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Levodopa-induced dyskinesia in Parkinson disease: Current and Evolving Concepts

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ABSTRACT

Levodopa-induced dyskinesia are common complications in Parkinson disease. Pathogenic mechanisms include phasic stimulation of dopamine receptors, nonphysiological levodopa-to-dopamine conversion in serotonergic neurons, hyperactivity of cortico-striatal glutamatergic transmission and overstimulation of nicotinic acetylcholine receptors on dopamine-releasing axons. Delay in initiating levodopa is no longer recommended as dyskinesia development is a function of disease duration rather than cumulative levodopa exposure. We review current and in-development treatments for peak-dose dyskinesia but suggest that improvements in levodopa delivery alone may reduce its future prevalence.

Keywords: Parkinson's disease; **Motor control;** Dyskinesia

Domain: Neuroscience, Clinical Research

INTRODUCTION

Dyskinesia, often referred to as levodopa-induced dyskinesia (LID) to recognize levodopa as the major contributor, is a motor complication arising in patients with Parkinson disease (PD) on chronic levodopa treatment, largely in a dose-dependent fashion—except when given as an infusion, such as in levodopa/carbidopa intestinal gel.[1] LID is phenomenologically recognized as chorea/choreathetoid movements appearing initially on the more affected body side. LID occurs in 40% of patients after 4 years on levodopa treatment, with a risk especially high in younger patients treated with higher doses of levodopa.[2]

This review focuses on aspects of phenomenology, pathophysiology, and therapeutics that have undergone revisions or updates in recent years, emphasizing those of most relevance for modern clinical care and future research. We highlight the under-recognized diphasic dyskinesia, which is often mischaracterized as a peak-dose phenomenon and therefore mismanaged. We review evidence that corrects the misinterpretation of prior clinical trial data surmising LID as a function of duration of levodopa exposure rather than duration of disease, justifying the inappropriate but still lingering recommendation to postpone levodopa treatment as long as possible to "delay" the appearance of LID.[3] We also review the latest pathophysiologic concepts at the molecular, synaptic, and network levels, in order to provide the rationale for currently available as well as emerging treatments.

Peak-dose vs. diphasic dyskinesia

Peak-dose dyskinesia. Chorea that may be generalized or affecting the more affected side or upper body often occurs during the therapeutic window of a levodopa dose cycle (ON

medication state) (Fig 1; **Supplementary Video 1**). Cervical-predominant chorea may appear as "head bobbing" (classically understood to be rhythmic to-and-fro movements of the head), but close inspection discloses no rhythmicity to these movements. With time, many patients demonstrate little or no "therapeutic window," which results in peak-dose dyskinesia throughout the dose-related benefit—referred to as "square wave".[4] While "classic" peak-dose dyskinesia is often associated with truncal and upper-limb predominant chorea, lower-body predominant chorea, considered "classic" diphasic, may predominate (**Supplementary Video 2**). Isolated orofacial dyskinesia appears to be more frequent in older-onset PD.[4]

Diphasic dyskinesia. This variant is also referred to as beginning- and end-of-dose or transitional dyskinesia, because it occurs as levodopa is becoming effective, toward the beginning of a dose cycle, or as it begins to wear off, toward the end of a dose cycle (Fig 1; **Supplementary Video 3**). Diphasic dyskinesia tends to have a more variable topographical distribution and be reported as more troublesome compared with peak-dose dyskinesia. When exclusively affecting the legs, ballistic or stereotypic alternating movements may predominate (Fig 2; **Supplementary Video 4)**.[5] Some of these movements may give rise to bizarre but highly stereotypical gait patterns.[6] It is distinct from but can evolve into wearing-off dystonia, typically expressed as toe curling, sometimes with plantar flexion or inversion.[7] A similar common low-dose phenomenon is early-morning dystonia (**Supplementary Video 5**).

Dyskinesia and levodopa

Levodopa is necessary but insufficient to generate LID. LID requires a pulsatile delivery (short half-life), a presynaptic nigrostriatal degeneration, and a relatively preserved post-synaptic

nigrostriatal system. In most atypical parkinsonisms, such as progressive supranuclear palsy, where the post-synaptic system is affected, levodopa rarely induces dyskinesia. While there is a dose-dependent increase in peak-dose dyskinesia when levodopa is administered orally,[8] such effect is lost when delivered continuously. Indeed, continuous levodopa infusion typically *reduces* pre-existent LID, even with a dose *higher* than that used orally.[1] This may be due to favorable pharmacodynamic effects of continuous levodopa delivery despite a higher area-under-the-curve and a more physiologic (tonic) stimulation of dopamine receptors.

Although levodopa is necessary for dyskinesia development, the clock for this complication begins to tick at disease onset rather than upon levodopa initiation. Long-term studies have consistently shown that motor complications develop with the same frequency and severity irrespective of whether levodopa was initiated early or late.[9] This was best demonstrated by a study on levodopa-initiation in sub-Saharan African PD patients, whose longer delay in receiving levodopa (mean, 4.2 years) than matched patients in Italy (1.8 years)[10] was associated with a shorter dyskinesia-free period. The exact same finding has repeatedly been reported in preclinical settings using both rodent and primate models of parkinsonism and dyskinesia, most animals being capable of displaying dyskinesia at first levodopa exposure if the lag time between lesion establishment and pharmacological challenge is long enough.[11] Such data have led to a modification of the concept of priming, proposing that it is the direct and intrinsic consequence of the loss of dopamine innervation of the striatum, with the first injections of dopaminergic drugs sensitizing but not inducing it.[11] The evidence collectively suggests that disease severity and levodopa dose are more important than duration of levodopa treatment for the development of dyskinesia in PD.[12] Furthermore, young age at onset, low body weight, female sex, and more

severe motor disability may represent important vulnerabilities and highlight an important contribution of levodopa dose in these high-risk groups.[13] Although greater risk for LID may be accrued in certain clinical subtypes (e.g., akinetic-rigid compared to tremor-dominant[14]) and genetic polymorphisms (e.g., the Val158Met variant of *COMT*[15]), these associations remain tentative and at present have little clinical application. Nevertheless, the bizarre but highly stereotypical gait associated with diphasic dyskinesia in young-onset PD patients may be more common in patients with *PRKN* (Parkin, PARK2) mutations.[16] Of note, diphasic dyskinesia has been found to be associated with the DRD3 p.S9G variant, with the AA genotype shortening it's time to onset after levodopa initiation.[17]

