

# Levodopa-induced dyskinesias in Parkinson's disease: emerging treatments

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**Abstract:** Parkinson's disease therapy is still focused on the use of L-3,4-dihydroxyphenylalanine (levodopa or L-dopa) for the symptomatic treatment of the main clinical features of the disease, despite intensive pharmacological research in the last few decades. However, regardless of its effectiveness, the long-term use of levodopa causes, in combination with disease progression, the development of motor complications termed levodopa-induced dyskinesias (LIDs). LIDs are the result of profound modifications in the functional organization of the basal ganglia circuitry, possibly related to the chronic and pulsatile stimulation of striatal dopaminergic receptors by levodopa. Hence, for decades the key feature of a potentially effective agent against LIDs has been its ability to ensure more continuous dopaminergic stimulation in the brain. The growing knowledge regarding the pathophysiology of LIDs and the increasing evidence on involvement of nondopaminergic systems raises the possibility of more promising therapeutic approaches in the future. In the current review, we focus on novel therapies for LIDs in Parkinson's disease, based mainly on agents that interfere with glutamatergic, serotonergic, adenosine, adrenergic, and cholinergic neurotransmission that are currently in testing or clinical development.

**Keywords:** motor fluctuations, dopaminergic/nondopaminergic systems, pharmacotherapy

## Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder with a wide spectrum of clinical features, including motor symptoms, gait and balance disorders, and cognitive, emotional, and behavioral deficits. The cardinal signs of PD reflect a decline in striatal dopamine (DA) due to the degeneration of neurons arising from the pars compacta of the substantia nigra. The application of levodopa restores DAergic transmission deficiency and provides remarkable symptomatic relief to the vast majority of patients with PD, and remains the most efficacious agent available for PD treatment. However, soon after the first clinical introduction of levodopa as an antiparkinsonian agent by George Cotzias,<sup>1</sup> it became apparent that the beneficial effect of levodopa is not permanent, and that its long-term use could cause a behavioral and molecular sensitization such that each exposure to a direct or indirect stimulant of DAergic transmission influences the response to a subsequent stimulus, a procedure known as priming. This narrows the therapeutic window of levodopa, and a variety of motor problems that are extremely disabling for the patient, known as motor-response complications, can occur. One of the most discomforting and frequent features of motor-response complications is the emergence of abnormal and involuntary movements affecting mainly the facial muscles, but also the neck, upper and lower limbs, and body axis, termed levodopa-induced dyskinesia (LID).

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Chorea and dystonia are the most frequent forms of LIDs, but ballismus and myoclonus can appear as well. The occurrence of LIDs is directly related to the plasma concentration of levodopa. Three main forms of LIDs have been characterized: 1) “peak-dose” dyskinesias are choreic movements related to high levodopa plasma concentrations; 2) diphasic on/off dyskinesias, which coincide with rising and decreasing plasma concentrations of levodopa and might include both chorea and dystonia; and 3) “off” dystonia, which is an often-painful dystonic posture, appears early in the morning or at night, and characterizes the unmedicated state where plasma levels of levodopa are very low.

Approximately 50% of patients with PD will experience LID roughly 4–5 years after initiation of levodopa treatment.<sup>2,3</sup> However, the percentage of PD patients experiencing troublesome LIDs (the ones interfering with normal activities) and requiring some intervention is actually much lower than 50%. The presence of LID significantly worsens the quality of life of the patients.<sup>4</sup> Moreover, in order to improve LID or to prevent its occurrence, the dose of levodopa is reduced and additional, less effective medication is added to the therapy. This significantly affects the effective control of parkinsonian symptoms and increases health care costs.<sup>5</sup>

## The pathophysiology of LID

The pathophysiology of LID is still not fully understood. Dyskinetic animals appear to have profound alterations at the pre- and postsynaptic level of the neural network of basal ganglia. Although current notions attribute these alterations to several factors, such as aging-related neurodegeneration, neuronal plasticity of DAergic and non-DAergic systems, and glutamatergic overabundance, it seems that the progressive neuronal loss in substantia nigra and the pulsatile chronic DAergic stimulation from levodopa are the key players not only for the appearance but for the severity of LID as well.

