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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Efficacy and safety of amantadine for the treatment of L-DOPA-induced dyskinesia

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Abstract

L-DOPA induced dyskinesias (LIDs) may affect up to 40% of Parkinson's disease (PD) and impact negatively health-related quality of life. Amantadine has demonstrated significant antidyskinetic effects in animal PD models and in randomized double-blind placebo-controlled trials (RCTs) in patients with PD. These effects are thought to be related to the blockade of NMDA receptors modulating cortico-striatal glutamatergic–dopaminergic interactions involved in the genesis of LIDs. There are three pharmaceutical forms of amantadine currently available in the market: an oral immediate-release (IR) formulation, which is widely available; an extended-release (ER) formulation (ADS-5102) which has been recently developed and approved by the FDA; and an intravenous infusion (IV) solution, which is not commonly used in clinical practice. RCTs with amantadine IR or ER, involving more than 650 patients have shown consistent and long-lasting reductions in LIDs. Interestingly, ADS-5102 not only reduced LIDs, but also reduced significantly at the same time the duration of daily OFF-time, a unique finding compared with other antiparkinsonian medications that usually reduce time spent OFF at the cost of worsening of LIDs. Amantadine IR might also have possible effects on other PD symptoms such as apathy or fatigue. The most common adverse reactions with amantadine are constipation, cardiovascular dysfunction including QT prolongation, orthostatic hypotension and edema, neuropsychiatric symptoms such as hallucinations, confusion and delirium, nausea and livedo reticularis. Corneal degeneration is rare but critical. In summary, amantadine immediate and extended-release are effective and safe for the treatment of LIDs.

Keywords Parkinson's disease · L-DOPA · L-DOPA-induced dyskinesia · Amantadine · Glutamate · NMDA receptors

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting about 1 person every 1000 in the fifth decade and 19 every 1000 above 80 years old (Pringsheim et al. 2014). Core motor symptoms are bradykinesia, rigidity, tremor and postural abnormalities (Hughes et al. 1992). Patients are also affected by secondary motor symptoms such as gait abnormalities, micrographia and speech problems, (Lang and Lozano 1998). Non-motor features, including cognitive and behavior dysfunction, sleep abnormalities, pain or autonomic disturbances, among others, are frequent and disabling (Chaudhuri and Schapira 2009).

L-DOPA remains the "gold standard" treatment for Parkinson's disease (PD) motor symptoms since its introduction in the 60s (Birkmayer and Hornykiewicz 1998). As documented in the placebo-controlled L-DOPA study in early PD (ELLDOPA), although L-DOPA clearly improves parkinsonism with a dose-related response, a 600 mg daily dose may

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also induce LIDs in 17% of patients after only 40 weeks of treatment (Fahn et al. 2004), while this figure attained 40% in other studies (Ahlskog and Muenter 2001). A post hoc study of the STRIDE-PD study showed that, in addition to L-DOPA dose, young age at onset, low body weight, North American geographic region, treatment with entacapone, female gender, and more severe Unified Parkinson's Disease Rating Scale (UPDRS) Part II score predicted the 4-year risk of developing LIDs (Olanow et al. 2013). Several studies suggest that LIDs impact negatively on health-related quality of life (Pèchevis et al. 2005; Damiano et al. 2000; Montel et al. 2009; Reuther et al. 2007; Perez-Lloret et al. 2017).

Motor complications remain a major unmet need for the management of PD. Many drugs have been developed to manage OFF episodes, including dopamine agonists, MAO-B and COMT inhibitors, but these drugs usually reduce time spent OFF at the cost of worsening of LIDs (Reichmann and Emre 2012). Up to now, amantadine is the only drug that has been considered "clinically useful" for the treatment of LIDs in the last evidence-based review from the Movement Disorders Society is amantadine (Fox et al. 2011). Amantadine is a synthetic tricyclic amine that belongs to the class of aminoadamantanes (Deleu et al. 2002). It was originally found to have inhibitory effects against several strains of the influenza virus during the 60s (Hubsher et al. 2012). Poskanzer and Schwab reported in 1969 the case of a 58-year parkinsonian woman who claimed an improvement in rigidity, tremor, and akinesia while taking amantadine for flu. The symptoms worsened upon stopping the medication. These effects were then tested in a sample of ten PD patients, of whom seven improved, followed by a 6-month trial in which 163 patients with PD added amantadine to their anti-PD therapy regimens. Results showed improvement in symptoms in 66% of patients with PD. These results were confirmed by forthcoming small uncontrolled trials.

The first "modern" data on the antidyskinetic effect of amantadine were published in the late 90s, closely following the reports on the antiglutamatergic properties of the drug and its potential role in LIDs (Goetz 1998). The objective of this review is to discuss the action mechanism, clinical pharmacokinetics, efficacy and safety of amantadine for LIDs. We searched PubMed with the string "Parkinson's disease AND amantadine", between 1980 and 2017. Amantadine's antiparkinsonian and potential neuroprotective effects will not be covered.

Mechanisms of amantadine antidyskinetic effect

The pathophysiological mechanisms of LIDs are covered in other articles of this Special Supplement and this section will focus on the molecular mechanisms that can explain the antidyskinetic effects of amantadine. Both mechanisms of LIDs and mechanisms of action of amantadine being not fully understood, it is not possible to propose a simple straightforward explanation. LID appears to be a complex set of phenomena. This complexity explains why, despite extensive preclinical and clinical research, few agents have successfully been shown to reduce dyskinesia or to successfully translate from preclinical to clinical settings. One reason has been that the majority of researches have focused on peak dose (high L-DOPA dose) dyskinesia, while many PD subjects may experience a mixture of peak and diphasic dyskinesia. Moreover, there is evidence for abnormalities in several neurotransmitter systems in LIDs and the traditional approaches, which usually focus on a single target, may not be appropriate and may account for failures in clinical translation (see Huot et al. 2013). Amantadine effects in the central nervous system are multiple, complex and not fully understood. Basically, the drug is known to exert antagonistic effects at the glutamate NMDA receptors and cholinergic muscarinic receptors. It is also known to increase dopamine synthesis and/or release and reduce dopamine reuptake.

