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Levodopa-induced dyskinesia: A historical review of Parkinson's disease, dopamine, and modern advancements in research and treatment

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Abstract

Over the past two decades, animal models of Parkinson's disease (PD) have helped to determine the plausible underlying mechanism of L-DOPA (levo-dihydroxyphenylalanine) induced dyskinesia following L-DOPA treatment. However, our understanding of the mechanisms related to this phenomenon remains incomplete. The purpose of this manuscript is to provide a comprehensive review of treatment protocols used for assessing the occurrence of L-DOPA-induced dyskinesia, L-DOPA absorption, distribution, drug/food interaction, and discuss current strategies and future directions. This review offers a historical perspective using L-DOPA in animal models of PD and the occurrence of L-DOPA-induced dyskinesia.

Keywords

Dopamine; L-DOPA; Diet; Parkinson's Disease

Introduction

Parkinson's disease (PD) is pathologically characterized by progressive degeneration of the substantia nigra dopaminergic neurons leading to motor symptoms such as bradykinesia, resting tremor, instability upon standing, and troubled walking [1]. Non-motor symptoms of PD include olfactory dysfunction, autonomic concerns (gastrointestinal and genitourinary problems), sleep disturbances, increased pain sensitivity, and cognitive deficits [1]. Most

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Competing Interests

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treatment strategies aim to use dopaminergic drugs to supplement central nervous system (CNS) neuron deficits. As dopamine is a charged molecule, it cannot pass the blood-brain barrier, making systemic administration non-viable. In addition, metabolizing enzymes such as monoamine oxidase, catechol-O-methyltransferase, and aldehyde dehydrogenase convert dopamine into inactive metabolites in peripheral blood, limiting the amount of dopamine reaching the CNS. Alternatively, L-DOPA (levo-dihydroxyphenylalanine), the precursor to dopamine, readily crosses the blood-brain barrier and has proven to be an effective treatment for alleviating PD motor symptoms when co-administered with carbidopa. Carbidopa inhibits dopa-decarboxylase enzymes to decrease the metabolism of L-DOPA in the periphery. Nonetheless, L-DOPA treatment is associated with the occurrence of motor complications and fluctuations over time, such as L-DOPA-induced dyskinesia (LID) [2, 3]. Patients commonly develop a “wearing-off” effect after L-DOPA intake leading to recurrence of PD symptoms after temporal benefit. LID and motor fluctuations can be observed within months of initiating therapy, indicating that disease progression and duration likely have a more significant influence on fluctuations than the duration of L-DOPA exposure [4].

LID can present in a wide variety of phenomenologies, including chorea, dystonia, ballism, or a combination of any of these hyperkinesias. Chorea presents as a quick, abnormal, and non-volitional movement of a particular limb initiated during movement, such as walking [5]. Dystonia features constant, and sometimes painful, muscle contractions representing the second most common dystonia behind chorea [5]. Ballism refers to rapid and grand flailing of the arms, often seen in conjunction with chorea [5]. LID is usually generalized or segmental and can be classified based on the timing of L-DOPA dosing, with “peak-dose dyskinesia” as the most common type [6]. LID can affect the quality of life and increase the risk of falls. Since the quality of life is subjective, studies have classified the severity of dyskinesia as either “troublesome” or “not troublesome” while patients were part of the “On” phase of L-DOPA treatment [5–7].

The frequency of LID varies from study to study, but prospective data suggest that LID might be present in 10–30% of patients in the first years of treatment [3, 8]. Around 94% of PD patients develop LID after 15 years of L-DOPA exposure [4]. Over the past two decades, L-DOPA treatment in animal models of PD has been used to study the underlying mechanisms of LID. Herein, we review the vast historical literature utilizing L-DOPA, starting from the first usage in PD patients developing LID, current use in animal models of PD, and alternative strategies for dopamine replacement therapy.

Methods

Literature search

A search was conducted via PubMed and Google Scholar to identify English language articles from any year, with keywords such as “L-DOPA” “LID” “Parkinson’s Disease” “Levodopamine” “dyskinesia” and looked specifically for animal models of mouse and rat. For researching historical perspective the same keywords were used and articles with the earliest publications concerning the topic were chosen. These papers included both animal models and reports from human trials.

Literature review

All results were reviewed by one author (CAH), except for dietary interactions which were reviewed by two authors (SA, CTR). Any duplicate articles were discarded and the remaining articles were reviewed for the inclusion criteria. Final studies meeting inclusion criteria were reviewed by three authors (DRM, ARZ, and HK). The final review was performed by two authors (DRM and HK).

Inclusion criteria

(1) The study must include a model of dopamine depletion, such as 6-OHDA or MPTP (2) lesioned animals were treated with L-DOPA, (3) L-DOPA treatment includes dosage and schedule within the manuscript, (4) data and observations were from the earliest source (historical perspective), (5)

Exclusion criteria

(1) Historical account was described in an earlier manuscript (historical perspective), (2) data reported did not coincide with L-DOPA treatment, (3) L-DOPA treatment did not include dosage or schedule, (4) Depletion method did not contain sufficient information for replication (e.g. lacking route of administration), (5) review articles that did not include primary literature.

Landmarks in the history of Parkinson's Disease, dopamine, and levodopa

First documented in 1817 by James Parkinson, patients presented with shaking palsy described as "involuntary tremulous motion, with lessened muscular power" [9] characterized the disease which would later bear his namesake. Parkinson delved into the progression of the disease first, by classifying its initial symptoms of weakness and trembling of a single limb [9] which then progressed to other limbs eventually resulting in difficulty with standing and sitting [9]. Daily tasks such as eating, sleeping, walking, and talking become nearly impossible without medication or assistance [9]. While this malady was first mentioned in the 1800s, it took over a century to begin discovering plausible mechanisms and treatment strategies.