Dyskinesia and disability

With therapeutic doses of levodopa, hypokinetic disability might be replaced with dyskinetic disability. As hypokinesia is generally more bothersome, patients usually prefer the dyskinetic to the parkinsonian state.[18] Although an undesirable outcome, dyskinesia is also generally a marker of treatment success: the point at which dopaminergic replacement has reached and surpassed the therapeutic window. PD patients who have never exhibited dyskinesia may be undertreated with potentially greater net disability, since the onset and offset of therapeutic and dyskinetic thresholds have been demonstrated to be similar. [12] Advanced levodopa-treated PD patients, thus, may alternate between tremor, gait freezing, or other parkinsonian features and LID (peak-dose and/or diphasic), with no "sweet spot" in between.

The highest tolerable doses of the dopamine agonists (pramipexole, ropinirole, rotigotine) exhibit lower efficacy than levodopa and may induce or worsen dyskinesia once patients begin

concurrent oral levodopa treatment. Therefore, rather than *delaying* dyskinesia, as proposed in the CALM-PD[19] and REAL-PET[20] studies, dopamine agonists are mostly incapable of extending their effect into and beyond the therapeutic window, defined by a period of optimal response to levodopa, to generate dyskinesia when given without levodopa. Importantly, the CALM-PD and REAL-PET studies, comparing pramipexole and ropinirole, respectively, to levodopa as early monotherapies, showed superior motor improvement and quality of life in the levodopa-treated groups. These endpoints were deemphasized whereas the greater incidence of dyskinesia in the levodopa-treated arm emphasized, ushering the "levodopa-sparing" by means of early initiation of dopamine agonists to avoid or postpone LID. Separately, the PD-MED trial (long-term comparison of L-dopa, dopamine agonists and monoamine oxidase B inhibitors as first-line treatment on 1,620 PD patients, with mean age ~70 years, recruited over 9 years and followed for a median of 3 years) also showed that dopamine agonists provided less overall benefit than levodopa despite the fact that the levodopa group had significantly more dyskinesia.[21]

PATHOPHYSIOLOGY

The current model of LID pathophysiology, mainly focused on peak-dose dyskinesia, hypothesizes the following events at the striatal level: pulsatile stimulation of dopamine receptors, excessive presynaptic swing of dopamine leading to increased receptor occupancy,[22] dissociation between low intrastriatal dopamine and high plasma and extracellular levodopa,[23] downstream changes in the post-synaptic compartment, and abnormalities in non-dopaminergic neurotransmitters. All of these events cause changes in the firing patterns and the oscillatory activity between the basal ganglia and the motor cortex, leading to excessive disinhibition of thalamocortical neurons and over-activation of the motor cortex. Understanding these

mechanisms of LID at network and synaptic levels can assist in the development of neuromodulatory or pharmacological interventions.

Network mechanisms

The mechanism of LID at the network level has been studied in PD patients using a variety of neurophysiological and neuroimaging methods, including local field potentials (LFP), transcranial magnetic stimulation (TMS),[24] voxel-based morphometry (VBM), and functional magnetic resonance imaging (fMRI).[25, 26] Classically, an excessive reduction of the firing rate in the globus pallidus pars interna (GPi) and in the subthalamic nucleus (STN) secondary to nonphysiological stimulation of dopamine receptors in the denervated striatum has been associated to LID.[27] Registration of LFP in animals and humans suggests that alterations in firing patterns, including changes in synchronization, may be more relevant than changes in firing rates. Animal studies show a strong coherence between the basal ganglia and frontal cortical activity during LID. Limited data from human subjects have examined the coherence between cortical and subcortical structures in patients treated with deep brain stimulation (DBS). Unlike the hypersynchronous activity in the beta-band (20-30 Hz) associated with the akinetic or "OFF" medication state, the hyperkinetic LID state is characterized by a reduction of power in the beta-band LFP activity,[28] hypersynchronous gamma oscillations between 60 and 90 Hz in the motor cortex and STN, and strong phase coherence between them, with no or minimal influence of voluntary movements.[29] Indeed, a novel adaptive (closed-loop) DBS device reduced LID by decreasing the voltage of stimulation when detecting a decrease in beta-band activity in the STN.[30]

An inconsistency of the classical firing-rate model in predicting LID is that it does not take into account the strong connections between the basal ganglia and the motor cortices. Abnormal synaptic plasticity has been demonstrated by TMS studies to arise from the primary motor cortex (M1).[24, 31] Beyond M1, functional and structural abnormalities have also been demonstrated by structural and functional neuroimaging in motor areas involved in motor planning and inhibition, such as the supplementary motor area (SMA) and inferior frontal cortex (IFC) (Table 1, figure 3).

Molecular and synaptic mechanisms

LID-generating mechanisms at the synaptic level show biochemical abnormalities associated with LID in dopaminergic[22] and non-dopaminergic receptors[32] and in striatal enzymes regulating dopaminergic signaling[33] (Fig 3). In this regard, alterations of the serotonergic system,[34] phosphodiesterase 10A (PDE10A),[33] and the glutamatergic system[35] support a pathogenic role of *N*-methyl-D-aspartate (NMDA) receptors in LID development (Fig 4).