Amantadine exerts a non-competitive antagonism with low-affinity of the *N*-methyl-D-aspartate (NMDA)-glutamate receptor subtype at the phencyclidine binding site, which is localized inside and at the sigma 1-binding site localized outside the cation channel (Kornhuber et al. 1991). Several pieces of evidence suggest that it is amantadine NMDA-blocking properties that are the most important to explain its antidyskinetic effects (Stoof et al. 1992; Lupp et al. 1992; Parsons et al. 1996). This is consistent with the observation that glutamate and NMDA receptors play a key role in the genesis of LIDs (Chase and Oh 2000; Huot et al. 2013). Several pieces of evidences suggest that LIDs are linked to loss of long-term depression and depotentiation at corticospinal synapses (Calabresi et al. 2015, 2016). Loss of depotentiation might destabilize neuronal circuits in the basal ganglia, thus generating LIDs. According to recent data, D1 overexcitation resulting from chronic exposure to L-DOPA might induce phosphorylation of the DARPP-32 protein, which in turn increases the levels of phosphorylated NMDA receptors, which is thought to be related to the loss of depotentiation (Calabresi et al. 2016). Another factor influencing the generation of LIDs is the molecular composition of NMDA receptors. Indeed, some studies have shown that dyskinetic rats show higher levels of GluN2A subunit and lower levels of GluN2B subunit (Calabresi et al. 2015). These alterations are associated with changes in the association between NMDA receptors and scaffolding elements, i.e., members of the membrane-associated guanylate kinase (MAGUK) protein family, such as postsynaptic density-95, synapse-associated protein-97 and synapse-associated protein-102.

This is indeed for its NMDA antagonistic effects that Chase and his colleagues chose amantadine in the 90s as

a candidate for testing the "NMDA hypothesis" of LIDs in animals and in humans. In normal subjects, the effect of amantadine on human motor cortex excitability was assessed using transcranial magnetic stimulation that modulates human motor cortex excitability. Amantadine decreased intracortical facilitation and increased late inhibition, reflecting glutamatergic modulation or a polysynaptic interaction of glutamatergic and GABAergic circuits (Reis et al. 2006).

Blockade of NMDA receptor by amantadine induces neuronal currents that may lead to a stabilization of other channels closed states (Blanpied et al. 2005). Therefore, by stabilizing the channel associated with the nicotinic receptor, ACh release from striatal interneurons is reduced, as shown in vitro (Stoof et al. 1992; Matsubayashi et al. 1997). Increased cholinergic tone has been considered as a factor associated with the genesis of LIDs (Perez-Lloret and Barrantes 2016). Thus, the effects of amantadine on cholinergic systems might contribute to its effects on LIDs. Clinically, amantadine induces antimuscarinic-like adverse reactions (dry mouth, dysuria and constipation). However, no benefit of antiparkinsonian antimuscarinic medications such as biperiden has been reported in dyskinetic PD patients, thus reinforcing the potential importance of nicotinic contributions to the antidyskinetic effect of amantadine.

Amantadine also affects dopamine synthesis and uptake. The relevance of such mechanisms to account for its clinical antidyskinetic effect remains, however, unclear, and would indeed better fit for accounting for its antiparkinsonian rather than antidyskinetic properties. In rats, amantadine 40 mg/kg significantly increased the activity of the aromatic L-amino acid decarboxylase (AADC) in the striatum and substantia nigra (Fisher et al. 1998). Similar results were obtained in healthy subjects receiving amantadine for 3 days at 100 mg daily dose by assessment of the decarboxylation rate of 6-[^{18}F]fluoro-L-DOPA (FDOPA), which is an exogenous substrate for AADC (Deep et al. 1999). Regarding dopamine uptake, amantadine 1 mM applied by microdialysis to the striatum of Wistar rats caused a significant increase of 50% in extracellular dopamine levels (Mizoguchi et al. 1994). This effect was might be mediated by inhibition of dopamine uptake caused by blockade of NMDA receptors, as non-competitive antagonists of NMDA receptor increase dopamine biosynthesis, turnover and synaptic release from striatal dopaminergic neuronal terminals in vitro (Heikkila and Cohen 1972; Jackisch et al. 1992) and in vivo (Takahashi et al. 1996).

Intuitively, it is difficult to reconcile in a simple way the fact that a drug that increases dopamine synaptic availability can reduce LIDs, as greater doses of dopaminergic medications increase LIDs consistently in animals and in humans. However, it is conceptually possible to argue that the manner dopamine is released in the synapse (pulsatile vs continuous) plays a key role in the genesis of the synaptic plastic abnormalities leading to LIDs, and that a drug that modifies dopamine release/uptake could therefore reduce LIDs (Grace 2008). The fact that the antidyskinetic effects of amantadine occur and disappear clinically quite rapidly, within a couple of days, might not fit well, however, with the concept that long-term plasticity is an important phenomenon involved in LIDs pathophysiology.

The same is true regarding amantadine effects on dopamine receptor functioning. In one study, the effects of amantadine treatments on the expression of dopamine receptors and the functional coupling to G proteins in rat striatal membranes homogenates were investigated (Peeters et al. 2002). This was done by measuring dopamine-induced stimulation of guanosine 5′-*O*-(gamma-[35*S*]thio)triphosphate (GTPgS), which has been shown to reflect activation of D2 receptors. Results showed a transient enhancement of dopamine-induced stimulation of GTPgS after a 4-day amantadine treatment. This effect was not related to changes in dopamine receptor availability. Furthermore, amantadine-treated animals exhibited hypersensitive dopamine transmission, as shown by exacerbated responses to a single apomorphine doses. Results of a binding study in rats confirmed that amantadine induced 10% increases in D2 receptor availability (Hesselink et al. 1999). Results with [11C]raclopride Positron Emission Tomography (PET), which is a marker of D2 receptor availability, showed coherent results (Moresco et al. 2002; Volonte et al. 2001). The relevancy for such finding to explain the antidyskinetic effect of amantadine is difficult to assess, but it might point out the importance of the activation of the D2 "indirect" striatopallidal pathway.