In an attempt to determine the synthesis of adrenaline from tyrosine, Casimir Funk proceeded through several reaction steps, yielding spindle-shaped crystals that readily oxidized in neutral and alkaline solutions to form a black substance [10]. The substance, D**L**-3,4-**d**ihydr**o**xy**p**henyl**a**lanine (L-DOPA), undergoes decarboxylation to form dopamine, the central neurotransmitter lost in PD [11]. The overarching clinical application of Funk's study was not considered until a half-century later. In the 1950s, additional experiments were conducted to determine how reserpine inhibited the uptake and storage of monoamine neurotransmitters, including norepinephrine, dopamine, serotonin, and histamine, in the synaptic vesicles [12, 13]. Arvid Carlsson surmised that because serotonin was depleted in rabbits after administration of reserpine, delivering serotonin should restore volitional motor control [12]. To test this, Carlsson administered the reserpine-treated rabbits to either the precursor for serotonin (5-hydroxytryptophan) or L-DOPA [12]. It was found that L-DOPA reversed the neurological dysfunction, establishing dopamine as not only a precursor

to other neurotransmitters but itself as an essential neurotransmitter [12, 14]. In 1959, Hornykiewicz began studying neurotransmitter levels in the striatum of post-mortem brains of Parkinson's patients, showing both noradrenaline and dopamine levels were decreased [15], establishing a potential contribution to the motor symptoms present in Parkinson's disease [15]. The findings of Funk, Carlsson, and Hornykiewicz established the foundation of showing that administration of L-DOPA, which restored the loss of dopamine levels in the brain of reserpine treated animals and alleviated the reserpine-induced rigidity, may provide alleviation of the similar symptoms observed in PD [12, 16]. This technique was later applied in 1967 by George Cotzias [17].

For more than 20 years following Carlsson's studies, the reserpine vesicular depletion model was the prevailing animal model to study PD. In 1971, Breese and Traylor found that 6-OHDA (6-hydroxydopamine) depletes noradrenaline and dopamine in rats' striatum [18], based on an earlier report by Ungerstedt suggesting depletion and neurodegeneration of substantia nigra dopaminergic neurons by 6-OHDA [19]. Since then, the 6-OHDA animal model of Parkinson's has been one of the most widely used animal models to induce Parkinson-like symptoms in rodents and primates [20, 21]. Advantages include the reproducibility of lesions, low cost, and well-established use through years of extensive research [21]. The 6-OHDA lesion mimics PD motor symptoms in humans by causing neuronal stress and microglial immune response [20]. Disadvantages relate to the limited role of demonstrating a slow, stepwise progression in different neuronal networks as seen in humans diagnosed with PD. In 1983, William Langston was confronted with mysteriously "frozen" young men and women who abused a tainted batch of synthetic heroin that later was found to be laced with the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyradine (MPTP) [22]. These patients exhibited severe motor symptoms resembling PD. Langston was able to "unfreeze" these patients by administering L-DOPA. [23]. Although Langston grappled with saving the lives of these patients, his breakthrough suggested that MPTP exposure destroys human substantia nigra dopamine neurons, further advancing PD research [22]. Later Sonsalla and Heikkila showed that repeated MPTP injections deplete dopamine in the rat striatum [24], thus confirming the hypothesis laid out by Langston. Transitioning from reserpine to toxin-induced PD models- 6-OHDA and MPTP- allowed the researchers to conduct PD-related research in rodents and primates.

In the early 1980s, research began to identify behavioral assays to assess the motor symptoms of PD. Ungerstedt and Arbuthnott established one of the earliest behavioral assays that included measuring rotational behavior in rats after 6-OHDA lesions of the nigrostriatal dopamine system [25]. Observing rotational behavior, they deduced that dopamine receptor agonists could alleviate Parkinson-like symptoms in 6-OHDA lesioned rats by lowering the instance of rotational behavior [25]. Later, Maria Cenci and colleagues established a battery of behavioral assays involving limb movement [26, 27]. The strengths and limitations of the mouse, rat, and non-human primate PD models are outlined in two recent review articles [20, 28]. These studies led to the discovery that prolonged L-DOPA therapy-induced non-volitional movements were coined as abnormal involuntary movements (AIMs), categorizing L-DOPA-induced dyskinesia (LID). To date, motor fluctuations and LID remain significant clinical problems in the management of PD patients. Relieving

parkinsonian symptoms without inducing dyskinesia is an unmet therapeutic need in most PD patients.

Levodopa-induced dyskinesia

L-DOPA combined with a peripherally acting dopa-decarboxylase inhibitor such as carbidopa or benserazide is a common treatment strategy to alleviate PD symptoms. A 1971 analysis of patients treated with L-DOPA to reduce their PD symptoms showed within one year that more than 40% of these patients exhibited LID side effects [29]. Observed LID symptoms consisted of repetitive jerks of a limb, involuntary muscle contractions, and writhing movements (typically of the hands and feet) [29]. The LID symptoms would appear as early as two months after beginning L-DOPA therapy and would more likely occur in those with severe PD [29]. In the early years of treatment, high doses of L-DOPA were commonly used in conjunction with “drug-free holidays,” defined as the withdrawal period from L-DOPA, which might contribute to the development of dyskinesia, as pulsatile stimulation of dopamine receptors has been postulated as an important mechanism relating to the development of motor fluctuations [30]. Additionally, many patients had a long disease duration prior to initiating treatment. Similar to PD patients, in primate models of PD, primates develop dyskinesia following L-DOPA therapy, where the severity of symptoms increases with greater nigrostriatal damage [31]. In monkeys exposed to systemic MPTP, Schneider found a direct relationship between latency and severity of degeneration of dopaminergic neurons in the caudate, the limited efficacy of L-DOPA in severe parkinsonism, and the presence of LIDs [31]. He found monkeys with mild parkinsonian symptoms did not develop dyskinesias; whereas almost all animals with severe Parkinson’s symptoms developed LID two to twelve days after initiation of L-DOPA treatment. Collectively, these observations combined with studies in rodent models of PD [26, 32, 33], led to the establishment of rating scales for L-DOPA-induced abnormal involuntary movements that can quantitatively assess dyskinetic behaviors in L-DOPA treated rodent models of PD.

It should be noted that while the LIDs in human and animal models of PD is likely due to dysregulation of dopamine release from dopaminergic terminals, the serotonergic system in the CNS has also been suggested to be involved in the manifestation of LID [34]. Serotonergic neurons are capable of producing dopamine, though this is not their main function [35, 36]. When exogenous levels are high, it is postulated that L-DOPA enters serotonergic neurons increasing dopamine synthesis and release from these neurons. Therefore, serotonergic neurons can exacerbate LID [34]. LID might negatively impact quality-of-life in PD patients and interfere and challenge adequate management of motor symptoms and fluctuations observed in the disease. Since animal models recapitulate LID, they provide a valuable experimental source to determine the effect of emerging technologies on LID and motor symptoms.

