of PD had developed dyskinesia [26]. In a series of 42 patients with autopsy-verified PD dyskinesia was the most common and earliest complication, with a rate of 62% developing dyskinesia after an average of 10 years of levodopa treatment [27].

Thus, whilst there may be a small group of patients who never develop LID [30], it is largely accepted that dyskinesias occur almost inevitably at the later stages of PD.

RISK FACTORS

Typically, LID only occur in patients with a good response to levodopa, i.e. mainly in patients with idiopathic PD on an effective dose of levodopa, although patients with multiple system atrophy may develop severe, and usually atypical, LID early in the disease. As mentioned above, there also appears to be a dose-dependence to the occurrence and severity of LID in PD and reduction in medication dose often improves or abolishes these [25, 31].

Dose and treatment duration have the strongest impact on dyskinesias prevalence [2]. For example, in the ELLDOPA trial 16.5% of patients randomized to 600 mg of LD daily developed dyskinesias after only 9 months of treatment versus 2.3% among those on 300 mg [32].

Although duration of treatment has been demonstrated to be an independent risk factor in generating LID [2, 33], it is possible that this, at least partly, also reflects *disease duration* [15, 19] and *severity* [34, 35], which has been shown to correlate highly

with treatment duration as well as rate of dyskinesias [2, 36].

It has also been recognized that LID tend to be more severe and occur more frequently and sooner in younger onset (before the age of 50) patients [2, 33, 37, 38]. The most statistically significant difference occurs between ages 40–49 and ages 50–79 and the increased risk of dyskinesia in patients with PD onset <50 appears to be concentrated in the first two years of L-dopa therapy [15, 39]. Thus, in patients with onset of PD before age 40 years up to 90% have developed dyskinesias after 5 years of treatment, and up to 100% after ten years [40, 41], whereas LID represent a relatively infrequent problem in patients with an age at onset over 60 years (53% in the 50–59 years of age onset group, 26% risk in the 60–69 years group and 16% in the over 70 years group [38]. Even when accounting for different disease durations, age of onset remained a significant factor.

This relationship between age of onset and development of LID may be at least partly due to genetic influences [19]. Some forms of genetically determined Parkinsonism at young onset have been reported to have a higher risk of developing LID [2, 41–44], and a higher prevalence of dyskinesias has been reported in patients with a family history of PD than those without [2, 43].

In particular, PARK2 (parkin), PARK 6 (pink-1) and PARK 7 (DJ-1) mutations, which are associated with young-onset PD, have been reported to have high rates of dyskinesia [45–47], and one study reported a higher risk of developing LID in LRRK2 parkinsonism compared to genetically undetermined PD [47, 48]. However, more recent studies reported that carriers of parkin or LRRK2 mutations did not have more LID than non carriers when matched for age and disease duration [49, 50].

Other genetic factors may also contribute to the variability in incidence, severity and latency from treatment onset, and result in different susceptibility to develop dyskinesia. For example, associations of occurrence of dyskinesias have been reported with polymorphisms in the dopamine receptor D2 and transporter gene [51], the TaqIA polymorphism located in the gene encoding the D2 receptor [52], the catechol-O-methyltransferase (COMT) gene [53] and the mu/opioid receptor gene [54], but not the APOE gene [55]. Additionally, a recent study found that a common functional polymorphism of the BDNF gene (val66met allele) was associated with a significantly higher risk of developing dyskinesias earlier in the course of treatment with dopaminergic agents [56], but

the importance of these results at the present time is not yet clear and these need to be replicated in other and larger populations.

Other factors suggested to be associated with a higher risk for dyskinesia are history of never smoking [57], gender [58], and lower body weight [59] (although, as the latter did not clearly predate the onset of dyskinesia, the causality of this relationship is not established). A negative correlation between resting tremor as an initial manifestation of PD and LID occurrence and severity has also been reported [60].

ASSESSMENT OF LID

One of the challenges facing the clinician or researcher dealing with LID is their accurate assessment and purely objective quantitative measurement devices have clear limitations [61]. Several rating scales have been used in clinical practice, including scales relying on observations by a physician, patient-kept diaries and questionnaires or scales combining these efforts.

However, the fluctuating nature of PD itself, the variability in the duration and severity of LID from day to day and even within the same day without any predictable pattern, and the lack of awareness of dyskinesias patients may represent considerable challenges to their assessment. Therefore, many trials use a complicated combination of these scales with video challenge, a more objective measure, in order to overcome these limitations [62].

An ideal instrument for dyskinesia assessment should be a single scale, able to capture patient perceptions, time factors of dyskinesia, anatomical distribution, objective impairment, and disability [63].

Recently, a systematic review by a task force of the Movement Disorders Society concluded that, among scales, the Abnormal Involuntary Movement Scale (AIMS) and the Rush Dyskinesia Rating Scale (RDRS) formally fulfill the criteria known as 'recommended', but both scales still have considerable limitations. The AIMS is a clinician-rated instrument to assess the severity of abnormal movements in different parts of the body. It was initially developed for the evaluation of tardive dyskinesia in psychiatric patients, but has been modified by several authors for its use in PD. The RDRS focuses on disability and the impact of dyskinesia on specific activities of daily living.