Amantadine effect on basal ganglia circuitry functioning has been assessed in some experiments. It has been shown that amantadine-reduced synaptic excitation of rat striatal slices containing medium spiny neurons, as measured by recording evoked excitatory postsynaptic potentials after electrical stimulation of the slices (Rohrbacher et al. 1994). In addition to the striatum, both the subthalamic nucleus and the GPi contain NMDA receptors (Obeso et al. 2008). Theoretically, amantadine should reduce subthalamic activity and output by inhibiting their activation. Notwithstanding, when amantadine effect on subthalamic neural activity was studied in intact or 6-hydroxydopamine (6OHDA)-lesioned rats, it increased significantly subthalamic firing rates (Allers et al. 2005). Amantadine was given intravenously, and thus these results might reflect the combined action of the drug on NMDA receptor at the subthalamic nucleus and elsewhere. Amantadine effect on striatofugal pathways was studied by dual probe microdialysis in 6OHDA hemi-lesioned dyskinetic mice and rats (Bido et al. 2011). L-DOPA caused increased GABA release in substantia nigra *Pars reticulata*, but not in the Globus Pallidus, which coincided with LIDs. Pretreatment with amantadine (40 mg/kg i.p.) prevented GABA rise and LIDs.

In summary, although amantadine has undisputable antidyskinetic properties that are consistently documented in animal models and PD patients (see below), the intimate mechanisms explaining such a property remain rather mysterious. Non-competitive antagonism at the NMDA receptors probably plays an important role. It is more difficult to link the known effects of the drug on dopaminergic mechanisms (release, synthesis and receptors) with its effects on LIDs. The impact of different doses and duration of exposure having been insufficiently explored, any conclusion on that matter can only be speculative at the moment, and further studies should be strongly encouraged. Moreover, other yet unknown effects on other transmitters or other mechanisms cannot be excluded.

Antidyskinetic effects of amantadine in vivo in animal models of PD with LIDs

Amantadine antidyskinetic effects have now been extensively studied in vivo in different rodent and primate parkinsonian models combining nigro-striatal denervation and L-DOPA exposure. Generally, such experiments have aimed at measuring behavioral changes considered to mimic the so-called "peak-dose" LIDs. A summary of such studies can be found in Table 1.

The antidyskinetic properties of amantadine have been assessed in 6OHDA-lesioned rodents, both in the rat and the mice. In a recent study by Bortolanza and colleagues, amantadine single doses of 10, 20 or 40 mg/kg were administered to lesioned rats with LIDs after 21 days of treatment with L-DOPA 20 mg/kg (Bortolanza et al. 2016). Amantadine dose-dependently reduced of global AIMs score over 180 min post-L-DOPA administration. The 20 mg/kg dose displayed significant antidyskinetic effect only during the first 60 min after L-DOPA. As shown in Table 1, other studies in rats and mice have yielded essentially similar results.

Chase and colleagues were pioneers in proposing in the 90s that the NMDA antagonistic properties of amantadine might be beneficial for the treatment of LIDs. They were also among the first to test this hypothesis in a non-human primate model of LIDs. In this experiment, four MPTP-lesioned monkeys under L-DOPA therapy received the drug in two different regimens: 1.25 or 2.5 mg/kg s.c. twice daily for 3–6 days (Blanchet et al. 1998). L-DOPA was also given at two different effective "low" and "high" doses (i.e., mean doses of 47.5 and 110 mg, respectively). When amantadine was co-administered with low doses of L-DOPA, it suppressed almost completely LIDs, but when its dose attained 2.5 mg/kg, L-DOPA antiparkinsonian effect was also compromised. Conversely, amantadine did not affect L-DOPA antiparkinsonian effect when the latter was administered at higher doses, while it reduced LIDs only at 2.5 mg/kg dose. These authors were not able to offer a convincing explanation for the reduction of antiparkinsonian L-DOPA effects at low doses. Amantadine was also shown to reduce

Table 1 Amantadine antidyskinetic properties in animal PD models

Study	Amantadine treatment	Antidyskinetic effect
6OHDA-lesioned C57BL/6 mice		
Lundblad et al. (2005)	40 or 60 mg/kg single doses (i.p.)	Significant reductions of 28.7 and 47.6 in AIM score
Bido et al. (2011)	40 mg/kg single doses (i.p.)	46% reduction
6OHDA-lesioned rats		
Dekundy et al. (2007)	20 or 40 mg/kg single doses (s.c.)	Significant dose-dependent reduction in AIMs score (20 and 50%, respectively)
Kobylecki et al. (2011)	5, 10, 20 mg/kg single doses (s.c.)	66 and 15% reduction ($p < 0.05$) with 20 and 10 mg
Bido et al. (2011)	40 mg/kg single doses (i.p.)	43% reduction ($p < 0.01$)
Paquette et al. (2012)	60 mg/kg single doses (s.c.)	40% reduction ($p < 0.05$)
Bortolanza et al. (2016)	10, 20, 40 mg/kg single doses (i.p.)	Dose-dependent reduction (90% with 40 mg, $p < 0.01$).
MPTP-lesioned monkey		
Blanchet et al. (1998)	1.25 or 2.5 mg/kg bid for 3–6 days (s.c.)	Low L-DOPA: 90% with both doses ($p < 0.01$) High L-DOPA: 33% with 2.5 mg dose ($p < 0.05$)
Hill et al. (2004)	0.01, 0.03, 0.1, and 0.3 mg/kg single doses (p.o.)	Significant reduction with 0.3 mg/kg. Levetiracetam potentiated this effect
Bibbiani et al. (2005)	2.5 mg/kg single doses (s.c.)	No significant effects
Kobylecki et al. (2011)	0.1, 0.3, 1.0 mg/kg single doses (p.o.)	Significant reduction with 0.3 and 1 mg doses
Bezard et al. (2013)	10 and 20 mg/kg single doses (i.v.)	Significant reduction with 20 mg/kg
Aron Badin et al. (2013)	2.5–10 mg/kg single doses (i.v.)	Significant reduction with 10 mg/kg
Johnston et al. (2013)	3 mg/kg daily for 2 weeks (p.o.)	Reductions of dyskinesia
Ko et al. (2014)	10, 20 and 30 mg/kg single doses (p.o.)	Dose-dependent reduction (100% with 30 mg, $p < 0.01$)