Evolution of therapeutic approaches in PD: from L-DOPA to Sinemet to gene therapy and management of motor complications

Since the approval of L-DOPA treatment by the FDA in 1975, L-DOPA has been a drug of choice to alleviate the cardinal symptoms of PD (tremor, rigidity, bradykinesia, and postural abnormalities) by replenishing the lost dopamine in the striatum [1]. In 1967, Bartholini and colleagues showed that inhibition of peripheral dopa-decarboxylase enzymes increases CNS catecholamine levels [37]. Therefore, Benserazide (Ro 4–4602), a peripheral decarboxylase inhibitor that does not cross the blood-brain barrier, can be co-administered with L-DOPA [37, 38]. The earliest documented L-DOPA treatment in human studies examined the efficacy of 5–24 mg/kg daily dosage of L-DOPA in PD patients in 1960 [38, 39]. Various daily dosages of 0.25 to 1 g L-DOPA were used until 1988 when FDA approved L-DOPA/carbidopa formulation (Sinemet®) with a maximum dosage of 800 mg/day, approximately eight pills of 25 mg carbidopa/100 mg L-DOPA [40]. Early longitudinal studies found no difference in motor, affect, and quality-of-life scores in PD patients receiving lower or higher than 800 mg L-DOPA as the daily dosage [40]. In the gut, L-DOPA shares a common transporter with other amino acids [41], and an acidic environment increases the solubility of L-DOPA, therefore, increasing its absorption rate [41]. To enhance efficiency, L-DOPA is commonly dosed before meals to avoid competition with amino acid transporters and improve absorption. This is particularly important with patients with marked motor fluctuations or in advanced stages of the disease. L-DOPA must be titrated for each individual patient to reduce functional disability while minimizing adverse effects. Prospective studies have shown that relatively large doses of L-DOPA (300–600 mg/day) might contribute to an increased risk of motor fluctuations [42, 43]. Treatment involving L-DOPA alongside a decarboxylase inhibitor represents the current standard of care. While supplementation of L-DOPA is a viable option for alleviating symptoms, gene therapy has shown promise in the neurodegenerative field with the potential to reduce motor disability.

Since the discovery of adeno-associated virus (AAV) in the mid-1960s [44], the possibility of using viral vectors to treat PD has been examined by many investigators, albeit without substantial success [1]. Transfer of dopamine gene has been postulated as a potential, important strategy to manage PD symptoms and its complications. In 1998, a study by Mandel et al. showed the benefits of gene therapy by injecting a viral vector for TH (tyrosine hydroxylase) and GCH1 (GTP cyclohydrolase 1), the precursor to BH4 (tetrahydrobiopterin) and a cofactor for TH shown in the rat basal ganglia [45]. Using the 6-OHDA model, AAV containing TH was injected ipsilaterally to the 6-OHDA treated striatum. Transduced striatal cells (>90% being neurons) were detected with TH up to one-year post-injection [45]. Later Cederfjäll et al. generated a dual vector harboring both TH and GCH1 genes [46] that restored the contralateral (to injected striatum) paw rotation in PD mice for 14 weeks and increased ipsilateral dopamine concentration in the vector treated mice compared to the control mice [46]. The glial-derived neurotrophic factor (GDNF) gene therapy was also tested to increase neuronal survival in PD animal models [1]. Monkeys injected with AAV encoding neurturin or aromatic amino acid decarboxylase (AADC), exhibited fewer motor impairments produced by MPTP lesions that lasted for ten months, without producing

dyskinesia [47, 48]. Neither study reached phase three clinical trial. There were several phase 2 studies published, and a new company is looking into phase 2 studies using a combination of gene transfer enzymes, AXO-Lenti-PD, while planning a phase 3 study next year [49, 50]. With an increase in our understanding of how L-DOPA is absorbed and competes with other proteins, studies described below have provided possible diet alterations that may benefit those with PD.

L-DOPA interactions with dietary proteins

As a large neutral amino acid, L-DOPA shares structural similarities to the precursors of endogenous dopamine synthesis: phenylalanine and tyrosine. While most dietary proteins are absorbed efficiently as di- and tripeptides along the small intestine via intestinal peptide transporter 1, free amino acids (including L-DOPA) can be absorbed via separate transport systems along the apical and basolateral membranes of enterocytes [51]. To date, only one study published in 2014 has attempted to determine transporters involved with L-DOPA absorption using in-vitro and in-vivo models [52]. Camargo et al. identified $b^{0,+}$AT-rBAT (SLC7A9-SLC3A1) as an antiporter that transports L-DOPA across the apical membrane of enterocytes. On the basolateral side, TAT1 (SLC16A10) appears to be the main L-DOPA transporter along with LAT2-4F2hc (SLC7A8-SLC3A2) to a lesser extent. Competition may occur for absorption at the apical membrane with the neutral and cationic amino acids, leucine and arginine (respectively), and basolateral efflux may be dependent on the postprandial presence of amino acids in the basolateral compartment. Further, modifying dietary protein intake during L-DOPA treatment in people with PD has been proposed to minimize inhibitory competition of L-DOPA during intestinal absorption.

Although administering L-DOPA with food may prevent potential side effects such as nausea, it is recommended that this medication is taken on an empty stomach 20–30-minutes prior to meals to maximize its absorption [53]. The American Academy of Neurology has recommended low protein (LPD) or protein redistributed (PRD) diets for those experiencing significant motor fluctuations [54, 55]. LPD is generally defined as consuming less than the recommended dietary allowance (RDA) of 0.8 g protein per kg body weight per day, and a PRD is defined as limited protein intake during the day and unrestricted intake in the evening. A limited number of clinical trials between the 1970s and 1990s have compared the effectiveness of the LPD and PRD and suggest that both LPD and PRD are able to improve the effectiveness of the L-DOPA treatments compared to a control diet. However, several limitations of these studies exist including small sample sizes, non-standardized control groups, and definitions of diets between studies [56–58].