The role of dopamine. Dopamine receptors occupy a prominent role in the pathophysiology of LID, even if any relationship between the two is affected by factors such as age and genetic background.[36] D1 receptor activation is a key factor for the development of LID. While a preferential selectivity by oral dopamine agonists for D2-D3 receptor subtypes with no affinity for D1 and D5 receptors[37] could explain for their lower prodyskinetic effects, activation of striatal D3Rs exert a synergistic effect on D1R-mediated transmission through direct intramembrane interaction.[38] Thus, the binding of pramipexole to D3R boosts D1R function,

which explains both its antiparkinsonian efficacy and its prodyskinetic effects. Rotigotine has also been shown to be a potent agonist at D1 receptors.[39]

LID is associated with several molecular changes at the striatal level likely mediated by overactivation of dopamine D1 receptors such as increased FosB and prodynorphin messenger RNA expression[40] and the initiation of two processes down-stream of likely linked to ERK (extracellular signal-regulated kinase) signaling pathways: an abnormal activation of mitogen- and stress-activated kinase-1 (MSK-1) and a phosphorylation of histone H3.[41] D1/DARPP-32 activation by levodopa induces phospho-ERK translocation in the nucleus and the consequent activation of MSK-1 which has a key role in the regulation of synaptic plasticity and transcriptional activity.[42] Abnormal regulation of MSK-1 facilitates the induction of LID and increase in striatal ΔFosB, possibly mediated by increased histone H3 phosphorylation at the FosB promoter.[43] The possible differential role of direct and indirect pathway spiny neurons in LID has been recently shown in a study using a new chemogenetic technology:[44] stimulation of Gq-coupled human M3 muscarinic receptors in direct-pathway spiny neurons caused a beneficial anti-parkinsonian effect in mice and a surge of LID; indirect pathway activation did not.

LID is associated with cortico-striatal plastic alterations at the synaptic level, shown by a reversal of long-term potentiation (LTP) or loss of "synaptic depotentiation".[45] The loss of this homeostatic synaptic mechanism was found to be associated with increased activity of the molecular cascade downstream of the D1 dopamine receptors leading to an increase in DARPP-32 phosphorylation.[45] A spike-timing dependent protocol has revealed that the homeostatic adaptation in intrinsic excitability of spiny neurons is lost in mice with LID,

suggesting an alteration of the number of cortico-striatal synapses[46] and a switch from bidirectional to unidirectional striatal plasticity.[47] An M4 muscarinic receptor allosteric modulator enabled LTP reversal and reduced dyskinetic behaviors in a primate model, suggesting muscarinic receptors as potential targets for pharmacotherapy against LID.[48] In line with these observations, a reduced bidirectional plasticity has also been observed in dyskinetic PD patients in the substantia nigra pars reticulata by LFP recording with DBS electrodes[49] and in the cerebral motor cortex using TMS.[50]

LID can also be associated with abnormal structural synaptic plasticity. In fact, both D1 and D2 receptor-positive spiny neurons have diminished spine density in the rodent-denervated striatum.[51] Surprisingly, however, long-term levodopa treatment causing dyskinesia restores spine density in D2 but not in D1 receptor-positive spiny neurons, suggesting that these morphological changes might represent structural underpinnings of LID in PD.

The role of glutamate. Hyperactivity of cortico-striatal glutamatergic transmission has been shown in animal models of PD and postulated in PD patients with LID, possibly resulting from receptor and molecular alterations at pre- and post-synaptic levels due to dopaminergic loss.[52] Dyskinetic rats have high striatal levels of the NMDA receptor GluN2A subunit but low levels of the GluN2B subunit in the post-synaptic compartment, suggesting a pathological redistribution of receptors between synaptic and extra-synaptic glutamatergic membranes in LID.[53] An altered ratio of synaptic striatal GluN2A/GluN2B-containing NMDA receptors has also been found in dyskinetic monkeys and in post-mortem tissue from dyskinetic PD patients. A cell-permeable peptide interfering with the GluN2A subunit interaction with protein post-synaptic density

protein 95 (PSD-95) reduced dyskinesia in LID models.[54] Recent studies identified a possible molecular partner in LID modulation through GluN2A subunits.[55] The interaction between the synaptic protein Rabphilin 3A (Rph3A) and GluN2A-containing NMDA receptors is increased in parkinsonian rats developing dyskinesia. A cell-permeable peptide interfering with this interaction decreases LID.[55]

***The role of the serotonergic system*.** In the face of striatal dopamine denervation, levodopa conversion to dopamine migrates to non-dopaminergic cells, particularly serotonergic raphe nuclei neurons.[56] Dopamine is then released by serotonergic neurons in a nonphysiological, unregulated manner in the extra-synaptic cleft where it might act as a "false transmitter", causing abnormal and pulsatile activation of striatal dopamine receptors.[57] Reducing abnormal dopamine release via presynaptic serotonergic 5-HT1A agonists can decrease dyskinesia in parkinsonian models.[58] Moreover, ablation of serotonergic transmission reduced LID[59] whereas transplants of serotonin-enriched grafts worsened LID in parkinsonian rats.[60]

***The role of other non-dopaminergic mechanisms*.** Within the basal ganglia, chronic pulsatile dopamine receptor stimulation leads to alterations in cholinergic, opioid, histaminic, adrenergic, and cannabinoid function.