LIDs caused by D1- or D2 agonists in MPTP-lesioned animals (Bibbiani et al. 2005), and its antidyskinetic effect in non-human primates has been repetitively and consistently confirmed in subsequent experiments (see Table 1). For example, amantadine has also been used as a "positive" comparator in animal studies assessing primarily the antidyskinetic effect of other drugs, including IRC-082451, a multi-targeting hybrid molecule with sodium channel blocking, antioxidant and cyclooxygenase inhibiting effects (Aron Badin et al. 2013), eltoprazine, a 5-HT1A/1B-receptor agonist (Bezard et al. 2013), or TC-8831, an agonist at nicotinic acetylcholine receptors (Johnston et al. 2013). In all these experiments, LIDs were reduced when monkeys received amantadine. Amantadine has also been used for the validation of novel LIDs animal models (Dekundy et al. 2007; Lundblad et al. 2005), and for the assessment of new rating scales of LIDs in animals (Sebastianutto et al. 2016). This demonstrates the reliability of its antidyskinetic response and illustrates the fact that the drug is now considered as a referential agent for the evaluation of LIDs in animal models.

Finally, other studies have shown that amantadine antidyskinetic effect can be potentiated by other medications such as levetiracetam (Hill et al. 2004), topiramate (Kobylecki et al. 2011) or fenobam (Ko et al. 2014). Only the combination of topiramate and amantadine has been assessed for LIDs in clinical trials, with negative results (Goetz et al. 2017).

Clinical pharmacokinetics

In healthy elderly subjects, amantadine IR is absorbed slowly and variably from the gastrointestinal tract after oral administration (Deleu et al. 2002). Bioavailability of the IR form is 85–90% (Aoki and Sitar 1988). The drug is extensively bound to tissues, and its apparent volume of distribution is inversely related to dose (Aoki and Sitar 1988). It has been hypothesized that this inverse relationship accounted, at least in part, for disproportionately high amantadine serum concentrations associated with neurotoxic side effects, at least in healthy young adults (Aoki and Sitar 1988). Plasmatic half life is 10–45 h, and steady-state concentrations are usually reached within 4–7 days in healthy elderly and parkinsonian subjects (Deleu et al. 2002). The drug is almost entirely eliminated by renal clearance, particularly renal tubular secretion.

Usual amantadine IR dose to achieve antidyskinetic effects is 100–300 mg (Alliance Pharmaceuticals 2010). Dose should be reduced in patients with renal insufficiency (Horadam et al. 1981). Hemodialysis only removed negligible amounts of the drug. Metabolism by acetylation affects 5–15% of each dose (Koppel and Tenczer 1985; Deleu et al. 2002). In cases of overdose, metabolites can be identified in plasma (Koppel and Tenczer 1985). There are many generics of the IR formulation available in the market. To the best of our knowledge, there are no published bioequivalence studies on them.

In a small study, plasmatic concentrations after oral 600 mg doses of the IR form to parkinsonian patients were 1500–1700 mcg/ml (Brenner et al. 1989). Serum and CSF concentrations were essentially similar. In another study, plasmatic steady-state concentrations were assessed in 78 patients (Nishikawa et al. 2009). Mean daily dose of amantadine was 135.1 ± 62.3 mg/day (range 50–300 mg/day). Mean plasma amantadine concentration ranged from 91 to 4400 ng/ml (mean 812.5 ± 839.5 ng/ml). Interestingly, plasma amantadine concentration of 3000 ng/ml or more was observed in four patients, out of whom three showed neuropsychiatric adverse reactions, thus suggesting that this might be the upper limit of the "therapeutic window".

The pharmacokinetic profile of Amantadine extended-release (ADS-5102, Gocovri®) has been designed to exhibit an initially slow rate of rise in amantadine levels during sleep and high levels in the morning and throughout the waking hours when given at bedtime (Oertel et al. 2017). According to Gocovri's Summary of Product Characteristics, median T_{max} for plasma amantadine after oral administration was around 12 h (range 6–20 h) (Adamas Pharmaceuticals 2017). Furthermore, accumulation ratio after repeated doses was 1.2–1.3, which is negligible and might contribute to reduced toxicity.

Clinical efficacy

Amantadine is the only drug with solid clinical evidence of an antidyskinetic effect in PD patients (Fox et al. 2011). There are currently three pharmaceutical forms available in the market, the oral immediate- (IR) or extended-release (ER) tablets and the intravenous infusion (IV) formulation. The IR tables are widely available, while the ER ones (ADS-5102) have been recently developed and approved in FDA, but still not in Europe. Finally, the IV solution is not commonly used in the clinical practice and is available in a minority of countries.

In this section, the most important clinical trials of the amantadine will be briefly reviewed. A summary of all trials can be found in Table 2.

