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CURRENT OPINION

# Recent Clinical Advances in Pharmacotherapy for Levodopa-Induced Dyskinesia

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**Abstract**
Onset of involuntary movement patterns of the face, body and limbs are known as dyskinesia. They mostly appear in association with long-term levodopa (L-dopa) therapy in patients with Parkinson's disease. Consequences include patient distress, caregiver embarrassment and reduced quality of life. A severe intensity of this motor complication may result in troublesome disability; however, patients typically prefer motor behaviour with slight, non-troublesome dyskinesia to 'OFF' states. Pharmacotherapy of dyskinesia is complex. Continuous nigrostriatal postsynaptic dopaminergic receptor stimulation may delay onset of L-dopa-associated dyskinesia, while non-physiological, 'pulsatile' receptor stimulation facilitates appearance of dyskinesia. In the past, there have been many clinical trial failures with compounds that were effective in animal models of dyskinesia. Only the *N*-methyl-D-aspartate antagonist amantadine has shown moderate antidyskinetic effects in small well-designed clinical studies. Amantadine is an old antiviral compound, which moderately improves impaired motor behaviour. Recently, there has been a resurgence of its use due to the US Food and Drug Administration approval of an extended-release (ER) amantadine formulation for treatment of L-dopa-induced dyskinesia. This pharmacokinetic innovation improved dyskinesia and 'OFF' states in pivotal trials, with a once-daily oral application in the evening. Amantadine ER provides higher and more continuous amantadine plasma bioavailability than conventional immediate-release formulations, which require administration up to three times daily.

**Key Points**

Extended-release (ER) amantadine formulations ameliorate levodopa-induced dyskinesia.

ER formulations provide higher amantadine plasma concentrations than immediate-release formulations, and are administered once a day at bedtime.

ER amantadine application is simpler than deep brain stimulation or an infusion regimen.

## 1 Introduction

Parkinson's disease (PD) is the second most frequent chronic neurodegenerative disease worldwide, with an incidence range from 8 to 18 per 100,000 individuals [1]. One estimate is that the number of PD cases will double by 2030 [2]. PD diagnosis is rare under the age of 50 years, but the incidence of PD considerably rises beyond the age of 60 years.

The term 'PD' describes a disease entity. It consists of various heterogeneous subtypes that closely resemble one another [3, 4]. Motor and non-motor symptoms and progression considerably differ in each affected individual. Diagnosis of PD is mostly made with the initially transient, then permanent, manifestation of 'cardinal' motor symptoms: rigidity, akinesia and resting tremor. Symptoms occur after the death of approximately 50–60% of nigrostriatal dopaminergic neurons. Unspecific non-motor features, such as depression or apathy, often precede the onset of impaired motor behaviour [3, 4].

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### 1.1 Treatment with Levodopa (L-Dopa) Induces Motor Complications

Levodopa (L-dopa) administration, combined with a dopa decarboxylase inhibitor (DDI), is the most efficacious and best tolerated dopamine-substituting drug. Sooner or later it is necessary to put PD patients on L-dopa to ameliorate closely related motor and non-motor symptoms [5].

The efficacy of L-dopa intake depends on peripheral gastrointestinal absorption, the closely related plasma appearance, its brain delivery via blood–brain barrier transporting systems and its neuronal conversion to dopamine by dopa decarboxylase in presynaptic dopaminergic neurons. All these components of oral L-dopa application are considerably influenced by the short plasma half-life of L-dopa, which lasts approximately 30–45 min [6].

This peripheral pharmacokinetic behaviour is centrally translated into a non-physiological, 'pulsatile' stimulation of postsynaptic dopamine receptors. This pattern generates gene and receptor dysfunction, alters more downstream not yet well-defined neuronal activity and contributes to imbalances of neurotransmitters, such as *N*-methyl-D-aspartate (NMDA) or serotonin (5-HT) [7–10].

To a certain extent, presynaptic striatal dopaminergic neurons may still compensate for these fluctuations of L-dopa and related dopamine levels via a presynaptic-located autoreceptor, which regulates presynaptic dopamine synthesis and dopamine release to the synaptic cleft. However, PD progression with emerging loss of presynaptic dopaminergic neurons reduces this existing compensatory capacity.