Acetylcholine is integral to striatal function. Cholinergic interneurons are modulated by dopamine and striatal dopamine release is regulated via a di-synaptic pathway involving cortical and thalamic glutamatergic inputs to the cholinergic interneurons with stimulation of nicotinic acetylcholine receptors on nigrostriatal axons.[61] Agonists at subtypes of nicotinic receptors have

been shown to reduce LID.[62] The mechanism may involve reducing dopamine release via a chronic desensitization or down-regulation of nicotinic receptors.[63] Muscarinic cholinergic receptor involvement in LID is less clear with cholinergic antagonists at M4 receptors possibly reducing dystonia but exacerbating chorea. Histamine H_2 receptors located within the striatum may reduce LID via modulation of acetylcholine.[64]

The opioid peptide precursors, pro-enkephalin and pro-dynorphin, are co-transmitters in the GABAergic striatopallidal pathways and function as neuromodulators. Many studies have shown increased levels of pro-dynorphin breakdown products linked to the expression of LID in animal models of PD.[65] Mu-subtype opioid receptors appear to modulate activity of the direct striatopallidal pathway and antagonists at this receptor may reduce LID.[66] Opioid signaling is complex, however, and other authors have shown increased LID with some opioid antagonists.[67]

The cannabinoid system is implicated in basal ganglia function, with endocannabinoids involved in glutamate/dopamine signaling and striatal plasticity.[68] Cannabinoid CB1 receptors are also highly expressed in the internal segment of the GPi, the output region of the basal ganglia.[69] The pharmacology is complex with both CB1 agonists and antagonists reducing LID.[70] Targeting the enzymatic breakdown of cannabinoids using fatty acid amide hydrolase inhibitors may also reduce LID.[71]

Noradrenergic signaling may also be involved in LID, although the mechanisms are unclear. Both alpha- and beta-adrenergic receptor antagonists can reduce LID in animal models.[72]

MANAGEMENT

Available oral pharmacological treatments

Diphasic LID is managed in a manner similar to wearing-off symptoms: increasing the individual levodopa doses, converting to a long-acting formulation of levodopa, or adding longer-acting dopaminergic medications (e.g., a monoamine oxidase B [MAO-B] inhibitor, catechol-O-methyltransferase inhibitor, or dopamine agonist). No clinical trials focused on diphasic dyskinesia have been reported. Anecdotally apomorphine was observed to reduce the duration of diphasic dyskinesia at doses higher than necessary to induce an "ON" phase.[73]

Below we summarize the available strategies assessed for direct effect against peak-dose LID for which sufficient evidence exists. We do not include drugs for which any anti-dyskinetic effect has been assumed indirectly, emerging from the "ON time without troublesome dyskinesia" endpoint used in clinical trials (e.g., safinamide) or because of a reduction in dopaminergic tone in "levodopa-sparing" interventions (e.g., dopamine agonists).

Amantadine. An NMDA antagonist, amantadine is the most widely used oral therapy for dyskinesia. The International Parkinson and Movement Disorder Society Evidence-based Medicine Committee classified amantadine as "efficacious" in the treatment of dyskinesia.[74] The safety of amantadine is considered acceptable, although side effects such as confusion, hallucinations, ankle edema, constipation, and dry mouth narrow the therapeutic window. ADS-5102 (amantadine extended release) was recently approved by the FDA "for the treatment of dyskinesia in patients with PD receiving levodopa-based therapy, with or without concomitant dopaminergic medications."[75] Compared with placebo, ADS-5102 274-mg significantly reduced

dyskinesia as measured by the Unified Dyskinesia Rating Scale, treatment difference, –7.9 ($P < .001$).[75] Additional studies will be needed to investigate the comparative efficacy between ADS-5102 and immediate-release amantadine.

Clozapine. Off-label targeting of $5HT_{2A/2C}$ receptors by this atypical antipsychotic has shown anti-LID efficacy in a single randomized controlled trial, without worsening PD motor symptoms, and has also been considered "efficacious".[76] Another proposed mechanism for its antidyskinetic action in low doses is D1 receptor antagonism.[77] However, clinical usefulness is limited due to safety issues.[74]

Levetiracetam. Off-label levetiracetam has yielded conflicting anti-dyskinetic efficacy and tolerability.[78] The purported anti-LID mechanism of action includes a change in the expression of certain transcription factors in the striatum.

Pharmacological treatments in clinical development

Several drugs with a variety of potentially relevant mechanisms of action, targeting receptors/neurotransmitters within the basal ganglia, are at various stages of clinical development (Table 2). Selection of potential symptomatic therapies for the management of PD has benefited from studies on the MPTP-treated macaque monkey, an excellent phenocopy of the motor symptoms and side effects of dopaminergic therapies.[79] This model has been widely used in the preclinical evaluation of the various experimental therapeutics.[79] Targets under evaluation exclusively in preclinical models are beyond the scope of this review.

Serotonergic targets. Although mixed agonists for both 5-HT1A and 5-HT1B receptors prevent the expression of LID, they may also reduce the therapeutic effect of levodopa.[80] Indeed, despite reducing dyskinesia the 5-HT1A agonist sarizotan failed in phase III studies partly due to worsening of motor symptoms.[81] Phase IIb studies of the clinically available 5-HT1A agonists, buspirone[82] and eltoprazine[83] are ongoing (clinicaltrials.gov *NCT02617017* and NCT02439125, respectively). The advantage of both of these agents is their rapid clinical availability if efficacy and tolerability are demonstrated in these studies. The added potential to reduce anxiety with such 5-HT1A agonists represents an additional benefit to PD subjects.