Immediate-release oral formulation

Verhagen Metman and colleagues conducted one of the first double-blind trials with amantadine in the late 90s (Verhagen Metman et al. 1998a, b). In a randomized, double-blind, placebo-controlled, cross-over study 18 advanced

Table 2 Clinical studies with amantadine for L-DOPA-induced dyskinesias

Study	Design	*n*	Amantadine	Main results
Oral immediate-release				
Verhagen Metman et al. (1998a, b)	R DB CO PC	18	300–400 mg for 3 weeks	65% improvement in UPDRS Part IV and AIMS. 44% decrease in OFF-time
Metman et al. (1999)	DB PC[a]	17	Average dose = 362 ± 14 mg for 7–10 days.	56% lower AIMS score compared to placebo on the initial acute study
Luginger et al. (2000)	R DB PC CO	11	300 mg for 2 weeks	50% reduction in LIDs patient diary and UPDRS IV 32 + 33 score
Snow et al. (2000)	R DB PC CO	24	200 mg for 3 weeks	24% reduction in RDRS
Paci et al. (2001)	R DB PC	20	300 mg for up to 8 months	38% reduction in RDRS (day 15). After 2–8 months, amantadine was withdrawn in all patients
da Silva-Junior et al. (2005)	R DB PC	18	200 mg for 3 weeks	45% reduction in UPDRS IV LIDs scores
Sawada et al. (2010)	R DB PC CO	36	300 mg for 27 days	64% reductions in RDRS
Wolf et al. (2010)	R DB PC[b]	32	Usual daily dose for 3 weeks	UPDRS IV 32 + 33 scores deteriorated in placebo but not in amantadine group
Goetz et al. (2013)	R DB PC	60	300 mg for 8 weeks	33% reductions in UDysRS and other scales
Ory-Magne et al. (2014)	R DB PC[b]	57	Mean dose 244 mg for 3 months	UPDRS IV 32 + 33 scores deteriorated in placebo but not in amantadine group
Oral extended-release				
Pahwa et al. (2015)	R DB PC	83	260, 340, 420 mg for 8 weeks	> 2-fold reduction in UDysRS with 340 and 420 mg
Pahwa et al. (2017)	R DB PC	189	274 mg for 25 weeks	> 2-fold reduction in UDysRS. Reduced OFF-time
Oertel et al. (2017)	R DB PC	77	274 mg for 12 weeks	> 2-fold reduction in UDysRS. Reduced OFF-time
Hauser et al. (2017)	OL UC	223	274 mg for up to 88 weeks	42% reduction in MDS-UPDRS IV score
Intravenous infusions				
Ruzicka et al. (2000)	OL UC	21	D1–7: 400 mg/2.5 h D8–21: 200–600 mg/day p.o.	50% improvement in AIMS. Reductions in UPDRS III and OFF-time
Del Dotto et al. (2001)	R DB CO PC	9	200 mg for 2 h	50% improvement in AIMS
Koziorowski and Friedman (2007)	OL UC	12	600 mg/day for 72 h during a L-DOPA "drug holidays"	Reductions in UPDRS Parts IV & III scores for up to 4 months

Study design: *DB* double-blind, *CO* cross-over, *OL* open-label, *PC* placebo-controlled, *UC* uncontrolled

Assessment tools: *AIMS* Abnormal Involuntary Movement Scale, *MDS-UPDRS* Movement Disorders Society-Unified PD Rating Scale, *UDysRS* Unified Dyskinesia Rating Scale, *RDRS* Rush Dyskinesia Rating Score, *LIDS* L-DOPA-induced dyskinesias

[a]Patients, who had participated in the previous 3-week study, were followed for 1 year. 7 to 10 days before 1-year assessment, they were assigned to the treatment that they had received during the last year [amantadine 13, no amantadine (replaced by placebo) 4]

[b]Patients had to be on stable doses of amantadine and were switched to amantadine or placebo

PD patients received amantadine or placebo for 3 weeks. At the end of each study arm, patients received an intravenous L-DOPA infusion and were assessed. The primary outcome was the modified Abnormal Involuntary Movement Scale (AIMS) and an abbreviated Unified Parkinson's Disease Rating Scale (UPDRS part III, items 20, 22, 23, 26, 29, and 31, describing tremor, rigidity, finger taps, leg agility, gait, and body bradykinesia). Amantadine dose averaged 350 ± 15 mg in the 14 patients who finished the trial. Dyskinesia scores during steady-state L-DOPA infusions were 60% lower with amantadine ($p < 0.001$). Abbreviated UPDRS III scores were non-significantly lower in patients on amantadine. UPDRS IV score was also lower with amantadine. Interestingly, amantadine plasmatic levels correlated significantly with the change in AIMS score ($r^2 = 0.57$, $p < 0.01$), suggesting a good dose–response relationship. Patients from this study were followed for up to 1 year (Metman et al. 1999) in a double-blind fashion. AIMS scores were 56% with amantadine at the end of follow-up. This suggested that amantadine effect was long lasting.

In a multi-center, double-blind, randomized, placebo-controlled, cross-over trial, 36 patients with PD and LIDs received amantadine (300 mg/day) or placebo treatment for 27 days with a 15-days wash-out in between (Sawada

et al. 2010). Rush Dyskinesia Rating Scale, the primary outcome, improved in 64 and 16% of patients treated with amantadine or placebo, respectively (adjusted odds ratio for improvement by amantadine 6.7, 95% confidence interval 1.4–31.5, $p < 0.01$). Amantadine positive effects have also been observed in other studies, employing several dyskinesia scale as outcomes, including the Rush scale (Snow et al. 2000; Paci et al. 2001), UPDRS IV Items 32 + 33 (da Silva-Junior et al. 2005; Luginger et al. 2000; Wolf et al. 2010), or the UDysRS (Goetz et al. 2013). The characteristics and main results from these trials are summarized in Table 2.

In the study from Paci and colleagues, including 20 PD patients, the antidyskinetic effect of amantadine was reported to last less than 8 months (Paci et al. 2001), which conflicted with the results from Verhagen Metman et al. (1999). This fueled a controversy on the duration of amantadine antidyskinetic effect. This topic was revisited in a double-blind placebo-controlled trial (Thomas et al. 2004). Forty advanced PD patients received amantadine 300 mg/day or placebo. Investigators retained the patients into the study until there was clear evidence that the treatment administered (i.e., either amantadine or placebo) was devoid of efficacy. After 15 days of amantadine treatment, there was a reduction by 45% in the total dyskinesia scores, vs < 1% in the placebo group. Notwithstanding, the improvements disappeared 3–8 months later both in placebo- or amantadine-treated patients.