The task force however affirmed that two more recent scales (PDYS-26 and UDysRS) have excellent clinimetric properties and appear to provide a reliable and valid assessment tool of dyskinesia in PD

of dyskinesia in PD. The Unified Dyskinesia Rating Scale (UDysRS) combines elements of the AIMS and RDRS into a single measure to assess both impairment and disability [64]; it contains a self-assessment by the patient as well as an examination by the physician. The PD Dyskinesia Scale-26 is a patient-based measure for quantifying the impact of dyskinesias on specific activities of daily living and quality of life of patients with PD [65]. However, these could only be considered “Suggested”, requiring further clinimetric testing.

MANAGEMENT OF LID

The clinical challenge is to find, first, a method to delay the onset of dyskinesias, whilst adequately treating the parkinsonian symptoms and, secondly, a treatment strategy to minimise established LID without worsening Parkinsonism.

In order to delay the onset of dyskinesias clinicians may choose to use dopamine agonists in place of levodopa in *de-novo* patients as first-line therapy [66], particularly if they are young and are therefore at increased risk of developing this complication. Lees and Stern first noted that patients taking the agonist bromocriptine alone, tended not to develop the motor side effects associated with levodopa therapy [67]. Since then a number recent studies have demonstrated that starting treatment with other dopamine agonists, including pramipexole [22], ropinirole [68], ropinirole prolonged release [69], and cabergoline [70], is effective for prevention/delay of dyskinesias, findings which have been summarised in a recent review of evidence based studies [71]. However, it should be noted that it has recently been suggested that of the occurrence of severe, clinically troublesome LID occurs at the same stage whether levodopa treatment is delayed or not [22, 35]. In addition there is increasing evidence that other factors reflecting advancing disease become more important at later stages and do not differ between those treated with levodopa and dopamine agonists [26, 72].

When LID have appeared, the simplest and most obvious strategy to reduce LID is to reduce the dose of dopaminergic therapy, but this almost inevitably leads to an unacceptable worsening of parkinsonian symptoms. It is widely believed that one of the major factors in promoting motor complications such as LID in PD is the artificial pulsatile dopaminergic stimulation which occurs as a result of pharmacological treatments [73] and thus more continuous dopaminergic

stimulation is sought as a means of avoiding or minimizing these. This can include adjusting dopaminergic treatment with smaller single-doses in case of peak-dose dyskinesia, or increased single-dose in patients with biphasic dyskinesia [73–75]. Many sustained-release preparations of levodopa have been employed but there is little evidence to show that this strategy is effective [8] and, in advanced PD with motor fluctuations, results from controlled studies suggest that CR preparations have a tendency to produce increasingly severe dyskinesias [76]. Therefore, for the management of peak-dose dyskinesias it may be helpful to replace controlled-release with immediate release of levodopa-carbidopa, which may be easier to adjust and duration of dyskinesias may be shorter [77]. Dopamine agonists have a longer duration of action and thus theoretically provide more continuous receptor stimulation. This can therefore be a useful strategy both for patients with dyskinesias as a ‘dopa-sparing’ technique with a smoothing of response. Strategies for providing continuous dopaminergic stimulation also include the administration of continuous subcutaneous infusions of the potent dopamine agonist apomorphine, which, particularly when used as monotherapy, can dramatically reduce established LID [78, 79] as well as direct intrajejunal infusion of Duodopa [80, 81]. However apomorphine and intrajejunal infusion of Duodopa are complex, require considerable patient and/or carer involvement, and are relatively expensive [82, 83]. Although good long-term results with apomorphine have been demonstrated in some centres, others found a considerable dropout rate, mainly due to painful subcutaneous nodules and it showed an insufficient control of motor signs and motor complications in a 5 years follow-up study [84]. Duodopa treatment is associated with frequent complications of the gastrostomy procedure [83, 85] and has been linked to the axonal peripheral neuropathy [86, 87], and clinical trial data are sparse.

Other methods targeting the non-dopaminergic pathways to avoid interfering with control of other aspects of the disease are also being explored [88, 89]. Of these, the drug amantadine has been used to treat PD for many years but its anti-dyskinetic properties, which are thought to be mediated via its glutamate NMDA receptor antagonism, have only been well demonstrated fairly recently [90–94]. It is effective and relatively easy to use, but it can produce side-effects (mainly anticholinergic) which mean that it is not suitable for all patients and there is a rate of non responders, that seem be associated at younger age of onset [95, 96].

A different approach is to try to target the dopaminergic system selectively to reduce dyskinesias without worsening parkinsonism, and clozapine, an 'atypical' neuroleptic, has shown promise in this respect [97–99]. However, its potential side-effect profile means that it cannot be used routinely and unfortunately controlled trials of similar but less toxic drugs, such as olanzapine and quetiapine have not shown equal effect [100, 101].