Novel glutamate targets. Tolerability of glutamatergic agents has been a major issue to date, with off-target side effects including confusion, hallucinations and ataxia. As noted above, the longer acting preparation of the NMDA antagonist, amantadine ADS-5102, was recently approved by the FDA. A second long-acting amantadine HCL extended release was also recently approved but no details of clinical studies have been reported to date. Their potential advantage is theoretically less night-time confusion/hallucinations, but this has not been examined in direct comparison with standard amantadine. Recent studies of allosteric modulators of NMDA receptors have also been suggested to be better tolerated due to more selective basal ganglia targeting and wider therapeutic index.[84] Abnormal cortico-striatal plasticity could theoretically be restored in part by the use of metabotropic glutamate receptor 5 (mGluR5) negative allosteric modulators, which reduce LID in rodent and primate models.[85, 86] Early clinical studies of several mGluR5 antagonists showed some short-term antidyskinetic benefits but side effects of worsened PD motor symptoms has limited further development .[87]

Many other targets have been previously investigated in phase II/III clinical trials but these have either failed to reduce LID to a significant or clinically meaningful level compared to placebo or they have been poorly tolerated. Several challenges exist in the translational field for novel drugs to reduce LID, ranging from animal models to clinical trial designs to the availability of clinically safe agents required to evaluate the target of interest. Future strategies in the field thus need to address these issues with improved translational methodology (including animal models, dyskinesia rating scales and factors related to the heterogeneity of PD) as well as technology to aid in the measurement of LID and the use of artificial intelligence to increase the scope of potential targets to evaluate.[88]

Advanced therapies (requiring invasive interventions)

Due to the paucity of optimal oral pharmacological treatments for LID, three advanced treatment strategies have been developed: DBS, infusion of levodopa-carbidopa intestinal gel (LCIG), and continuous subcutaneous apomorphine infusion (CSAI).

Deep brain stimulation. DBS is an invasive neurosurgical technique that delivers continuous electrical stimulation in specific brain areas by means of electrodes connected to an implantable pulse generator placed in the upper chest. Two main targets are used to treat LID in PD: the STN and the GPi.[89] STN DBS has a profound ameliorative effect on LID due to at least 3 mechanisms: 1) reduction of medications by 50-60%, as consistently seen by many prospective studies;[90] 2) stimulation of pallido-thalamic fibers in the zona incerta; and 3) plastic changes of the basal ganglia circuits that modulate levodopa responsiveness. A longstanding debate on the perceived superiority of STN over GPi inspired the execution of randomized prospective studies.

The meta-analysis of 3-year results of these comparative studies concluded that the two targets are comparable in the short term, but GPi is significantly better than STN in reducing LID.[91] This finding confirms that GPi-DBS has a direct and profound anti-dyskinetic effect, regardless of any post-surgical modification in the dosage of dopaminergic therapies.

Infusion of levodopa-carbidopa intestinal gel. LCIG allows the continuous infusion and reliable absorption of levodopa in the jejunal lumen, leading to sustained plasma levels. The system requires the endoscopic placement of a gastrostomy tube with an inner jejunal extension (PEG-J), connected to a pump that holds replaceable cassettes of 2 g of levodopa. Retrospective studies and recent prospective trials have confirmed a significant reduction in LID.[92] A post-hoc analysis of the 1-year data from LCIG pivotal studies in the subgroup of patients defined by ≥1 hour of ON time with troublesome dyskinesia demonstrated a reduction compared to baseline within this small cohort (n=144) despite higher total daily levodopa doses, suggesting a beneficial pharmacodynamic effect.[1] Some LCIG patients may develop disabling diphasic LID in the morning and at the end of the day when levodopa levels rise and wear off, respectively.[93] Diphasic LID may be misinterpreted as peak-dose in some LCIG-treated PD patients (see Supplementary Video 3); their proper management requires increasing the dose of LCIG or adding other dopaminergic medications.[93]

Continuous subcutaneous apomorphine infusion. Apomorphine is the only dopamine agonist administered subcutaneously, with the strongest D1 and D2 receptor affinity and shortest half-life. A meta-analysis of 390 patients from 21 uncontrolled open-label studies over a mean time frame of 24.8 months (6–57 months) reported a mean LID reduction of 36%.[94] The improvement

in LID severity depends in part on the extent to which oral dopaminergic medications with short half-life, such as levodopa, can be replaced by CSAI. In some cases this may require doses that are not tolerated, especially by elderly patients (e.g., confusion, psychosis, worsening of coexisting dysautonomia). Also, a common long-term complication of infusion is the occurrence of subcutaneous nodules. As a result, many centers in Europe use CSAI as a bridge treatment for fluctuating patients waiting to receive LCIG or DBS.[95] This treatment modality is under evaluation in the US.

To date, no randomized studies comparing the aforementioned 3 strategies have been performed. A study comparing STN DBS and LCIG reported an overall similar short-term effect on motor fluctuations although STN DBS may have been more effective against LID and associated with fewer adverse events.[96] A pharmacological study comparing the acute and chronic effects of levodopa in a relatively small group of patients receiving either STN DBS, LCIG, or CSAI concluded that DBS was the best strategy for LID reduction.[97]

Conclusions and future directions

LID is one of the most studied but also least optimally managed treatment complications in PD. A limitation of clinical research rests in the difficulty in categorizing dyskinesia as peak-dose versus diphasic, given the phenomenological overlap. This has resulted in combining patients with different dyskinesia types and presumably different pathophysiologic mechanisms in clinical studies. Further work is needed to develop consensus guidelines for translating candidate therapies from clinical trials, proper LID models to guide drug development, and levodopa dosing and formulations to extend half-life. In addition, one important challenge to the

establishment of effective anti-dyskinetic therapies is the high placebo effect demonstrated in a number of studies.[98] Rigorous, placebo-controlled trials will be important to better define the true treatment effect of any future intervention.