The use of LPD with co-administration of L-DOPA remains controversial in comparison to PRD. People with PD are at increased risk for loss of lean body mass and subsequent protein-calorie malnutrition, which may be exacerbated while following an LPD. More evidence exists on the effectiveness of PRD compared to LPD [59]. A systematic review of PRD from Cereda et al. found that people with PD following a PRD experienced more “On” time with L-DOPA while consuming an average protein intake closer to the RDA (0.8 g/kg body weight/day). However, 0.8 g protein/kg body weight/day may not be sufficient for optimal protein intake in some people with PD due to increased energy expenditure

as a previous study demonstrated people with PD are more likely to be in a negative nitrogen balance (i.e., catabolic state) compared to controls while consuming an average protein intake of 1.1 g/kg/day [60]. The decline in nutritional status and body mass index over time is of concern while following LPD and PRD as this is correlated with increased disease severity [61, 62]. The use of these diets should be implemented with caution and targeted to people with PD who are more likely to benefit from altered diets. A more recent retrospective study by Virmani et al. found only 5.9% of people with PD on L-DOPA experienced motor fluctuations correlated with protein intake timing [63]. These people generally were prescribed a higher daily dosage of L-DOPA and experienced more motor fluctuations and dose failures. Future studies should aim to confirm the appropriate usage, efficacy, and safety of these diets in larger randomized control trials.

Novel approaches and current management of dyskinesia

Management of dyskinesia requires an individualized approach based on the specific dynamic and occurrence of dyskinetic movements, severity, side effects, and related impairment of daily activities. In patients with peak-dose dyskinesia, smaller doses of L-DOPA administered more frequently should be considered. Reducing or eliminating add-on medications such as MAO-B inhibitors or COMT inhibitors (particularly if a limited benefit or if adverse events are present) can alleviate LID. For patients receiving longer-acting formulations of L-DOPA, such as Sinemet controlled-release (CR), the absorption tends to be erratic with a stacking effect over the course of the day with a subsequent increase in dyskinesia during evening hours. This could be addressed by switching patients to a different L-DOPA formulation administered through the course of the waking time [6, 64]. Treatment of diphasic dyskinesias is more challenging but useful strategies include decreasing the total daily dose of L-DOPA and increasing the dose of a dopamine agonist or adding Amantadine. The risk and frequency of dyskinesia is less in patients receiving dopamine agonists than patients receiving L-DOPA, possibly due to the longer half-life [65]. If the associated end of dose wearing off is a concern along with dyskinesia, the use of L-DOPA extended-release (Rytary®) has shown a reduction in “off” time without troublesome dyskinesia. Advanced management options like infusion therapies or deep brain stimulation can provide remarkable control of LID and should be considered in patients with refractory symptoms.

Amantadine is a non-selective, low-affinity noncompetitive NMDA antagonist with anti-glutamatergic properties. Amantadine ER (GOCOVRI®) was approved for the management of LID in 2017. The safety and efficacy of amantadine ER were evaluated in two, phase 3 randomized, double-blind, placebo-controlled clinical trials. The primary efficacy endpoint in both studies reported a change in the total score of the Unified Dyskinesia Rating Scale from baseline to week 12. There was a significant difference in total dyskinesia scores compared to placebo (8 and 14 points in each study respectively). Also, in both studies, amantadine demonstrated a significant increase in “on ” time, without troublesome dyskinesia, and a significant reduction in “off” time compared to baseline on PD motor diaries [66, 67]. Prior studies also showed that regular amantadine 100 mg twice daily resulted in a significant decrease in total dyskinesia scores by 24% along with a reduction in time “ON with dyskinesia“ [68–70].

Side effects may limit the use of amantadine and these include hallucinations, constipation, orthostatic hypotension, dizziness, sedation, myoclonus, livedo reticularis, hair loss, and ankle edema. Overall, 20% of patients who received amantadine discontinued treatment versus 8% of patients who received placebo in clinical trials of Amantadine ER. These adverse events are likely more relevant in older patients or patients with more severe disease or complex motor and non-motor phenotypes and these populations are not representative of the cohorts studied in pivotal trials.

LID can be difficult to manage in certain PD patients due to worsening parkinsonism and motor fluctuations with a reduction of medications. Additionally, certain patients exhibit brittle, marked dyskinesia even with low doses of L-DOPA. Deep brain stimulation (DBS) is an excellent alternative for patients with refractory symptoms. Several studies including randomized and comparative trials have reported a reduction in dyskinesia with Pallidal (GPi) or subthalamic nucleus (STN) stimulation around 89% and 62% in most studies respectively [71]. A meta-analysis also showed that GPi-DBS offered a more robust reduction in dyskinesia compared to STN-DBS. However, data from patients' diaries showed similar efficacy during "on" time without dyskinesia and there are differences in sample size and a longer follow-up time among different studies. Also, several studies suggest that the anti-dyskinetic effect of STN DBS is mostly dependent on medication reduction compared with a direct anti-dyskinetic effect of GPi DBS [72]. Randomized, controlled studies of L-DOPA/Carbidopa Intestinal Gel (LCIG) have shown significant results in "off" time and "on" time without troublesome dyskinesia as well as in "on" time without any dyskinesia (difference between groups 2·28±0·90hrs;) [73]. Continuous subcutaneous infusion of apomorphine is a well-established and effective treatment for refractory "off" periods and peak-dose dyskinesias in PD. This therapy is available only in certain countries around the globe. Large case series and observational studies report a significant reduction in dyskinesia despite a maintained increase in "on" time [74, 75].