The controversy about the possibly waning antidyskinetic effect of amantadine on the long-term has been revisited using the wash-out design, where PD patients treated with amantadine for LIDs were randomly switched to placebo or remained on amantadine in double-blind conditions. A first study failed to find significant between-group differences, probably due to insufficient power, while LIDs worsened in patients switched to placebo and they did not change in those who were maintained on amantadine (Wolf et al. 2010). The AMANDYSK trial conducted by the French NS-Park/F-CRIN network, and then clearly showed that amantadine kept significant antidyskinetic properties in patients who had been treated with amantadine for LIDs for 3 years on average (Ory-Magne et al. 2014). AMANDYSK was a 3-month, multi-center, randomized, double-blind, placebo-controlled, parallel-group, wash-out study conducted in 57 amantadine-treated (mean daily dose of 250 mg/day for 3 years) dyskinetic patients with PD. The primary endpoint was the change from baseline to last visit of a dyskinesia UPDRS part IV score (items 32 + 33, i.e., LIDs "duration" and "disability"). The UPDRS items 32 + 33 score increased more in the "discontinuing" group (those who were switched to placebo) [+ 1.7; 95% confidence interval (CI) 0.9/2.4] than in the "continuing" group (those who remained on amantadine unchanged) (+ 0.2; 95% CI − 0.4/0.8), with a significant between-group difference ($p < 0.003$). This finding supports the fact that in such a population, the beneficial effect of amantadine on dyskinesia was still present on the long term. Interestingly, apathy (as measured by caregivers) and fatigue scores tended to worsen more in patients randomized to placebo than amantadine, suggesting potential non-motor effects of the drug.

Extended-release oral formulation

Results from three randomized, double-blind, placebo-controlled studies with ADS-5102, i.e., the EASED, EASE LID and EASE LID 3 studies, have been recently published (Pahwa et al. 2015, 2017; Oertel et al. 2017).

In the Phase II EASED study, 83 PD patients with troublesome LIDs were assigned to placebo or one of three doses of amantadine (260, 340, 420 mg) administered daily at bedtime for 8 weeks (Pahwa et al. 2015). LIDs, as measured by the Unified Dyskinesia Rating Scale (UDysRS), improved significantly with the 340 mg [least-square (LS) mean treatment difference = − 11.3 (95% CI − 19.1, − 3.5), $p < 0.005$] and 420 mg [LS mean treatment difference = − 10.0 (95% CI − 17.8, − 2.2), $p < 0.013$] doses. The duration of ON time without troublesome dyskinesia, as measured by home diaries, increased with all doses. MDS-UPDRS item measuring the functional impact of LIDs also improved with all doses. Finally, Clinical Global Impression of Change (CGI-C) scores were significantly better with ADS-5102 340 mg.

The EASE LID was a phase III trial, in which 126 patients were randomized to ADS-5102 274-mg (equivalent to amantadine hydrochloride 340 mg/day) or placebo (Pahwa et al. 2017). At week 12, the least-squares mean (SE) change in the Unified Dyskinesia Rating Scale score—UDysRS—(i.e., the primary endpoint) was − 15.9 ± 1.6 for amantadine ER and − 8.0 ± 1.6 for placebo (treatment difference, − 7.9; 95% CI − 12.5 to − 3.3; $p < 0.001$). Improvements persisted throughout the 24-weeks follow-up period. UDysRS scores were also improved by − 4.5 points (95% CI − 7.4 to − 1.6, $p < 0.003$) and − 4.2 (− 7.8 to − 0.7, $p < 0.02$) at weeks 12 and 24. MDS-UPDRS IV functional impact of dyskinesia scores was also lower with amantadine both at week 12 and 24. Finally, and interestingly, OFF time decreased significantly on amantadine ER by − 0.9 h (− 1.6 to − 0.2; $p = 0.02$) at week 12 and − 0.8 (− 1.6 to − 0.0, $p < 0.04$) at week 24. This is the first time that a drug demonstrated that it could improve concomitantly parkinsonism (OFF time) and LIDs, while in general, interventions that improve OFF time do so at the cost of worsening of LIDs.

The EASE LID 3 trial was a confirmatory Phase III study, including 73 PD patients with ≥ 1 h of troublesome dyskinesia and at least mild functional impact were randomized to placebo or ADS-5102 once daily at bedtime for 13 weeks (Oertel et al. 2017). At week 12, least-squares mean change

in the UDysRS was −20.7 (standard error 2.2) for ADS-5102 and −6.3 (standard error 2.1) for placebo (treatment difference −14.4, 95% confidence interval −20.4 to −8.3, $p < 0.0001$). OFF time decreased 0.5 h (standard error 0.3) for ADS-5102 from a baseline mean of 2.6 h and increased 0.6 h (standard error 0.3) for placebo from a baseline mean of 2.0 h (treatment difference −1.1 h, 95% confidence interval −2.0 to −0.2, $p < 0.02$).

In a long-term open-label safety study, which included patients of the EASE LID and LID 3 trials, MDS-UPDRS part IV scores were reduced by ADS-5102 and remained stable for up to 64 weeks (Hauser et al. 2017). MDS-UPDRS Parts I–III mean scores showed relatively small changes from baseline at each measured time point across all groups.

Intravenous formulation

As mentioned earlier, amantadine IV is not commonly used in the clinical practice. Notwithstanding, its efficacy has been assessed by Ruzicka et al. (2000) in an open-label study, and by Del Dotto et al. (2001) in double-blind, randomized, cross-over study in nine patients (Table 2). In addition, it has also been tested as a "dopaminergic drug holidays" with some success (Koziorowski and Friedman 2007) (Table 2). This interesting use has not been further tested, to the best of our knowledge.