The stimulation of DA receptors in a noncanonical, noncontinuous way due to the short half-life of levodopa is thought to induce secondary modifications in striatal medium spiny neurons.<sup>6</sup> These modifications include changes in the intracellular signal-transduction pathways, in the expression of genes, and in the synaptic efficacy of DA and other neurotransmitter receptors. The affected corticostriatal transmission and plasticity sensitize the striatum in a way that expression of LIDs is facilitated. Indeed, dyskinetic rats showed a loss of synaptic depotentiation in response to low-frequency synaptic stimulation in comparison to nondyskinetic rats.<sup>7</sup>

Despite existing data suggesting the opposite,<sup>8,9</sup> a growing body of evidence indicates that progressive DAergic degeneration in substantia nigra lowers the threshold required for LID to occur, thus amplifying the dyskinesiogenic effect of levodopa. Animals with nigrostriatal lesions were at a significantly higher risk of developing LIDs after levodopa administration when compared to less lesioned controls.<sup>10</sup> In addition, the percentage of DAergic loss in substantia nigra is positively correlated with the severity of levodopa-induced involuntary movements in a rat model.<sup>11</sup> These findings were indirectly confirmed by the finding that in dopamine-responsive dystonia, where in contrast to PD the nigrostriatal terminals are preserved, the chronic administration of levodopa is not related to the development of LID.<sup>12</sup> One model that could explain the close relation between nigrostriatal denervation and LID is based on the dysregulation of release and reuptake of DA from the synaptic cleft. In the normal brain as well as in the early phase of PD, where only minor nigrostriatal degeneration is observed, exogenously administered levodopa is incorporated in DAergic neurons, converted to DA, and released via vesicles in the synaptic cleft. The action of DA at the synapse is terminated by its clearance across the presynaptic membrane with the action of the DA-reuptake transporter. With disease progression and further DAergic cell loss, this machinery of DA conversion and regulation is severely compromised, and the availability of DA depends highly on the pharmacokinetic characteristics and the bioavailability of exogenous levodopa, which explains the occurrence of LIDs in relation to levodopa dosage. Moreover, other cells, such as serotonergic neurons, try to compensate for the DAergic loss by converting exogenous levodopa to DA. However, these cells are not equipped with the proper regulatory machinery at the presynaptic level, which results in a defective release and reuptake of synaptic DA, thus leading to an abnormal and irregular postsynaptic stimulation of the striatal DA receptors.<sup>13–16</sup>

## Emerging treatments for LID

Treating LID or preventing its appearance is an open challenge in the field of PD treatment. In the last few decades, the consensus that providing continuous DAergic stimulation would modulate the expression of LIDs led to the development of several therapeutic approaches that unfortunately were found to be only partially effective. These approaches were based on the use of DA agonists that reduced the risk of motor complications, but were proved to be less effective regarding the control of parkinsonian symptoms in comparison to levodopa, and most importantly were associated with

serious adverse effects. The *N*-methyl-d-aspartate (NMDA) antagonist amantadine, despite being far from a perfect drug, is the only widely used antidyskinetic agent in everyday clinical practice (see details later in this paper). On the other hand, the introduction of Duodopa and deep-brain stimulation made possible the reduction of daily levodopa dosage and proved to be very beneficial, especially for patients with severe disabling LIDs.<sup>17,18</sup> However, both interventions are invasive, restricted to specific selection criteria and certainly not side effect-free.

In recent years, great effort has been made to characterize non-DAergic mechanisms that contribute to LID expression. These include changes in glutamatergic, serotonergic, adenosine, adrenergic, and cholinergic neurotransmission. The pharmacological targeting of compounds related to those systems could reduce or prevent and delay the development of LIDs. Therefore, preclinical and clinical research is currently focused on developing and testing novel agents that influence both DAergic and non-DAergic transmission (for clinical trials see Table 1).

### Glutamate-receptor antagonists

There are ample data suggesting an active involvement of glutamate receptors (GluRs) in the acute expression and development of LID. Although several mechanisms have been suggested, it seems that changes in thalamo- and corticostriatal glutamatergic transmission are of significant importance. The striatum receives massive cortical and thalamic glutamatergic inputs. In PD patients with LID, an increase in NMDA-, metabotropic Glu (mGlu)-, and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor binding have been reported.<sup>19</sup> This might explain the loss of spines in medium spiny neurons, since DAergic neurons in the substantia nigra appear to be hypersensitive to glutamatergic action.<sup>20</sup> The Glu-mediated neuronal degeneration in turn facilitates the expression of LIDs after levodopa treatment, as mentioned earlier.