Open-label embryonic dopamine cell neurotransplantation has been performed by several groups for the past two decades with reports of persistent benefit in PD symptoms in some patients. The procedure appears to be relatively safe and well tolerated [76, 77]. Nonetheless, controlled trials have yielded mixed efficacy results. A common adverse event observed in several patients was the increase of dyskinesias after transplantation allegedly due to increased dopaminergic production in the striatum from the transplanted cells [76, 77]. Management was similar to LID with clinical improvement with medication reductions in most patients [76, 77]. However, a portion of patients (around 15% in a long-term randomized trial) developed persistent choreodystonic dyskinesia despite prolonged discontinuation of L-DOPA [78]. Other groups reported similar adverse events in patients implanted with human embryonic mesencephalic tissue [79]. This situation became clinically a unique challenge as patients reported marked impairment in daily activities requiring marked medication reductions or the use of dopamine depleters (leading to worsening parkinsonism). Data from clinical studies suggest that dopamine produced by the transplanted cell is responsible for dyskinesia. Overall features supporting this hypothesis include a phenomenology that strongly resembles that of typical LID, statistically significantly greater fluorodopa (FD) uptake by FDOPA PET than implanted patients without dyskinesia, greater fluorodopa uptake in the ventral and posterior left putamen on

PET compared to the subjects who did not develop persistent dyskinesia, the time course of the dyskinesia compatible with the gradual outgrowth of graft neurites over months to years and a strong correlation with clinical improvement [80]. The mechanism of off-medication dyskinesia following fetal nigral transplantation is not known. A possible factor proposed include potential graft overgrowth with excess dopamine production (however, neither striatal FD uptake on PET nor post-mortem analyses indicate increased dopaminergic activity).

Abnormal pulsatile or discontinuous stimulation of striatal receptors has been implicated in the development of dyskinesia in PD. Then, transplantation might have been expected to reduce dyskinesias by increasing the number of striatal dopamine terminals that can store dopamine and buffer fluctuations in striatal dopamine concentration. Another possibility is that the transplanted cells might have been associated with intermittent dopamine release or receptor activation. This could be due to variable graft placement in the striatum within "hot spots," leading to abnormal synaptic connectivity, or focal areas of graft rejection. Similarly, regional increases in FD uptake in the ventral and dorsal putamen of transplanted patients might have caused local variations in dopamine storage and release [81]. However, no significant regional changes in striatal FD uptake on PET have been reported. Finally, another possibility is that dyskinesia represents a prolonged form of diphasic dyskinesia due to partial or incomplete dopaminergic reinnervation of the striatum, impaired function in implanted dopaminergic neurons, or altered striatal synaptic connectivity [82].

Serotonergic neurons are a significant source of dopamine release in striatal synapses and they possess the enzymes necessary to convert L-DOPA into dopamine. When L-DOPA is administered to PD patients, synaptic dopamine levels oscillate as serotonergic neurons metabolize L-DOPA to dopamine but fail to autoregulate in response to elevated dopamine levels [83]. Experimental animal evidence suggests that the administration of a selective 5-HT_1 agonist dampens serotonin neuron-derived dopamine release in animals [84]. One of the proposed hypotheses relevant for the development of LID includes presynaptic denervation and aberrant dopamine handling by serotonergic neurons; however, they lack dopamine auto-receptors and dopamine transporters, which leads to unregulated dopamine efflux and defective clearance of dopamine, resulting in LID [85]. Because of the potential role of these receptors in LID, a variety of different agents with variable selectivity of serotonin receptors have been studied for LID in PD.

One consistent concern in clinical studies in the occurrence of worsening parkinsonism, particularly with non-selective 5-HT2A and 5-HT2C receptor agonists like ritanserin and mianserin [86]. A double-blinded, multicenter, open-label study found no improvement in LID in PD patients treated with the partial 5-HT1A agonist sarizotan. This lack of efficacy was speculated to be due to limited agonistic activity in specific receptors, a prominent placebo effect, and dose limitations due to lower potency dopamine D2 receptor antagonism with worsening motor symptoms [87]. Piclozotan reduced LID in PD patients in a randomized pilot study in a small number of PD patients but further development is pending. Eltoprazine, a selective partial agonist for 5-HT1A and 5-HT1B receptors, was shown to have an anti-dyskinetic effect in animal models and in a small, randomized placebo-controlled pilot study of 24 patients with LID. Eltoprazine (5 and 7.5 mg) significantly

reduced dyskinetic symptoms, as measured by both the Clinical Dyskinesia Rating Scale and the Rush Dyskinesia Rating Scale [88]. Further studies are necessary to establish their utility in clinical practice. Adenosine A2A receptor antagonists have failed to provide a clear benefit in LID in clinical studies. Other potential novel treatments leveraging new pharmacological mechanisms include the development of opioid receptor modulators, ß-arrestins, glutamate mGlu5 receptor, and AMPA receptor glutamate antagonists.

Administration of L-DOPA in animal models of Parkinson's Disease

Animal models of PD provide valuable research tools to study the underlying mechanism of LID. There is currently no consensus in the literature about the dose, route of administration, or the duration of L-DOPA administration.

Dopamine depletion and pharmacological route of administration.

To derive a standard experimental model of L-DOPA administration, we surveyed the literature for the most frequently observed protocols utilizing a lesion method that would induce Parkinson-like symptoms as well as L-DOPA therapy, summarized in Table 1. In mice, the most frequently used model systems include pharmacological procedures inducing dopaminergic damage with 6-OHDA and MPTP as well as genetic manipulations such as MitoPark, Pitx3, and alpha-synuclein. Of 6-OHDA depleted animals, infusion of the toxin unilaterally into the medial forebrain bundle was prominent, with striatum and substantia nigra pars reticulata less frequently targeted. MPTP is more commonly administered intravenously, although subcutaneous injection has also been employed. L-DOPA administration predominantly occurs through intraperitoneal (i.p.) injection, subcutaneous (s.c.) injection or oral administration (Table 1). Furthermore, because peripheral decarboxylases metabolize L-DOPA, the decarboxylase inhibitor benserazide is commonly co-administered with L-DOPA.

Dosage.

Across many studies, L-DOPA dosages have widely varied from as low as 1 mg/kg to as high as 300 mg/kg. Some of these studies investigated the effect of consistent dosage administration while others examined the consequences of dose escalation. In Ahmed et al. (2019), a single cohort of mice received 5 mg/kg/day injection of L-DOPA for nine days showing a gradual increase of abnormal involuntary movement (AIM) score. Whereas, a study by Shimozawa et al. in 2019 delivered 200 mg/kg/day orally and found that consistent high doses of L-DOPA inhibited aggregation of alpha-synuclein, a protein often associated with Parkinson's disease [89]. In Lundblad et al. 2005, mice administered L-DOPA with a range of 20 to 30 mg/kg/day consecutively for 21 days exhibited increasing AIM scores over the first 16 days that gradually decreased over the next 6 days. However, experimental groups never reached the low AIM scores seen in the vehicle group [90].