Presynaptic synthesis, storage and regulation of dopamine release for adequate striatal postsynaptic dopamine receptor activation increasingly depends on exogenously supplemented dopaminergic agents. L-Dopa itself is also more and more converted to dopamine in 5-HT neurons, which are not controlled by dopamine-sensitive autoreceptors. Thus, use of this 5-HT pathway contributes to more pronounced peaks and troughs of dopamine concentrations in the nigrostriatal and mesolimbic system. As a result, fluctuations of motor and non-motor behaviours appear [11–15]. These fluctuations are one of the most relevant adverse effects of long-term L-dopa/DDI treatment.

### 1.2 Benefit of L-Dopa on Motor Behaviour Changes During Parkinson's Disease (PD) Progression

L-Dopa dosing and response mirrors progression of PD to a certain extent (for review, see Müller and Möhr [14]). Early PD patients have longer-lasting beneficial L-dopa effects and only require L-dopa intake two or three times daily. At this stage, presynaptic striatal dopaminergic neurons may compensate for fluctuations of L-dopa and dopamine concentrations. However, as PD progresses, with increasing loss of presynaptic dopaminergic neurons, the compensatory capacity of fluctuating L-dopa levels goes down due to neuronal death of presynaptic dopamine-synthesising neurons.

The duration of clinical benefit, the so-called 'motor response' derived from each oral L-dopa dose, shortens due to the declining therapeutic window to obtain relief from motor symptoms by L-dopa. At this stage, patients initially experience return of motor impairment before the next L-dopa intake. This so-called 'wearing-off' phenomenon is predictable because it is related to the previous drug intake [13–15].

Further advance of PD requires higher L-dopa dosing; however, the resulting motor complications become unpredictable and more intense and the relationship to drug intake gets progressively lost.

### 1.3 Hypotheses on Dyskinesia Generation in PD Patients

In addition to the aforementioned considerations, one also assumes functional disturbances in the basal ganglia. Loss of nigral dopaminergic neurons induces abnormalities in the connectivity between the motor cortex and striatum. Another theory suggests that loss of nigrostriatal dopaminergic neurons induces postsynaptic plastic changes with supersensitivity of postsynaptic dopaminergic neurons [16]. There are also suggestions that several other non-dopaminergic systems, including glutamatergic, γ-aminobutyric acid-ergic, serotonergic, histaminergic, adenosine and cannabinoid receptors, play an important role in the development of L-dopa-induced dyskinesia (for review, see Fabbrini et al. [17] and Cerri et al. [18]).

However, the pathogenesis of L-dopa-induced dyskinesia is not well-understood. It is known that, in contrast to PD patients, humans without PD do not develop dyskinesia during long-term treatment with L-dopa. PD patients with young age at disease onset, and thus longer L-dopa lifetime exposure or high L-dopa dosages, are particularly at risk for developing dyskinesia. This was shown, for example, in the L-dopa 600 mg arm in the L-DOPA study or in the STalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) study, in contrast to the LEvodopa in EArly Parkinson's disease (LEAP) study with its exposure to lower L-dopa doses [19–21].

### 1.4 Clinical Phenomenology of Dyskinesia

Generally, motor complications are a combination of dyskinesia and 'OFF' states. Both depend on the pharmacokinetic behaviour of short-lived dopamine-substituting

compounds, such as L-dopa. As a result, pulsatile stimulation of nigrostriatal dopaminergic receptors takes place centrally. 'ON'-state dyskinesia mostly appears during a period with maximal relief from motor symptoms ('peak-dose' dyskinesia). Other kinds of dyskinesia are diphasic; they emerge soon after L-dopa intake, when the patient turns 'ON', or when the L-dopa response wears 'OFF' again.

Various dyskinesia forms exist. The most frequent movement sequences are chorea, athetosis, dystonia, stereotypy, ballismus, or a combination of these [22–25]. The intensity of dyskinesia ranges from mild to completely disabling, and it occurs in addition to motor fluctuations during both 'ON' and 'OFF' periods. Patients themselves tend to ignore mild dyskinesia symptoms, since they induce little disability; most PD patients prefer to have small intervals with dyskinesia and remain in the 'ON' state rather than have less dyskinesia with more time spent 'OFF'. Conversely, severe dyskinesia may cause considerable disability in advanced PD patients, potentially inducing pain, severe speech and swallowing problems, and contributing to weight loss. Such symptoms also may become exhausting or even life-threatening due to shortness of breath because of diaphragmatic dyskinesia [24, 26]. The intensity of dyskinesia is closely associated with stress and emotion; for example, dyskinesia worsens during exposure to all kind of stressors.