The current state of therapy for LID is promising, with numerous pharmacologic and nonpharmacologic treatment options. Besides the newly approved extended-release oral formulation of amantadine, a range of molecular and neuromodulative therapies are under evaluation in the therapeutic pipeline. It is conceivable that future improvements in levodopa delivery alone, through long-acting levodopa preparations or infusion systems,[99] may prevent the pharmacodynamic alterations associated with short-acting oral levodopa, and thus lower the prevalence of LID if initiated early.

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AJE conceived of the article and its structure, and all authors contributed text for specific sections.

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Figure legends

Figure 1. Time course of diphasic dyskinesia according to 3 different theoretical plasma levodopa concentrations. This diagram illustrates the 4 theoretical pharmacokinetic states of a

single dose of levodopa (LD) as it increases (Y axis) over a 4-hour approximate time horizon between LD doses (X axis; although shown of similar magnitude, the width of each state is variable within and between patients). The therapeutic window (ON state, optimal clinical benefits) becomes virtual with disease progression, encroached by the sub- and supra-therapeutic windows. The subtherapeutic window is divided into the OFF (loss of clinical benefits with reemergence of parkinsonian features) and "transitional" states. The latter may result in periods of diphasic dyskinesia (A, at both ends of the LD dose cycle) or longer, more disabling diphasic dyskinesia states (C) that could be mistaken for peak-dose square wave response (A, during the peak concentration). Pharmacotherapeutic strategies will differ in each scenario: LD dose should be reduced (or amantadine considered) in A but increased in C; LD dose interval may be shortened in B. An acute apomorphine or levodopa challenge can resolve uncertainty as it reduces or eliminates diphasic dyskinesia but leaves unchanged or worsens peak-dose dyskinesia.

DiDysk = diphasic dyskinesia; LD = levodopa (adapted from Verhagen Metman and Espay, Neurology 2017); OFF: reemergence of parkinsonian features; ON: optimal clinical benefit.[100]

Figure 2. Common topographic patterns among various forms of dyskinesia in Parkinson disease. Right-sided onset of disease is assumed for all cases. A. Peak-dose levodopa-induced dyskinesia tends to involve the upper trunk, neck, and arms, particularly on the more affected side; B. Hemidyskinesia with arm-greater-than-leg involvement can also be a manifestation of peak-dose dyskinesia, especially among young-onset PD patients; C. Diphasic dyskinesia affects the legs to a greater extent than any other body part; D. Unilateral foot dystonia on the more affected side is the typical manifestation of OFF dystonia (still a low-dose phenomenon);

E. Facial choreoathetotic movements and hand posturing may occur in advanced PD patients; F. Facial dystonia with feet dyskinesias are a topographical distribution atypical for PD and suggestive of multiple system atrophy. Darker shades of gray emphasize greater severity. (Figure commissioned to Martha Headworth. Adapted with permission from Espay.[101]) Printed with permission from Mayfield Clinic.

MSA= multiple system atrophy; PD = Parkinson disease.

Figure 3. Functional and structural network abnormalities in motor cortical areas and their connections with the basal ganglia and the cerebellum. At the network level, the supplementary motor area (SMA) and the inferior frontal cortex (IFC), which are involved in motor programming and inhibition, have been shown to be dysfunctional or structurally abnormal in Parkinson disease-associated levodopa-induced dyskinesia. The solid red arrow refers to decreased inhibition from the cerebellum to the primary motor cortex (M1). Arrows refer to connectivity studies. Increased (green arrows) and decreased (dotted red arrows) connectivity between the putamen and M1, pre-SMA/SMA, and primary sensory area (SM1) has been shown in patients with LID.

Figure 4. Main neurotransmitter terminals implicated in the induction of levodopa-induced dyskinesia Within the striatum, dopaminergic terminals (red terminal) release dopamine while D2 autoreceptors and uptake processes also control synaptic DA levels. DA binds striatal postsynaptic D1 receptors inducing the formation of cAMP via adenylyl cyclase, which in turn favors the activation (black arrows) of PKA, able to phosphorylate and activate DA- and cAMP-regulated phosphoprotein of 32 KDa and ERK. Activated pERK induces an

abnormal activation of MSK-1 and the final phosphorylation of histone H3. p-DARPP-32 inhibits (dotted lines) protein phosphatase 1. Glutamate is released from cortico-striatal terminals (light blue terminal) into the striatum and activates NMDA receptors, whose activity increases intracellular levels of Ca^{2+}. Increased intracellular calcium levels facilitate the production and release of endocannabinoids which in turn act on CB1 receptors at presynaptic terminals, limiting glutamate release. Presynaptic modulation of glutamate and DA release is also achieved by the activation of opioid receptors. The serotonergic afferents (green terminal) release serotonin into the striatum which is regulated by 5-HT1 autoreceptors. These afferents take up levodopa, convert it to DA, and then release DA in an unregulated fashion. Finally, cholinergic acetylcholine interneurons (yellow terminal), by overstimulation of nACh receptors on dopaminergic terminals, contribute to the abnormal DA-release (see text for details and information on other mechanisms).

5-HT = serotonin; 5-HT1 = 5-hydroxytryptamine receptor 1; AC = adenylyl cyclase; ACh = acetylcholine; ATP = Adenosine triphosphate; Ca2+ = calcium; cAMP = cyclic adenosine monophosphate; CB1 = cannabinoid receptor type 1; D1 = dopamine D1 receptor; D2 = dopamine D2 receptor; DA = dopamine; eCBs = endocannabinoids; GABA = gamma-aminobutyric acid; GluN2A/2B = NMDA receptor subunits 2A and 2B ratio; eCBs = endocannabinoids; ER = endoplasmic reticulum; Glu = glutamate; MSK1 = mitogen- and stress-activated kinase-1; nACh = nicotinic acetylcholine receptors; NMDA = *N*-methyl-D-aspartate; pERK = phospho-extracellular signal-regulated kinases; PDE10A = phosphodiesterase 10A; P-H3 = phospho-histone H3; PKA = protein kinase A; p-DARPP-32 = phosphorylated dopamine- and cAMP-regulated phosphoprotein 32 kDa; PP1 = protein phosphatase 1; SPN = spiny projection neuron.