### NMDA antagonists

Significant changes in the synaptic abundance of NMDA receptors have been found in the striata of dyskinetic animals.<sup>21</sup> Moreover, abnormal phosphorylation and synaptic redistribution of several NMDA-subunit receptors seem to play an important role in the expression of dyskinesias, and have been reported in the dyskinetic state.<sup>22–24</sup> Despite existing data at the preclinical level showing the antidyskinetic effect of several NMDA modulators, the results from clinical trials using NMDA antagonists for the treatment of LID have

been so far not that exciting. This is mainly due to the limited therapeutic effect and the potentially serious adverse effects associated with a nonselective blockade. Therefore, no agent of this group, including amantadine, has been approved for the treatment of dyskinesia.

Amantadine, a low-affinity, noncompetitive NMDA-receptor antagonist, proved to be effective in reducing LIDs in preclinical and clinical settings, providing strong evidence for the involvement of the glutamatergic system in the pathophysiology of LIDs. Early animal studies showed that amantadine improved LIDs without significant loss of the levodopa-induced antiparkinsonian benefit.<sup>25,26</sup> Later, a significant number of clinical trials confirmed these results in patients with PD.<sup>27–30</sup> However, other studies raised questions about the duration of the antidyskinetic effect of amantadine, and the results were controversial. Thomas et al reported loss of effect after 9 months,<sup>31</sup> whereas other studies reported long-term benefits from amantadine.<sup>27,32</sup> Recently, it has been shown that treatment with amantadine prior to the use of levodopa neither delayed onset of LID nor reduced the incidence of LID.<sup>33</sup>

Currently, there is an ongoing multicenter, randomized, double-blind, placebo-controlled study to evaluate the tolerability and efficacy of each of three dose levels of ADS-5102 oral capsules, an extended-release formulation of amantadine, dosed once daily for the treatment of LID in subjects with PD. The use of ADS-5102 is expected to improve safety and tolerability of amantadine via the stabilization of its plasma concentrations during the day and overnight (NCT01397422).<sup>34</sup>

Other agents that block NMDA receptors have also been tested in PD patients with motor fluctuations. In randomized clinical studies, remacemide, an uncompetitive NMDA-receptor antagonist, and riluzole, an antiglutamatergic compound that can also inhibit NMDA receptors noncompetitively, showed no antidyskinetic effect,<sup>35,36</sup> whereas dextromethorphan reduced dyskinesia by only 30%–40% without affecting the beneficial effect of levodopa.<sup>37</sup> Dextromethorphan is rapidly and extensively metabolized by hepatic cytochrome P450 (CYP)-2D6. Therefore, without blocking CYP2D6, plasma dextromethorphan levels in some recipients have been undetectably low.<sup>38</sup> A clinical trial to evaluate the efficacy, safety, and tolerability of AVP-923 capsules containing 45 mg dextromethorphan and 10 mg quinidine (a potent CYP2D6 inhibitor) compared to placebo for the treatment of LID in patients with PD is currently recruiting participants (NCT01767129).<sup>39</sup>

Memantine is also a potent nonselective NMDA inhibitor, and its efficacy against LIDs has been tested in an early

study, with no improvement reported.<sup>40</sup> However, a recent small double-blind, placebo-controlled pilot study in PD patients with axial symptoms and motor fluctuations showed that memantine slightly reduced LIDs.<sup>41</sup> Accordingly, the introduction of memantine to daily medication significantly improved LID in several patients with motor complications, whereas other antidyskinetic drugs failed to do so.<sup>42,43</sup> Given the good tolerability and safety of memantine and the aforementioned positive reports, a clinical trial designed to evaluate the efficacy of memantine further for the treatment of LIDs would have been of significant value.