In an earlier work by Lundblad et al., L-DOPA was administered over a range of escalating doses (range: 2–54 mg/kg L-DOPA, 2–12 mg/kg Benserazide) [2]. The experiment took place in three phases where group 1 mice received 2, 6, and 27 mg/kg/day i.p. L-DOPA, respectively. Group 2 mice received 6, 18, and 54 mg/kg/day, respectively [2]. AIM scores

significantly increased beginning with the second phase and further increased during the third phase for all four AIMs that were observed; locomotive, orolingual, axial, and limb. A. In Keifman et al., researchers discovered a significant association between various L-DOPA administration levels regarding the AIM score. In this study, the amount of L-DOPA administration gradually increased from 3, 6, 9, and 20 mg/kg/day over the course of 12 days [91]. The AIM score reached significance at 9 and 20 mg/kg compared to injection levels of 3 and 6 mg/kg [91]. While this study investigated stimulation of striatonigral terminals exacerbating dyskinesia, it is important to note the effects of increasing L-DOPA dosage can increase AIM scores regardless of additional stimulation paradigms. A study by Speck et al. in 2019 administered three different doses of L-DOPA (30, 50, and 70 mg/kg) daily for three weeks and found a positive correlation between increasing doses of L-DOPA and increased AIM score [92]. Similarly, a study by Ruiz-DeDiego and colleagues increased the L-DOPA dose from 3, 6, and 12 mg/kg/day for nine consecutive days, three days for each dose with a concomitant increase in AIM score [93]. They found that within each dose, there was a leveling out or decrease in the AIM score over three days [93]. These data support the interpretation that the dosage of L-DOPA administered directly induces abnormal and worsening LID symptoms.

To study the neurobiology of L-DOPA, a peripheral DOPA decarboxylase inhibitor, such as benserazide, was frequently co-administered. Like L-DOPA dosages, no consistent amount of benserazide is administered with respect to the weight of the animal or quantity of L-DOPA administered, although clinical formulations utilize a 4:1 ratio of L-DOPA:decarboxylase inhibitor. Table 1 summarizes the existing information about L-DOPA and benserazide dosage, frequency, and route of administration, in animal models of PD.

Concluding remarks

A cogent protocol outlining the administration of L-DOPA in preclinical models of PD is necessary to determine the efficacy and troubleshoot the potential problems that can help to develop better therapeutic strategies. From the literature surveyed, we formulated a frequently used protocol that can increase the rigor and reproducibility of future studies attempting to create a Parkinson-like model in mouse investigations. The protocol is constructed based on studies presented in Table 1. While within the confines of published literature, this protocol has yet to be directly examined. The simplified protocol is presented below.

Simplified protocol for L-DOPA and benserazide administration

- Deplete unilaterally with 6-OHDA infusion to medial forebrain bundle or striatum
- Select animals exhibiting asymmetrical rotational behavior
- L-DOPA administration:
  - 5 – 20 mg/kg L-DOPA, i.p., 1–2 times daily
  - 12 −15 mg/kg benserazide, i.p. 1–2 times daily

This review highlights the importance of research within the field of neurodegenerative disorders and provides an extensive outline for the care, treatment, and study of Parkinson's disease within a mouse model.

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Table 1.

Summary of animal models using L-DOPA to alleviate lesion-induced Parkinsonisms

First Author	Year	Purpose of Study	Lesion Method	Lesion Region	Unilateral or Bilateral	L-DOPA Dosage(s)	Benserazide Dosage(s)	Carbidopa Dosage(s)	Treatment Administration Method
Ogawa	1987	Changes in dopamine and norepinephrine levels following MPTP administration in mice	MPTP	N/A: Intraperitoneal injection	N/A	200 mg/kg	N/A	N/A	Intraperitoneal injection
Fredriksson	1990	Establish efficacy of L-DOPA treatment in MPTP treated mice	MPTP	N/A: subcutaneous injection	N/A	5, 10, 20, 40, 80 mg/kg	N/A	N/A	Subcutaneous injection
Ogawa	1994	Alteration of lipid peroxidation by chronic L-DOPA administration	6-OHDA	N/A: Intracerebroventricular injection	N/A	100 mg/kg	N/A	N/A	Intraperitoneal injection
Zhou	1995	Role of dopamine to central nervous system function and development	Tyrosine hydroxylase inactivation	N/A	N/A	50 mg/kg	N/A	N/A	Intraperitoneal injection
Szczypka	1999	Feeding behavior of dopamine deficient mice restored by L-DOPA administration	Tyrosine hydroxylase inactivation	N/A	N/A	50 mg/kg	N/A	12.5, 25 mg/kg	Intraperitoneal injection
Smith	2003	Impact of L-DOPA pulsatile administration in marmosets	MPTP	N/A: subcutaneous injection	N/A	5, 7.5, 12.5 mg/kg	N/A	N/A	Oral
McCormack	2003	Neuroprotection of L-DOPA to paraquat-induced neurodegeneration	Paraquat	N/A: Intraperitoneal injection	N/A	100 mg/kg	12.5 mg/kg	N/A	Intraperitoneal injection
Lundblad	2004	LID in mouse model of Parkinson's disease	6-OHDA	Medial forebrain bundle or striatum	Unilateral	2, 6, 18, 27, 54 mg/kg	2, 6, 12 mg/kg	N/A	Intraperitoneal injection
Lundblad	2005	Pharmacological profile of L-Dopa and LIDS/AIMS	6-OHDA	Striatum	Unilateral	20–30 mg/kg	12 mg/kg	N/A	Intraperitoneal injection
Pavón	2006	Development of model of LID similar to humans	6-OHDA	Striatum	Unilateral	25 mg/kg	10 mg/kg	N/A	Intraperitoneal injection
Yu	2006	Characterize interaction between caffeine and L-DOPA to alleviate motor symptoms	6-OHDA	Striatum	Unilateral	2 mg/kg	2 mg/kg	N/A	Intraperitoneal injection
Chalimoniuk	2007	Effect of low and high dose L-DOPA on nitric oxide synthase and guanylyl cyclase expression	MPTP	N/A: Intraperitoneal injection	N/A	10, 100 mg/kg	2.5, 25 mg/kg	N/A	Intraperitoneal injection