## 2 Current Treatment Approaches for Dyskinesia in PD Patients

### 2.1 Delay of Dyskinesia

It is well-known that continuous nigrostriatal postsynaptic dopamine receptor stimulation (continuous dopaminergic stimulation [CDS]) improves motor complications. Dopamine agonists have a long half-life and thereby provide CDS. This may reduce the risk of dyskinesia onset, as shown with ropinirole in a trial lasting 5 years [27].

Generally, ergoline and non-ergoline dopamine agonists directly stimulate postsynaptic dopamine receptors. They support CDS due to their long half-life (i.e. cabergoline has a half-life of 24 h) or provide long-lasting stimulation of postsynaptic dopamine receptors (i.e. lisuride with its short half-life of 2 h).

All these pharmacological approaches help to spare oral L-dopa dosing and thus reduce the consequences of intermittent L-dopa brain delivery with pulsatile stimulation of dopaminergic receptors. Careful and cautious L-dopa titration may also contribute to delayed dyskinesia onset.

### 2.2 Surgical Approaches

Lesion or deep brain stimulation (DBS) of the medial globus pallidus, in particular, improves dyskinesia. Both methods reduce the excitatory drive on thalamic and motor cortical nuclei [28–30]. However, the electric stimulation pattern of DBS also enhances the endogenous synthesis and continuous release of biogenic amines. Concomitantly, homovanillic acid concentrations increase in urine [31]. Thus, these neurochemical DBS effects hypothetically resemble CDS performed with drugs (i.e. with L-dopa or apomorphine). However, this surgical approach may have severe long-term disadvantages in the clinic. For example, DBS increases the risk of personality changes and cognitive disturbances [32].

Other surgical treatment options include continuous subcutaneous infusions of apomorphine or intestinal L-dopa gel (LCIG). Both therapies reduce 'OFF' time and dyskinesia [11, 33, 34]; however, they are expensive and require caregiver support for the demanding pump systems, and they are only applicable in well-selected PD patients [11, 33–36]. Accordingly, oral application of antidyskinetic agents remains the best and most easy-to-perform option for PD patients.

### 2.3 Approved Antidyskinetic Drugs

Reduction of the glutamatergic input on the nigrostriatal dopamine system is a proven option to reduce dyskinesia according to experimental and clinical investigations [37, 38].

One approach is pharmacological antagonism of NMDA receptors with amantadine. Amantadine is an antiviral drug approved for the treatment of dyskinesia in patients with PD receiving L-dopa [39]. Its moderate effects on motor impairment were coincidentally discovered in a female PD patient taking 200 mg daily for antiviral prophylaxis [40, 41]. Subsequently performed investigations with different amantadine formulations confirmed this initial observation (e.g. Muhlack et al. [42], Müller et al. [43, 44]).

Experimental findings describe three mechanisms of action. Amantadine modulates the dopamine system [45]. Presynaptic and postsynaptic actions at dopaminergic terminals and release of intraneuronal dopamine from extravesicular stores were shown, in addition to NMDA antagonism and mild anticholinergic effects [45–47].

Amantadine (1-adamantanamine) is a tricyclic amine that is mainly excreted via urine. Two immediate-release (IR) formulations have mostly been employed in the past. Amantadine hydrochloride is given orally; maximum plasma concentrations appear between 1 and 4 h postdose and the half-life is about 15 h [48]. An alternative is the salt amantadine sulphate with its oral and intravenous application route (currently available in Germany and Austria only). The

conventional oral amantadine formulations are commonly titrated up to 200 mg/day [48].

A new extended-release (ER) formulation of amantadine (Gocovri™; Adamas Pharma, LLC, Emeryville, CA, USA) has also recently been approved by the US Food and Drug Administration (FDA) for the treatment of dyskinesia in PD patients on L-dopa therapy with or without concomitant dopamine-substituting medications. The recommended dosage is 274 mg once daily at bedtime, which corresponds to amantadine hydrochloride 340 mg [49].

The innovation of this new ER preparation is that oral administration of the capsule achieves high plasma drug concentrations (approximately 1500 ng/mL) throughout the day, which cannot be obtained with typical administration of amantadine IR [49].