During the last few years, a number of studies have tested selective NMDA antagonists in the treatment of LIDs, though without impressive results so far. The NMDA-subunit NR2B-specific inhibitor CP-101,606 prevented the expression of levodopa-induced motor complication in a rat model of PD<sup>44</sup>; however, another study using a different animal model failed to report its beneficial antidyskinetic effect.<sup>45</sup> CP-101,606 has been tested in a randomized, double-blind, placebo-controlled clinical trial and failed to improve parkinsonism, showing only mild antidyskinetic action. Moreover, tolerability issues have been raised, since dose-related side effects, such as amnesia and dissociation, have been reported.<sup>46</sup>

Neu-120 is a highly potent and selective uncompetitive NMDA-receptor modulator aiming at reducing LID. It also inhibits monoamine oxidase B (MAO-B) and glycogen synthase kinase-3 $\beta$  activities *in vitro*, but does not interact with other receptors, transporters, or enzymes. Neu-120 has been tested in several experimental models of PD and a completed Phase I study (unpublished data, <http://www.neurim.com/products>), and currently a clinical trial is evaluating its efficacy in reducing LID in patients with advanced-phase idiopathic PD and motor-response complication (NCT00607451).<sup>47</sup>

### Metabotropic glutamate-receptor antagonists

mGlu receptors (mGluRs) are found abundantly in the basal ganglia, and they regulate neuronal excitability and synaptic functions. A significant number of preclinical studies have highlighted the involvement of mGluRs in the pathophysiology of LIDs. Pharmacological and neuroimaging studies failed to report an involvement of mGlu2/3 receptors in LID,<sup>48,49</sup> and thus the mGlu5 subtype seems to play a key role in the treatment of LIDs.

mGlu5Rs interact strongly with NMDA receptors and amplify their currents. Antagonists of mGlu5 reduce overactivity of NMDA receptors and resulting overexcitability, both important factors in the expression of LIDs.

Interestingly, several studies suggested a neuroprotective role of the mGlu5 blockade, possibly by delaying neuronal degeneration.<sup>50,51</sup> The results from preclinical studies testing mGlu5 inhibitors against LIDs are exciting.<sup>52–55</sup> Perhaps the first study to report that mGlu5 antagonists may prove useful for the symptomatic treatment of LID was Dekundy et al. In this study, MTEP (((2-methyl-1,3-thiazol-4-yl)ethynyl)pyridine) alleviated LID (at 2.5 and 5 mg/kg) in 6-hydroxy-DA-lesioned rats.<sup>56</sup>

mGlu5 antagonists have been recently tested in humans as well. AFQ056, a novel mGlu5 antagonist, reduced LIDs in an animal model without affecting the antiparkinsonian effect of levodopa.<sup>57</sup> In the clinical setting, two studies by Berg et al demonstrated that AFQ056 successfully alleviated established LIDs without worsening other parkinsonian features. Patients with moderate-to-severe LID (study 1) and severe LID (study 2) on stable DAergic therapy received 25–150 mg AFQ056 or placebo twice daily for 16 days. Using dyskinesia and involuntary-movement scales, both studies showed that AFQ056-treated patients exhibited a statistically significant clinical improvement in comparison to placebo-treated patients. Mild side effects, such as fatigue, psychiatric and gastrointestinal disorders, and most commonly dizziness, have been reported in both studies. Worsening of dyskinesia associated with stopping treatment was the most common serious adverse effect in both studies.<sup>58</sup> Another recent clinical trial tested AFQ056 in several doses versus placebo, and demonstrated that with 200 mg daily a significant antidyskinetic effect without worsening of motor symptoms. However, similar to previous studies, AFQ056 was associated with increased adverse effects, with dizziness, fatigue, hallucination, and dyskinesia being the most common.<sup>59</sup> A clinical trial to assess the long-term safety, tolerability, and efficacy of AFQ056 is ongoing (NCT01173731).<sup>60</sup>

A randomized, double-blind, placebo-controlled clinical study on safety and tolerability of dipraglurant (AX48621), a negative allosteric modulator of mGlu5, was recently published. The secondary objectives of the study included the evaluation of the compound's efficacy in reducing LID compared with placebo in patients with PD. Dipraglurant showed no adverse effect on levodopa efficacy, increased daily "on" time without dyskinesia, reduced daily "off" time, and improved dyskinesia. No safety or tolerability issues have been raised (NCT01336088).<sup>61</sup>

### AMPA-receptor antagonists

The promising antidyskinetic results from NMDA-receptor antagonism prompted many researchers to investigate other

receptors of the glutamatergic system, such as the AMPA receptors, as potential contributors in the expression of LID. More evidence regarding the involvement of AMPA receptors came from early studies in primates, where talampanel, an AMPA-receptor antagonist, enhanced the antiparkinsonian effect and improved LIDs.<sup>62</sup> Several clinical studies (NCT00108667,<sup>63</sup> NCT00036296,<sup>64</sup> NCT00004576<sup>65</sup>) evaluated the effect of talampanel in PD and LID, but so far no data have been published.