Supplementary Video legends

Supplementary Video 1. Peak-dose dyskinesias as generalized chorea. This 58-year-old man with 10-year-history of PD demonstrates generalized chorea with arms and neck predominance. The movements are maximal during the peak-dose effect of levodopa and disappear in the wearing off/subtherapeutic window. Left arm dystonia is brought out during walking.

Supplementary Video 2. Peak-dose dyskinesia predominantly in the legs. A 63-year-old man with 8-year history of PD demonstrates leg chorea with no or minimal upper-body involvement that is, by history, peak-dose in nature.

Supplementary Video 3. **Diphasic dyskinesia predominantly in the legs**. This 56-year-old man with a 14-year history of PD, on treatment with levodopa-carbidopa enteral infusion, demonstrates leg-predominant chorea as a manifestation of diphasic dyskinesia. The movements disappear when levodopa infusion is increased, or an extra oral levodopa dose takes effect.

Supplementary Video 4. This 52-year-old man with a 12-year history of PD demonstrates generalized chorea, suspected initially to represent peak-dose dyskinesia, but proven to be diphasic by its attenuation within minutes after subcutaneous apomorphine 0.2 mL (from Verhagen Metman and Espay, *Neurology* 2017)

Supplementary Video 5. Early-morning (off) dystonia. Foot dystonia appears most prominently in the morning on the most affected side in this 64-year-old woman, shown here 8

years after symptom onset. Onset of action of levodopa eliminates the dystonia (not shown). Note intermittent episodes of resting hand tremor when sitting and walking, emphasizing under-therapeutic medication state.

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Table 1. Pathophysiology studies on levodopa-induced dyskinesia in humans.

Year	Subjects	Methodology	Outcome Measures	Main findings in PD-LID vs PD-no-LID
2012[31]	HC = 10; PD-stable = 17; PD-no-LID = 18; PD-LID = 20	TMS	LTP-like and LTD-like plasticity of most affected M1	Lack of LTP-like plasticity and paradoxical potentiation after inhibitory TBS after acute LD challenge
2016[29]	PD-LID = 2	LFP	ECoG of M1 and LFP of STN	60-90 Hz oscillations in M1 and STN and strong phase coherence between M1 and STN
2013[102]	HC = 24; PD-no-LID = 30; PD-LID = 29	Structural MRI	Cortical thickness (whole brain)	↑ thickness in the right inferior frontal sulcus
2013[102]	HC = 40; PD-no-LID = 33; PD-LID = 33	Structural MRI	VBM and cortical thickness (ROI: IFC, cingulate cortex, SMA and pre-SMA, basal ganglia, SN, red nucleus, STN, cerebellum)	↑ GM volume in IFC (bilateral) and midbrain in early onset PD-LID. ↑ GM volume in IFC (bilateral), SMA and pre-SMA in late onset PD-LID. ↑ cortical thickness of IFC (bilateral) in early onset PD-LID. ↑ cortical thickness of left IFC in late onset PD-LID
2015[25]	fMRI: PD-no-LID = 12; PD-LID=12. TMS: PD-LID = 11	RS-fMRI and TMS	Functional connectivity of bilateral IFC, SMA/preSMA, M1, STN, thalamus, striatum and cerebellum. TBS (sham, inhibitory, facilitatory) over right IFC or M1	↓connectivity of right IFC with left M1 and ↑connectivity of right IFC with right putamen in ON. Inhibitory TBS reduced LID when applied over the right IFC in PD-LID
2016[103]	PD-no-LID = 12; PD-LID = 12	RS-fMRI + Structural MRI	Functional connectivity and VBM (ROI: bilateral putamen, SMA, SM1, right IFC)	↓connectivity after LD between SM1 and the putamen in the most affected hemisphere. ↓connectivity after LD between SMA and the putamen was correlated to LID severity. No structural abnormality in SM cortex, SMA, ICF, putamen
2012[104]	PD-no-LID = 10; PD-LID = 10	fMRI	Neural correlates of externally and internally triggered visuomotor tasks	↑ activity in SMA and ↓ activity of right IFC during the visuomotor tasks, correlated to dyskinesia severity
2015[105]	PD-no-LID = 12; PD LID = 12	fMRI	Neural correlates of successful and erroneous "Stop" responses in a stop-signal reaction time	During successful stop responses, ↓ activity of right IFC in ON and ↑ activity of right IFC in OFF; during failed stop responses, ↑ activity of MFC in ON
2014[106]	HC = 13; PD-no-LID = 13; PD LID = 13	fMRI	Neural correlates of GO and NoGO responses to stimulus-response mapping task	↑ activity in preSMA and bilateral putamen in NoGo trials before developing LID. Finding correlated to severity of LID
2015[26]	PD-no-LID = 13; PD LID = 13	fMRI	Functional connectivity between basal ganglia and M1 or pre-SMA during a visuomotor task	LD ↑ connectivity between putamen and M1 during movement suppression (in a NoGo task). Finding correlated to severity of LID