Drawbacks of all available amantadine formulations include a certain incidence of livedo reticularis, mostly in the lower limbs, and pedal oedema. Distinctly less common, but more troublesome, are the cognitive adverse effects such as confusion, visual hallucinations and insomnia, which promptly disappear with drug discontinuation. Generally, these cognitive adverse effects are mostly reported in individuals with an underlying pre-existing cognitive dysfunction. The predominant renal amantadine excretion requires cautious use of amantadine in patients with impaired kidney function. Occasional occurrences of dry mouth and blurred vision are probably related to the mild anticholinergic properties of amantadine.

A pharmacokinetic/pharmacodynamic analysis in animal models showed that the amantadine 50% effective plasma concentration ($EC_{50}$) required to significantly reduce dyskinesia is 1400 ng/mL (or 9 µM) across multiple species, from mice to non-human primates [50]. This $EC_{50}$ is consistent with the known half-maximal inhibitory concentration ($IC_{50}$) of amantadine for inhibition of the NMDA receptor in striatal neurons (12 µM) [50].

In small clinical studies, an IR formulation of amantadine hydrochloride improved dyskinesia. However, the long-term effect of this amantadine IR preparation is still under debate [38, 51]. The reported average benefit of amantadine IR application on dyskinesia was 4.9 months versus 1.3 months for placebo. PD patients who switched to placebo following a mean of 3.4 years on treatment with amantadine IR experienced worsening of dyskinesia within a median of 7 days [38, 51, 52].

Most PD patients show no problems during daily intake of amantadine IR doses between 81 and 161 mg. However, higher dosing, which may provide greater antidyskinetic benefit, is less well-tolerated. Usually clinicians administer amantadine IR in divided doses, even though this compound has a relatively long half-life (approximately 17 h) [50], to try to reduce the onset of adverse effects.

Randomised, placebo-controlled, double-blind pivotal trials showed the antidyskinetic efficacy of amantadine ER, i.e. in the ADS-5102 programme (Table 1). An additional clinical benefit was the concomitant reduction in 'OFF' times. Both pivotal phase III ADS-5102 studies on the 274 mg capsule had identical inclusion criteria within a similar study design [53–55]. However, only the EASE LID (ADS-5102 Extended Release Capsules for the Treatment of Levodopa Induced Dyskinesia) trial investigated the antidyskinetic effect over a longer study interval. Generally, the ER formulation had a good safety profile and was well-tolerated. Visual hallucinations were found to be the most frequent, clinically relevant adverse effect. Pooled analyses confirmed this outcome, its long-term benefit, and its safety and tolerability profile [49, 54, 56–59]. Table 1 reports essential excerpts of the three clinical pivotal amantadine ER trials. The higher dosing and modified ER delivery of amantadine ameliorated dyskinesia and 'OFF' times in L-dopa-treated PD patients. As already mentioned, amantadine is not only a NMDA antagonist. One may assume that the observed 'OFF'-time reduction may also result from its previously discussed modes of action [60]. In comparison to the available generic amantadine salts, the innovation of this therapy does not result from a new

**Table 1** Summary of the antidyskinetic efficacy of amantadine extended release in the ADS-5102 programme

| Study | Duration (weeks) | Total difference from placebo (change in the total UDyRS score) | Total difference from placebo (h) |
|---|---|---|---|
| EASED (274 mg outcomes) [58] | 8 | −11.3*** | OT: 3***<br>OFFT: −0.9 (ns) |
| EASE LID-2 [56] | 25 | −7.9*** | OT: 2.8***<br>OFFT: −0.9* |
| EASE LID-3 [55] | 13 | −14.4*** | OT: 1.9**<br>OFFT: −1.1** |

Least square mean values are given

*EASED* Extended Release Amantadine Safety and Efficacy in Levodopa induced Dyskinesia, *EASE LID* Extended-Release Capsules for Levodopa Induced Dyskinesia in Parkinson's disease, *ns* not significant, *OFFT* 'OFF' time, *OT* 'ON' time without troublesome dyskinesia, *UDyRS* Unified Dyskinesia Rating Scale, *$p < 0.05$, **$p \leq 0.01$, ***$p < 0.001$

mode of action but from another pharmacokinetic, and thus pharmacodynamic, behaviour.