Recently, three clinical studies testing perampanel, a selective non-competitive AMPA-type Glu-receptor antagonist, have been published. All of them reported no significant changes in PD symptoms and dyskinesia in any perampanel group versus placebo.<sup>66–68</sup> To the best of our knowledge, no further clinical trials testing AMPA-receptor antagonists have been announced.

## $\alpha$ 2-Adrenergic-receptor antagonists

A significant number of studies have suggested an important role for  $\alpha$ - and  $\beta$ -adrenergic receptors in the expression of the dyskinetic phenotype. Most of the studies have been focused on the  $\alpha$ 2-adrenergic-receptor antagonists idazoxan and fipamezole, and both have been found to be effective in reducing LID when administered in animals.<sup>69–71</sup>

The data in the clinical setting, though, are somehow controversial. Idazoxan showed antidyskinetic properties in patients with LID,<sup>72</sup> but the same dosage in another trial proved to be ineffective and caused adverse effects.<sup>73</sup> Fipamezole was tested in a double-blind, randomized, placebo-controlled, dose-escalating 28-day study in patients with LID from the US and India, and was found to be effective only in the US subpopulation.<sup>74</sup> Two other studies to evaluate mainly safety and tolerability issues, as well as the maximum tolerated dosage in patients with PD who are receiving levodopa, have been conducted (NCT01140841,<sup>75</sup> NCT01149811<sup>76</sup>). To our knowledge, no results have been published so far.

## Adenosine A<sub>2A</sub>-receptor antagonist

Presynaptic A<sub>2A</sub> adenosine receptors are abundantly expressed in basal ganglia, and can modulate  $\gamma$ -aminobutyric acid (GABA)-ergic synaptic transmission by increasing the excitability of medium spiny neurons in the striatum and by enhancing GABA inhibition in globus pallidus projection neurons. On the other hand, DA in the intact caudate–putamen dampens this activity. Hence, in the DA-depleted caudate–putamen in PD, A<sub>2A</sub>-receptor antagonists could modulate striatopallidal output balance and alleviate

parkinsonian symptoms by preventing the excessive activity of striatopallidal neurons.<sup>77,78</sup>

Additionally, A<sub>2A</sub> adenosine receptors participate in the planning and execution of movements, probably by influencing D<sub>2</sub>- and D<sub>1</sub>-receptor activity.<sup>79</sup> Similarly to Glu, adenosine-receptor activity is increased in the parkinsonian state, and this might inhibit motor activity.<sup>80</sup> The A<sub>2A</sub> adenosine-receptor antagonists modulate (probably via regulation of specific neuropeptides, such as dynorphin and enkephalin) the effects of chronic levodopa administration in synaptic plasticity and contribute possibly to the expression of LID.<sup>81</sup>

This profound implication, despite the relative lack of solid data on the effectiveness of A<sub>2A</sub> adenosine receptor antagonists against LID in the preclinical setting, led several researchers to test adenosine A<sub>2A</sub>-receptor antagonists in patients with PD. Preladenant (Sch 420814), a potent and selective competitive antagonist of the A<sub>2A</sub> adenosine receptor, showed promising results in mouse models of movement disorders,<sup>82,83</sup> but failed to influence LID positively in a Phase II, double-blind, randomized trial where “on” time troublesome or nontroublesome dyskinesia was included as a secondary outcome.<sup>84</sup> However, a significant increase in “off” time has been reported. A subsequent long-term, multicenter, open-label safety and tolerability extension of that study in subjects with fluctuating PD has been recently published. The improvement in “on” and “off” times was sustained, but no antidyskinetic effects have been reported; on the contrary, the preladenant group showed increased dyskinesia rates.<sup>85</sup>