Safety

Toxicology data and drug use during pregnancy

Mutagenesis has not been observed in in vitro studies (Alliance Pharmaceuticals 2010). Amantadine deleterious effects on the central nervous system were assessed in CF-1 mice (Kaefer et al. 2010). Amantadine 15 mg/kg did not induce DNA damage and had no effects on memory, locomotion, exploration or motivation in mice. However, higher doses increased DNA damage in brain tissue, produced locomotor disturbances severe enough to preclude testing for learning and memory effects, and induced stereotypy, suggesting neurotoxicity (Kaefer et al. 2010). A study using postmortem human brain tissue of patients previously treated with amantadine failed to show changes in the hippocampus, retrosplenial cortex, and cingulate gyrus (Kornhuber et al. 1991).

Amantadine should be avoided in women who are pregnant or trying to become pregnant, as it may induce teratogenesis and increased risk of miscarriage (Seier and Hiller 2017).

Adverse events in clinical trials

In a recent meta-analysis, it was shown that the risk of any adverse event was higher in patients under amantadine immediate-release vs placebo patients (RR 1.86, 95% CI 1.38–2.52) (Kong et al. 2017). According to the Summary of Product Characteristics, the most common adverse events with amantadine IR (5–10%) are nausea, dizziness, and insomnia (Alliance Pharmaceuticals 2010). Depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension, headache, somnolence, nervousness, dream abnormality, agitation, dry nose, diarrhea and fatigue are observed less frequently (1–5%) (Alliance Pharmaceuticals 2010).

Most frequent adverse events in the clinical trials with the ER formulation were orthostatic hypotension, hallucinations, dry mouth, nausea and edemas (Table 3). In an 88-week open-label follow-up study, 49.3% of patients on amantadine ER experimented adverse drug reactions (ADRs) (Hauser et al. 2017). Discontinuation due to ADRs occurred in 8.2% of patients. Most frequent adverse events were falls (25.1%), hallucinations (19.3%), peripheral edema (13.0%), constipation (12.6%), livedo reticularis (8.1%), nausea (8.1%), dry mouth (7.2%), insomnia (7.2%), and dizziness (6.7%).

Table 3 Adverse events in clinical trials with amantadine extended-release

	Pahwa et al. (2015)	Pahwa et al. (2017)	Oertel et al. (2017)
Amantadine dose (mg)	340	274	274
Constipation (%)	23.8 vs 9.1	15.9 vs 5.0	8.1 vs 0
OH symptoms (%)	28.6 vs 4.5	22.2 vs 0	10.8 vs 0
Hallucination (%)	23.8 vs 0	31.7 vs 1.7	8.1 vs 5.3
Dry mouth (%)	19.0 vs 0	17.5 vs 0	13.5 vs 2.6
Confusion (%)	14.3 vs 4.5	–	–
Nausea (%)	14.3 vs 4.5	–	13.5 vs 2.6
Edema (%)	–	23.8 vs 0	–
Livedo reticularis (%)	–	9.5 vs 0	–

Percentage of patients with each adverse event in the amantadine vs placebo groups is shown

OH orthostatic hypotension

Post-marketing surveillance

As amantadine IR has been on the market since the 60s, the amount of post-marketing surveillance data is abundant. In this section, the most important findings will be discussed.

Neuropsychiatric adverse reactions are frequent and expected with amantadine, due to the blockade of the NMDA and muscarinic receptors. Hallucination is one of the most common adverse drug reactions. In addition, abrupt changes in amantadine dosage can produce a severe withdrawal syndrome, which might include delirium, catatonia, or neuroleptic malignant syndrome (Fryml et al. 2017). These cases can be treated effectively by amantadine IV infusion (Marxreiter et al. 2017). Serotonin syndrome (Cheng et al. 2008) or dropped head syndrome (Kataoka and Ueno 2011) have also been reported. Impulse control disorders have also been positively related to amantadine prescription, both in case reports and large cross-sectional studies (McNamara and Durso 1991; Weintraub et al. 2010). A potential confounding effect of high dopaminergic therapy doses, which usually accompany amantadine usage, might not have been, however, completely accounted for in these studies. In fact, amantadine has been reported to have short-term efficacy for pathological gambling in a double-blind cross-over trial (Thomas et al. 2010). This result is inconsistent with the aforementioned results of case reports and epidemiological surveys (McNamara and Durso 1991; Weintraub et al. 2010). It has been proposed that LIDs and ICD might share molecular mechanisms and cognitive mechanisms of habit learning (Voon et al. 2009). Therefore, the role of amantadine on ICDs is not clear and should be further studied.

Orthostatic hypotension (OH) is a frequent ADR to amantadine, as shown in clinical trials. In a cross-section trial conducted by our group, the risk of OH increased dose-dependently with amantadine (Perez-Lloret et al. 2012). The mechanism leading to OH is not clear, but it might be related to alteration of cardiovascular reflexes (Korchounov et al. 2004). Finally, a case of inappropriate antidiuretic hormone secretion with amantadine has been reported (Alonso Navarro et al. 2009).

QT prolongation might be observed in patients treated with amantadine. Notwithstanding there is a paucity of clinical studies on the matter and further objective data should be welcome. Even if there are no recommendations on the Summary of Product Characteristics, electrocardiogram monitoring might be useful, especially in the elderly, in patients with long QT interval or in patients with renal failure. Arrhythmias can be observed with overdosage (see below).

Livedo reticularis has also been observed during clinical trials in PD and may affect up to 40% of patients (Quaresma et al. 2015). It is a purplish-red mottling of the skin, sometimes described as fishnet-like that may affect upper or lower extremities (Faulkner 2014). Even if it is harmless, it is a frequent cause of treatment abandon (Rana and Masroor 2012).

Corneal adverse reactions such as superficial punctuate keratitis, punctuate subepithelial opacification, epithelial edema and stromal edema although ocular toxicity are rare but critical (Kim et al. 2013). A recent cohort study in 8195 Taiwanese PD patients revealed an incidence of corneal edema of 1.5 (vs 1.0% in the control group, $p < 0.004$), which was increased by amantadine in a dose-dependent fashion (Lee et al. 2016). The effect of amantadine on corneal endothelial cells has been assessed in 169 PD patients and age- and gender-matched controls (Chang et al. 2010), showing significant toxicity. Furthermore, many changes were permanent and dose-dependent. The report of a case with acute visual loss after beginning amantadine suggests that dose-independent hypersensitivity may also play a role (Kubo et al. 2008).