Year	Subjects	Methodology	Outcome Measures	Main findings in PD-LID vs PD-no-LID
2012[32]	HC = 12; PD-drug naive = 9; PD-no-LID = 10; PD-LID = 10	PET	Binding of ^{18}F-MK-9470, a selective radioligand for type 1 cannabinoid receptor	No specific changes of type 1 cannabinoid receptor in PD-LID, but only in the overall PD group compared to HC
2014[82]	HC = 12; PD-no-LID = 12; PD-LID = 24	PET	Binding of: ^{11}C-DASB, 5-HT transporter; ^{11}C-raclopride, striatal DA levels.	^{11}C-DASB binding in caudate/putamen comparable in PD-LID and PD-no-LID. ↑ striatal synaptic DA concentrations in PD-LID, decreased by buspirone which induced an anti-dyskinetic effect
2015[107]	PD-drug naive = 10; PD-no-LID = 10; PD-LID = 10	PET	Binding of: ^{11}C-DASB, 5-HT transporter; ^{18}F-FP-CIT, DA transporter. ^{11}C-DASB to ^{18}F-FP-CIT binding ratio	^{11}C-DASB to ^{18}F-FP-CIT binding ratio ↑ in the putamen
2015[108]	HC = 12; PD-no-LID = 12; PD-LID = 12	PET	Binding of: ^{11}C-DASB, 5-HT transporter; ^{11}C-raclopride, striatal DA levels. ^{11}C-DASB to ^{18}F-FP-CIT binding ratio. ROI: globus pallidus	^{11}C-DASB binding in globus pallidus ↓ in PD-no-LID compared to PD-LID and HC. ↑ pallidal synaptic DA in PD-LID
2015[33]	HC = 12; PD-no-LID = 12; PD-LID = 12	PET	Binding of ^{11}C-IMA107, a highly selective PDE10A ligand	↓^{11}C-IMA107 in caudate, substantia nigra and thalamic nuclei in PD-LID. ↓11C-IMA107 in caudate and putamen correlated to more severe LID
2016[34]	HC = 12; PD-no-LID = 11; PD-LID = 17	PET	Binding of: ^{11}C-DASB, 5-HT transporter; ^{18}F-FP-CIT, DA transporter. ^{11}C-DASB to ^{18}F-FP-CIT binding ratio	^{11}C-DASB to ^{18}F-FP-CIT binding ratio ↑ in the putamen

Only studies dated 2012 or older are included. 5-HT = 5-hydroxytryptamine (serotonin); AIMS = abnormal involuntary movement scale; BOLD = blood oxygenation level dependent; DA = dopamine; ECoG = electrocorticography; fMRI= functional MRI; GM = grey matter; GPi= globus pallidus pars interna; HC = healthy controls; IFC = inferior frontal cortex; LD = levodopa; LFP = local field potential; LID = levodopa-induced dyskinesia; LTP = long-term potentiation; M1 = primary motor cortex; MFC = medial frontal cortex; NA = not available; PDE10A = phosphodiesterase 10A; PET = positron emission tomography; ROI = region of interest; RS = resting state; SM1 = primary sensorimotor cortex; SMA = supplementary motor area; SN = substantia nigra; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale; TBS = theta burst stimulation; TMS = transcranial magnetic stimulation; VBM = voxel based morphometry.

Table 2. Therapies in clinical research development for levodopa-induced dyskinesia.

Drug	Mechanism of Action	Dyskinesia Endpoint/ Duration	Clinical Relevance
ADS-5102 (Amantadine extended release; GOCOVRI™)	Glutamate antagonist (NMDA receptor antagonist)	UDysRS / 12 weeks	Dose-dependent decrease in dyskinesia with secondary benefit of reduced OFF time.[1-3] *Approved by FDA in 2017*
Amantadine HCl Extended Release (OSMOLEX ER™)	Glutamate antagonist (NMDA receptor antagonist)	UDysRS / 98 days	Phase III studies, NCT02153645 (ALLAY-LID I) / NCT02153632 (ALLAY-LID II). No results published. *Approved by FDA in 2018 based on PK equivalence with amantadine*
Dextromethorphan/Quinidine (AVP-923-45)	Sigma-1 receptor-agonist and glutamatergic/ monoaminergic modulator	UDysRS / 2 weeks	Phase II crossover study, minimal clinical benefit (n = 13); well tolerated[109]
Eltoprazine	Serotonin agonist Mixed 5-HT1A/1B receptor agonist	Clinical Dyskinesia Rating Scale; acute dose UDysRS / 84 days	Phase IIa; acute dosing reduced peak-dose dyskinesia (n=22) compared with placebo; no worsening of PD motor scores; AEs: nausea and dizziness[83] Phase IIb DBRCT; 2.5 – 7.5mg/d NCT02439125 Results pending
Buspirone	5-HT1A receptor agonist	AIMS / acute dose UDysRS / 12 weeks Force plate measurements / 6-h LD dose cycle UDysRS / 6 weeks	Subgroup from PET imaging study; acute dosing reduced LID during a levodopa challenge versus placebo (n = 24); more effective in subjects with milder LID than with severe LID; no worsening of PD motor scores. AEs: drowsiness and dizziness[82] Phase III study; NCT02617017 (BUSPARK) –evaluating efficacy of buspirone in PD-LID. Results pending Phase II study; NCT02589340 (BUS-PD) – evaluating the efficacy of buspirone in combination with amantadine in reducing PD-LID. Results pending
Foliglurax (PXT002331)	Positive allosteric modulator of mGluR4	Dyskinesia rating not defined. Hauser diary/28 days	Phase IIa study; NCT03162874 (AMBLED) –for LID-PD and end of dose wearing off. Results pending
Zonisamide	Channel modulator	UDysRS / 12 weeks	Phase IV open-label study; NCT03034538 – evaluating 2 doses for tolerability and efficacy for PD

			dyskinesias. Results pending
NLX-112 (befiradol or F13640)	5-HT1A receptor full agonist	no information available	Inhibits LID in rodent models of PD;[58] phase II study results pending
IRL790	Dopamine D3 receptor agonist	UDysRS / 4 weeks	Phase IIa study; NCT03368170 – evaluating IRL790 as an adjunctive treatment for PD-LID. Results pending

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