First Author	Year	Purpose of Study	Lesion Method	Lesion Region	Unilateral or Bilateral	L-DOPA Dosage(s)	Benserazide Dosage(s)	Carbido paDosage(s)	Treatment Administration Method
		in the striatum and midbrain							
Zhang	2007	Regulation of striatal serotonergic signaling in 6-OHDA lesioned animals by L-DOPA administration	6-OHDA	Medial forebrain bundle	Unilateral	10, 50 mg/kg (mouse), 100 mg/kg (rat)	7.5, 12.5 mg/kg (mouse), 25 mg/kg (rat)	N/A	Intraperitoneal injection
Darmopil	2008	Molecular phenotype of tyrosine hydroxylase immunoreactive neurons in the striatum after dopamine depletion and L-DOPA administration	6-OHDA	Striatum	Unilateral	15 mg/kg	6 mg/kg	N/A	Intraperitoneal injection
Chen	2008	Role of dopamine in oxidative stress of dopaminergic neurons with L-DOPA treatment	MPTP, 6-OHDA	N/A: Intraperitoneal injection (MPTP), medial forebrain bundle (6-OHDA)	N/A (MPTP), Unilateral (6-OHDA)	300 mg/kg	100 mg/kg	N/A	Intraperitoneal injection
Santini	2009	Role of ERK phosphorylation state on LID	6-OHDA	Striatum	Unilateral	20 mg/kg	12 mg/kg	N/A	Intraperitoneal injection
Santini	2009	mTOR regulation of LID	6-OHDA	Striatum	Unilateral	10, 20 mg/kg	7.5, 12 mg/kg	N/A	Intraperitoneal injection
Darmopil	2009	Dopamine receptor D1 activation as a critical regulator of LID onset	6-OHDA	Striatum	Unilateral	25 mg/kg	10 mg/kg	N/A	Intraperitoneal injection
Ding	2010	ERK activation induces LID	6-OHDA	Medial forebrain bundle	Unilateral	25 mg/kg	6 mg/kg	N/A	Intraperitoneal injection
Galter	2010	Evaluate biochemical and behavioral phenotypes of MitoPark mice	MitoPark	N/A	N/A	4, 20 mg/kg	4 mg/kg	N/A	Intraperitoneal injection
Francardo	2011	Comparison between striatal, medial forebrain bundle, and substantia nigra pars compacta 6-OHDA lesions	6-OHDA	Medial forebrain bundle, striatum, and substanti a nigra	Unilateral	3, 6 mg/kg	12 mg/kg	N/A	Intraperitoneal injection
Thiele	2011	Dissection of direct and indirect striatal outputs in LID	6-OHDA	Medial forebrain bundle	Unilateral	3, 4.5, 6, 12 mg/kg	0.75, 1.125, 1.5, 3 mg/kg	N/A	Intraperitoneal injection
Smith	2012	Relationship between extent of 6-OHDA and LID severity	6-OHDA	Medial forebrain bundle, striatum, and	Unilateral	2, 6, 12, 25 mg/kg	2, 6, 12, 12 mg/kg	N/A	Subcutaneous injection

First Author	Year	Purpose of Study	Lesion Method	Lesion Region	Unilateral or Bilateral	L-DOPA Dosage(s)	Benserazide Dosage(s)	Carbido paDosage(s)	Treatment Administration Method
				substanti a nigra					
Espadas	2012	Time Course of L-DOPA treatment regulation of tyrosine hydroxylase immunoreactivity	6-OHDA	Striatum	Unilateral	25 mg/kg	10 mg/kg	N/A	Intraperitoneal injection
Quik	2012	Role of nicotinic acetylcholine receptors in regulation of LID	6-OHDA	Medial forebrain bundle	Unilateral	3 mg/kg	15 mg/kg	N/A	CT Subcutaneous injection
Quik	2013	Deletion of nicotinic acetylcholine receptors on exacerbation of LID	6-OHDA	Medial forebrain bundle	Unilateral	3 mg/kg	15 mg/kg	N/A	Intraperitoneal injection
Li	2013	Determination of priming necessity for LID onset	Pitx3−/−	N/A	N/A	6 mg/kg	5 mg/kg	N/A	Intraperitoneal injection
Zaitone	2013	Enhancement of L-DOPA response by melatonin	MPTP	N/A: intraperitoneal injection	N/A	100 mg/kg	N/A	10 mg/kg	Oral
Suárez	2014	Relationship between L-DOPA administration and dopamine receptor D1 sensitivity and morphology of striatal medium spiny neurons	6-OHDA	Striatum	Unilateral	25 mg/kg	10 mg/kg	N/A	Intraperitoneal injection
Won	2014	Influence of cholinergic tone on LID severity	6-OHDA	Medial forebrain bundle	Unilateral	1 mg/kg	12.5 mg/kg	N/A	Intraperitoneal injection
Thiele	2014	Synaptic plasticity abnormalities in 6-OHDA lesioned cortico-striatal synapses	6-OHDA	Medial forebrain bundle	Unilateral	4.5 mg/kg	1.124 mg/kg	N/A	Intraperitoneal injection
González-Aparicio	2014	Role of TRPV1 receptor in LID	6-OHDA	Medial forebrain bundle	Unilateral	20 mg/kg	10 mg/kg	N/A	Intraperitoneal injection
Park	2014	Adenylyl cyclase inhibition prevents onset of LID	6-OHDA	Substant ia nigra pars compact a	Unilateral	20 mg/kg	12 mg/kg	N/A	Intraperitoneal injection
Mango	2014	GABAergic neurotransmission in striato-nigral terminals in LID	6-OHDA	Striatum	Unilateral	6 mg/kg	4.5 mg/kg	N/A	Intraperitoneal injection
Solís	2015	Examine the interplay between nitric oxide generation and LID in Pitx3−/− mice	Pitx3−/−	N/A	N/A	10 mg/kg	10 mg/kg	N/A	Intraperitoneal injection
Shan	2015	Interaction between degeneration severity and treatment onset	MitoPark	N/A	N/A	10 mg/kg	5 mg/kg	N/A	Intraperitoneal injection