Finally, amantadine may also cause other less studied adverse reactions. For example, it has been reported to cause Patulous Eustachian tube syndrome, which produces symptoms of aural fullness and autophony (Boyd and Silverman 2013). Acute respiratory failure has also been reported in one case (Cattoni and Parekh 2014). Anemia may also be seen with amantadine, which may result from accelerated clearance of erythrocytes due to suicidal erythrocyte death or eryptosis (Foller et al. 2008).

Overdosage and intoxication

Drug overdose can result in cardiac, respiratory, renal, and central nervous system toxicity (Pimentel and Hughes 1991; Schwartz et al. 2008; Snoey and Bessen 1990). Cardiac dysfunction includes arrhythmia, tachycardia and hypertension (Pimentel and Hughes 1991; Sartori et al. 1984). The lowest reported acute lethal dose was 1 g. Acute toxicity may be attributable to the anticholinergic effects of amantadine.

There is no specific antidote for amantadine, but the treatment with physostigmine has been reported to effectively control central nervous system toxicity (Alliance Pharmaceuticals 2010). Furthermore, the administration of urine acidifying drugs may increase drug clearance, as renal proximal reabsorption is dependent on a bicarbonate transporter (Goralski et al. 1999).

Conclusion

The efficacy and safety of amantadine IR have been documented in relatively old randomized, double-blind, controlled trials of imperfect quality due to heterogeneous sample sizes, follow-up periods and outcomes. Nevertheless, based on such evidence, the International Parkinson and Movement Disorders Society concluded that amantadine

IR is "clinically useful" for the treatment of LIDs (Fox et al. 2011). The evidence supporting the clinical utility of amantadine ER (ADS-5102) is supported by three recent trials of better quality, which included larger (although limited) samples, with longer follow-up periods (up to 6 months), and used more standardized and valid assessment of LIDs (i.e., UDysRS and home diaries). The FDA has recently approved this 274 mg ER formulation of amantadine (presented as equivalent to 340 mg/day of the IR formulation) for the treatment of LIDs. Theoretically, once-daily intake of amantadine ER at bedtime might offer some benefits over the IR formulation, including increased compliance and better tolerance, as it exhibits a slow initial rise in plasma concentration, a delayed Tmax of 12 h with sustained high plasma concentrations during waking hours, when LIDs and OFF symptoms can be most bothersome. Unfortunately, direct double-blind head-to-head parallel or switch sequential comparisons of both formulations are lacking. The exact equivalence between the IR and ER doses is not clear, which might complicate attempts to compare their clinical effects. Moreover, the IR formulation can be used at flexible doses (from 100 to 400 mg/day), while the ER formulation 274 mg ADS-5102 once nightly is the sole dose that has been assessed in Phase III, as it was considered as providing the best balance between efficacy and safety from the Phase II study. At the moment, the added value of the novel ER formulation is therefore uncertain, while the cost-effectiveness of using this novel but more expensive formulation rather than older and cheaper generics of the IR formulation remains to be demonstrated.

Amantadine has also some antiparkinsonian effects which are poorly known, but explains its traditional use as monotherapy in early PD. Results of a recent meta-analysis showed significant reductions of UPDRS motor scores with amantadine IR (Kong et al. 2017). Notwithstanding, size effect was 1.86 points, which is below the 6.1 minimal clinically important difference (MCID) (Hauser et al. 2014). The effects of amantadine ER on OFF-time seem more robust, in the sense that they were detected in two randomized placebo-controlled trials (Pahwa et al. 2017; Oertel et al. 2017), and approached the MCID of 1.0–1.3 h (Hauser et al. 2014). This is quite a unique profile, as all other antiparkinsonian drugs marketed to reduce time spent OFF do so at the expense of a worsening of LIDs. Finally, some non-motor symptoms might respond to amantadine treatment as suggested by Ory-Magne et al. (2014) for apathy and fatigue. A positive effect of amantadine on fatigue has been reported in other neurological disorders (Van Reekum et al. 1995; Zifko 2004), and this should be better tested in PD patients. To our best knowledge, there is no information yet about the effects of amantadine ER on non-motor symptoms.

The impact of the early use of amantadine on the subsequent development of LIDs is unknown. It is theoretically conceivable that this strategy may provide a long-term "disease-modifying" effect, preventing the emergence or reducing the risk of subsequent LIDs. The French NS-Park/FCRIN network is currently testing this hypothesis in the PREMANDYSK trial (NCT01538329), a randomized, double-blind, placebo-controlled study that is prospectively following for 18 months 200 patients with early PD (< 3 years from diagnosis) who have been treated with L-DOPA for less than 1 year and are still free of LIDs. The primary objective of this study is to demonstrate that early combination of amantadine (200 mg/day) to L-DOPA decreases the rate of subjects who will develop LIDs.

One of the factors limiting widespread clinical use of amantadine is the many adverse drug reactions associated with its use, including neuropsychiatric symptoms and cardiovascular dysfunction, especially at high doses which are most effective for the treatment of LIDs. Doses of amantadine IR used in clinical practice to manage LIDs are usually 200–300 mg per day. The daily dose for ER amantadine assessed in Phase III studies was 274 mg/day (considered to be equivalent to 340 mg amantadine IR), induced up to 20% of hallucinations, leg edema and dizziness, while AEs leading to treatment discontinuation occurred in 21% patients vs 7% on placebo. This is not trivial. Amantadine should probably be avoided, or doses kept to the minimum possible in patients with other risk factors for these conditions. Results from the study of Verhagen Metman et al. (1998b) indicated that 8 mcg/ml are related to a 50% reduction in LIDs, which according to previous results can be achieved with doses between 100 and 200 mg/day of amantadine IR (Nishikawa et al. 2009). There have not been proper dose-finding studies which might justify the efficacy of lower doses to be used in high-risk patient populations, and further dose-finding studies are required to improve the care of our patients.

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