Istradefylline, another adenosine A<sub>2A</sub> antagonist, proved to be mildly effective in relieving wearing-off fluctuations in PD patients. However, similarly to preladenant, regarding the troublesome and nontroublesome dyskinesia, the addition of the drug was associated with a slight increase in “on” time with dyskinesia, and dyskinesia was reported as an adverse event more commonly in istradefylline- than in placebo-treated groups.<sup>86–89</sup> In the most recent study, in 610 patients with PD and motor fluctuations, the primary outcome – reduction in “off” time – was not met, but 40 mg istradefylline per day significantly improved motor score (Unified PD Rating Scale [UPDRS]). However, as previously mentioned, the most commonly reported drug-related adverse effect was dyskinesia (placebo, 2.5%; 20 mg/day istradefylline, 8.5%; 40 mg/day istradefylline, 6.4%).<sup>88</sup>

Bara-Jimenez et al suggested in an early study that only after lowering the levodopa dose did istradefylline show a clear antidyskinetic effect,<sup>90</sup> yet more data and clinical trials are needed in order to further test this finding.

Recently, a double-blind, randomized, placebo-controlled study of the safety and efficacy of tozadenant (SYN115) in PD patients with “wearing-off” fluctuations, including evaluation of dyskinesia as a secondary outcome measure, was published. Patients in tozadenant-treated groups, especially those who received 120 mg and 180 mg, reported significant improvement in primary outcomes, without any effect on the expression of troublesome dyskinesias in comparison to placebo.<sup>91</sup>

### Nicotinic acetylcholine-receptor agonists

Nicotinic receptors have been also implicated in the expression of LID in PD. Nicotinic receptors colocalize with DA receptors,<sup>92</sup> and although the mechanism by which the activation of nicotinic receptors influences the expression of LIDs remains unknown, it is believed that this effect is mediated via regulation of DA release in striatum.<sup>93</sup>

Nicotine, a nonspecific agonist of nicotinic receptors, is very effective in preventing the occurrence of LIDs and reducing established LIDs in several parkinsonian animal models.<sup>94–97</sup> However, all the preclinical results come from just one laboratory, and thus should be interpreted with caution. The antidyskinetic efficacy of nicotine has been rather disappointing in clinical settings. Nicotine is poorly tolerated, showing side effects related to the autonomic nervous system, possibly due to its nonspecificity towards critical nicotinic receptors.<sup>98</sup> Interestingly, SIB-1508Y, despite being selective for  $\alpha_4\beta_2$  nicotinic acetylcholine-receptor agonists, showed very low tolerability as well, and the randomized placebo-controlled study testing its efficacy in patients with PD had to be redesigned.<sup>99</sup>

Pharmacological studies with nicotinic-receptor agonists have focused on their potential to improve parkinsonian symptoms, but none of them included the antidyskinetic effect as a primary outcome. Improvement in motor scales have been reported by Villafane et al,<sup>100</sup> while Vieregge et al, in a randomized double-blind study, suggested that transdermal nicotine as an add-on treatment is not effective for the treatment of PD symptoms.<sup>101</sup> Recently, a study where nicotine dehydrate bitartrate was given as an oral capsule instead of a transdermal patch was completed, but to date no data have been published (NCT00957918).<sup>102</sup>

At the preclinical level, there is growing evidence that the nicotine-mediated improvement in LIDs involves specific receptors’ subunits.<sup>103,104</sup> Therefore, in the future, drugs that act more selectively at specific subunits of nicotinic receptors could be an attractive approach for the treatment of LIDs.

### Partial dopamine agonists

Partial DA agonists are pharmacological agents able to occupy DA receptors fully (mainly  $D_2$  or  $D_3$ ) without producing the maximum pharmacological response, as the full agonists do. This might stabilize the DAergic tone in the DA-depleted network, thus preventing the appearance of motor fluctuations and LID, especially when a mild antiparkinsonian effect is required.