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		time with LID severity							
Chiu	2015	Effect of L-DOPA administration on adult neurogenesis	6-OHDA	Substantia nigra pars compacta	Bilateral	100 mg/kg	25 mg/kg	N/A	Oral
Shen	2015	Interaction between M4 muscarinic receptor signalling in dopamine depleted mouse and primate LID models	6-OHDA (mouse), MPTP (primate)	Medial forebrain bundle (mouse), N/A: intraven ous (primate)	Unilateral (mouse), N/A (primate)	1.5, 3, 6 mg/kg (mouse), 9–17 mg/kg (primate)	12 mg/kg (mouse), N/A (primate)	N/A (mouse), 2.25–4.25 mg/kg (primate)	Intraperitoneal injection (mouse), oral (primate)
Urs	2015	Regulation of beta-arrestin signalling in LID	6-OHDA (mouse and rat), MPTP (primate)	Striatum (mouse), medial forebrain bundle (rats), N/A: intravenous (primates)	Unilateral (mouse and rat), N/A (primate)	20 mg/kg (mouse), 6 mg/kg (rat), 20 mg/kg (primate)	12.5 mg/kg (mouse), 15 mg/kg (rat), N/A (primate)	N/A (mouse and rat), Not stated (primates)	Subcutaneous injection (mouse), intraperitoneal injection (rat), oral (primate)
Keber	2015	Identify new factors inducing LID	6-OHDA	Medial forebrain bundle	Unilateral	6 mg/kg	12 mg/kg	N/A	Intraperitoneal injection
Charbonnier-Beaupel	2015	Transcriptomic analysis in striatal areas after 6-OHDA administration	6-OHDA	Striatum	Unilateral	20 mg/kg	12 mg/kg	N/A	Intraperitoneal injection
Gellhaar	2015	Long-term effects of L-DOPA in MitoPark mice	MitoPark	N/A	N/A	8 mg/kg	2 mg/kg	N/A	Intraperitoneal injection
dos-Santos-Pereira	2016	Amelioration of LID through cannabidiol and capsazepine administration	6-OHDA	Striatum	Unilateral	25 mg/kg	10 mg/kg	N/A	Intraperitoneal injection
Sebastianutto	2016	Evaluation of objectivity in abnormal involuntary movement scores	6-OHDA	Medial forebrain bundle	Unilateral	3, 6 mg/kg	12 mg/kg	N/A	Intraperitoneal injection
Park	2016	Role of Gadd45β in LID	6-OHDA	Substantia nigra pars compact a	Unilateral	20 mg/kg	12 mg/kg	N/A	Intraperitoneal injection
Morigaki	2017	Association of olfactory type G-protein alpha and LID development	6-OHDA	Striatum	Unilateral	20 mg/kg	12 mg/kg	N/A	Intraperitoneal injection
Ruiz-DeDiego	2018	LID symptom changes with Ras-ERK hyperactivation	6-OHDA	Striatum	Unilateral	5, 10, 20 mg/kg	10 mg/kg	N/A	Intraperitoneal injection
Ryu	2018	Studying the effect of metformin on LID	6-OHDA	Substantia nigra pars compact a	Unilateral	20 mg/kg	12 mg/kg	N/A	Intraperitoneal injection
Keifman	2018	Optostimulation of medium spiny neuron terminals in substantia nigra pars reticulata	6-OHDA	Medial forebrain bundle	Unilateral	2, 3, 9, 20 mg/kg	6, 12 mg/kg	N/A	Intraperitoneal injection

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		induces dyskinesia							
Nuber	2018	Biochemical and behavioral characterization of non-tetramer forming alpha-synuclein mutations in response to L-DOPA treatment	Alpha-synuclein mutation	N/A	N/A	12.5 mg/kg	12.5 mg/kg	N/A	Intraperitoneal injection
Speck	2019	Effect of physical exercise on LID	6-OHDA	Striatum	Unilateral	30, 50, 70 mg/kg	12.5, 25, 35 mg/kg	N/A	Intraperitoneal injection
Shimozawa	2019	L-DOPA/ Benserazide administration suppression of alpha-synuclein propagation	Intracerebral injection of alpha-synuclein	Striatum	Unilateral	200 mg/kg	75 mg/kg	N/A	Oral gavage
Ahmed	2019	Pharmacologically reducing the presence of LID	6-OHDA	Medial forebrain bundle	Unilateral	5 mg/kg	5 mg/kg	N/A	Subcutaneous injection
Sano	2019	Effect of zonisaide administration on the exacerbation of LID	6-OHDA	Medial forebrain bundle	Unilateral	20 mg/kg	12 mg/kg	N/A	Intraperitoneal injection
Liu	2019	Synergism of resveratrol and low dose L-DOPA in symptom alleviation	MPTP	N/A: intraperitoneal injection	N/A	5, 8 mg/kg	N/A	N/A	Intraperitoneal injection
García-Montes	2019	mGluR5 knockdown attenuates LID	Pitx3−/−	N/A	N/A	10 mg/kg	10 mg/kg	N/A	Intraperitoneal injection
Huh	2019	Co-administration of ukgansan with L-DOPA to reduce neuronal damage, motor dysfunction, and LID	6-OHDA	Striatum	Unilateral	20 mg/kg	10 mg/kg	N/A	Intraperitoneal injection
Iggena	2019	Interaction between physical activity and memory retrieval in dopamine depleted mice	MPTP	N/A: Intraperitoneal injection	N/A	20 mg/kg	5 mg/kg	N/A	Intraperitoneal injection
Naskar	2019	Melatonin regulation of dendritic spine density in MPTP treated mice	MPTP	N/A: Intraperitoneal injection	N/A	5 mg/kg	N/A	0.5 mg/kg	Oral gavage
Liu	2020	Ameliorative interaction between ACT001 and low dose L-DOPA	MPTP	N/A: Intraperitoneal injection	N/A	5, 8 mg/kg	N/A	N/A	Intraperitoneal injection