## 3 Relevance for the Maintenance of PD Patients

### 3.1 Amantadine: A Well-Known PD Drug with Additional Properties

Generally, amantadine is looked upon as an old, well-known compound with a modest efficacy for the treatment of motor behaviour in PD patients. Amantadine is also employed in other indications, for instance it may help to improve fatigue in patients with multiple sclerosis or with traumatic brain injury [61–63]; however, this is mostly 'off-label' due to the lack of so-called 'evidence-based medicine' trials. Accordingly, the effects of amantadine on vigilance, attention or alertness have also been described in PD patients, but randomised controlled trials (RCTs) failed to confirm these effects [44, 64–67]. Conventional amantadine salts are normally administered in the first half of the day to prevent sleep disturbances during the night.

### 3.2 Advantages of Extended-Release Amantadine

The amantadine ER capsule was applied in the evening in clinical trials. One must speculate why this ER amantadine did not considerably alter sleep as a clinically relevant adverse effect in the pivotal study programme [50, 56–59]. One may assume that the more continuous amantadine delivery may be responsible, despite the higher plasma concentrations of amantadine [50]. Another advantage of the amantadine ER formulation is the once-daily administration regimen, which simplifies the sometimes rather complex drug intake scenario, particularly in advanced PD patients with their well-known adherence problems [68]. This is not a well-recognised issue in the study world, with its close patient monitoring in combination with well-selected study participants. Nevertheless, long-term acceptance and use of ER formulations of amantadine in the real world of PD patient care will show their real value.

The successful amantadine ER study programme also underlines that higher dosing with accordingly higher plasma concentrations of an applied compound may contribute to better efficacy, particularly in the treatment of chronic disorders. Regulatory authorities support dosing restrictions for safety and tolerability reasons. However these dosing limitations may prevent additional benefits in the real world, as shown in this case with antidyskinetic effects with higher amantadine plasma bioavailability.

A standardised head-to-head comparison of a higher and more frequent dosing regimen with amantadine IR versus amantadine ER administration once a day may now also be considered. However, the value of once-daily administration of this amantadine ER formulation in the real world should not be underestimated. Here, generally, drug treatment of advanced PD patients becomes more and more complex and requires an individually titrated drug combination regimen with close and continuous patient surveillance [5]. Pivotal studies have demonstrated that this novel amantadine formulation is effective against dyskinesia in PD patients and a switch from conventional amantadine to ER amantadine was efficacious and well-tolerated [54].

### 3.3 Further Potential Antidyskinetic Drugs

There is still an unmet need to develop further treatments against L-dopa-induced dyskinesia in PD patients. As already mentioned, dyskinesia ameliorates with low exposure or better tolerability to all kind of stressors, or even, to a lesser extent, with placebo [69]. The antidyskinetic efficacy of drugs (i.e. the atypical antipsychotic clozapine with its benzodiazepine-like metabolites, or other sleep-inducing or antidepressant compounds, such as buspirone, mirtazapine, quetiapine and topiramate) has been investigated in small trials or in case series. They report both positive and negative outcomes [70–75]. Due to the heterogeneity of dyskinesia and PD itself, currently no new, more generally valid treatment approach is likely to appear on the horizon for the treatment of PD patients in the clinic. Experimental trials in animal PD models with L-dopa-induced dyskinesia repeatedly report beneficial effects of various approaches, probably due to the standardised and uniform generation of dyskinesia. However, the subsequently performed clinical trials if performed at all, often fail to reproduce this beneficial effect. A future realistic alternative may be an easy-to-handle subcutaneous L-dopa pump application [76]. Such a device should deliver L-dopa in a similar way to an insulin pump application in diabetes mellitus, i.e. in a continuous manner adapted to the patients' needs. Currently, subcutaneous infusion of apomorphine or enteral infusion of an L-dopa-containing gel are available; both provide continuous drug delivery to the brain [33, 77].

## 4 Conclusion

The causes of L-dopa-induced dyskinesia are not well-understood and probably have a multifactorial origin. Their clinical presentation is heterogeneous and, accordingly, their treatment is complex. Positive experimental outcomes with promising compounds have typically failed to translate to use in the clinic in the past. Dyskinesia therapy in PD patients includes cautious and careful titration of PD drugs or implementation of costly techniques, including DBS or

continuous infusion of dopamine-substituting compounds. In contrast, daily one-time application of amantadine ER formulations is simple. It showed antidyskinetic efficacy in clinical trials, but the real value of this pharmacokinetic innovation of an old PD drug will be evaluated in the real world of maintenance of PD patients in the future.

## Compliance with Ethical Standards

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