Other non-dopaminergic pharmacological agents, which have been investigated, include agonists of 5-HT_{1A} receptor such as sarizotan [62], antiepileptic drugs as levetiracetam [102, 103], the adenosine A_{2A} receptor antagonist preladenant [104] and safinamide [105], a potent, highly selective and reversible inhibitor of monoamine oxidase B (MAOB) and dopamine reuptake with antiglutamatergic effects. Further study is needed to evaluate their efficacy in minimizing the risk for dyskinesias. In addition, Fipamezole, α 2-adrenergic receptor antagonist, has been assessed, reporting a reduction in dyskinesia without worsening of parkinsonian symptoms in the MPTP-lesioned primate model of PD [106]. However, clinical studies with idazoxan, another α 2-adrenergic receptor, showed conflicting results [107]. Perampanel, selective AMPA receptor antagonist, has also been assessed, without significant effect [108].

Finally, other promising non dopaminergic compounds in early stage of development are Pardoprunox [109], a partial agonist at D₂ and D₃ receptors and full agonist at 5 HT₁ receptors, the α 4b₂ and α 6b₂ nicotinic subtype receptors [110] and the negative allosteric modulators of mGluR5 AFQ-056 and ADX48621 [111, 112].

Advances in knowledge of functioning of basal ganglia and in surgical techniques, lead to a reemergence of surgery PD in the last 25 years, directed mainly at advanced PD complicated by disability from motor fluctuations, dyskinesia, and tremor that are medically intractable [113, 114].

In recent years, DBS of GPi and STN have replaced largely lesioning techniques (thalamotomy, pallidotomy, or subthalamotomy), being largely reversible, without or minimal tissue damage, and allowing adjustment of settings according to clinical need [113, 115].

Studies showed that STN-DBS leads to a reduction of disabling dyskinesias by about 60% [116] and DBS of the GPi lead to an immediate reduction of levodopa-induced disabling dyskinesias of about 80% [117].

A recent study comparing DBS of both the GPi and STN suggests that both targets might offer similar motor benefits [118], but that the use of dopaminergic

medications decreased more for the STN DBS group than for the GPi DBS group. This difference may influence the DBS target chosen for patients. Thus, for some patients a reduction of medications may contribute to a better quality of life, for other a reduction may not be desirable [119].

In comparison, the best adjunctive medications developed in the last 25 years improve "off" time in PD by 1–2 hours, whilst DBS improves "off" time by 5–6 hours, allows a substantial reduction in medications in many patients, and often eliminates dyskinesias entirely [120].

Besides procedural surgical complications, such as hemorrhages or central nervous infections [121], complications of STN-DBS include cognitive side effects, such decreased fluency verbal, apathy, impulsivity, and postoperative depression [122–125]. Therefore, this treatment is mainly considered in patients without significant active cognitive or psychiatric problems [113].

Recently, also bilateral cerebellar rTMS has been reported to show persistent clinical beneficial effects in reducing peak-dose LID [126], but further study is needed to assess and refine the method.

EFFECT OF LID ON QUALITY OF LIFE (QOL)

It is clear that LID are disabling and carry with them significant co-morbidity especially when severe. Patients complain that they are socially embarrassing, and prevent or impede their daily activities including vital tasks such as eating and drinking, when they may be at their worst [61, 127]. In addition, they are associated with weight loss [78], which can present a major problem in PD, and other symptoms such as breathlessness and even vomiting [128]. Therefore one would expect LID to have a significant effect on QOL and some studies have reported worse QoL scores in patients with dyskinesias, particularly biphasic dyskinesias [129–131]. However, once confounding factors such as disease severity and treatment duration were accounted for, clinical studies have mostly failed to show such association between dyskinesias and poor QoL [2, 132]. One explanation for this result could be that often dyskinesias are mild with little impact on daily living, whereas only a smaller group of patients with advanced disease have severe, disabling dyskinesia. In addition, if only patients with a good response to levodopa develop dyskinesia they would be expected to have a better quality of life than those receiving little anti-parkinsonian benefit from their medication [2].

This hypothesis is supported by results by Marras et al. who found that LID were associated with a better QoL in the first few years of treatment even after accounting for the difference in UPDRS scores of parkinsonism. In advanced disease, a proportion of patients have dyskinesias severe enough to require deep brain stimulation (DBS) surgery and in the subgroup with more severe, disabling dyskinesia these are associated with poorer QoL. However, after disease duration of more than 10 years, dyskinesias that are clinically relevant and require medication adjustments are often not the primary clinical concern [26, 28, 29, 133] and, despite the high rate of dyskinesias with longer follow-up, may therefore have less relative impact on patients' QoL in the overall population.

As the trend for more quality of life measures to be introduced into clinical trials continues, we will gain more information in the important area of improvement of overall QoL with treatment of dyskinesias, accounting for different disease variables and subgroup characteristics. This will help to ensure that improvement in objective rating ratings of dyskinesia severity are translated in subjective benefit for the patients.

DISCLOSURES

All the authors have contributed to the work and agree with the findings.

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