Aripiprazole, a partial agonist of  $D_2$  DA and 5-hydroxytryptamine<sub>1A</sub> (5-HT<sub>1A</sub>) receptors with known antipsychotic action, was well tolerated and reduced significantly the intensity and the frequency of LID in PD patients, while other antidyskinetic treatments failed to do so.<sup>105</sup> Similarly, preclinical data revealed the antidyskinetic profile of another partial DA  $D_2$  agonist, pardoprunox.<sup>106</sup> At the clinical level, pardoprunox was assessed regarding UPDRS motor score<sup>107</sup> as well as “on” time without troublesome dyskinesias,<sup>108</sup> and was found to be effective in comparison to placebo. Doses up to 18 mg/day were well tolerated.<sup>109</sup>

Aplindore has also been tested in patients with PD, but no data have been published yet (NCT00623324).<sup>110</sup>

### Monoamine oxidase-B inhibitors

The pharmacological action of MAO-B inhibitors is the blockade of the enzymatic metabolism of DA in the brain, thus increasing DA concentrations. Based on the idea that an adjunct therapy to levodopa could delay the occurrence of LID, several studies have investigated the effect of MAO-B inhibitors in LID. Waters et al showed that in PD patients who were experiencing motor fluctuations under treatment with levodopa, the time in a dyskinesia-free state was significantly increased in the selegiline patients compared with the placebo group.<sup>111</sup> Similarly, rasagiline increased daily “on” time without troublesome dyskinesia when used as an add-on therapy in patients with PD and motor fluctuations.<sup>112</sup>

Safinamide, a novel MAO-B and Glu-release inhibitor, reduced LID and increased the duration of the antiparkinsonian response of levodopa in parkinsonian animals.<sup>113</sup> Several other clinical studies have investigated the effect of safinamide in patients with early PD without motor fluctuation. In a recent placebo-controlled, double-blind trial, a large cohort of patients with mid- to late-stage idiopathic PD with “wearing-off” symptoms and LIDs under optimal treatment received safinamide (50 mg or 100 mg) or placebo as an add-on therapy. In the 50 mg safinamide group, patients showed significant increases in “on” time without worsening of LIDs, whereas in patients who had severe dyskinesia (Dyskinesia

**Table 1** Clinical trials for the treatment of LIDs in PD

Pharmacological class	Substance (references of completed clinical trials)	Outcome*
NMDA antagonists	Amantadine <sup>27–33</sup>	Effective against LIDs, controversy concerning the duration of antidyskinetic effect
	ADS-5102 <sup>34</sup>	NCT01397422 (ongoing trial)
	Remacemide <sup>35</sup>	No antidyskinetic effects
	Dextromethorphan <sup>37</sup>	Reduced dyskinesia by 30%–40%
	AVP-923	NCT01767129 (ongoing trial)
	Memantine <sup>40–42</sup>	Possibly effective against LIDs, good tolerability and safety
	CP-101,606 <sup>46</sup>	Mild antidyskinetic effect, no improvement in parkinsonism, side effects
mGluR antagonists	Neu-120	NCT00607451 (status unknown)
	AFQ056 <sup>58,59</sup>	Reduced established LIDs, no negative effect on parkinsonism, safety and tolerability concerns NCT01173731 (ongoing trial)
AMPA antagonists	Dipraglurant (AX48621) <sup>61</sup>	Improved parkinsonism and dyskinesia NCT01336088 (completed)
	Talampanel	NCT00108667, NCT00036296, NCT00004576 (all trials completed, but no published data available)
$\alpha$ 2-adrenergic receptor antagonists	Perampanel <sup>66–68</sup>	No antidyskinetic effects
	Idazoxan <sup>72,73</sup>	Controversial results concerning effectiveness and adverse-effects profile
	Fipamezole <sup>74</sup>	Only partially effective NCT01149811, NCT01140841 (completed, no published data available)
Adenosine A <sub>2A</sub> receptor antagonist	Preladenant (Sch 420814) <sup>84,85</sup>	Increase in dyskinesia rates, improvement in parkinsonism
	Istradefylline <sup>86–90</sup>	Improvement in UPDRS, increased dyskinesia rates
	Tozadenant (SYN115) <sup>91</sup>	No effect in dyskinesia, improvement in parkinsonian symptoms
Nicotinic receptors agonists	Nicotine <sup>98,100,101</sup>	Serious adverse effects NCT00957918 (completed, no published data)
	SIB-1508Y	Very low tolerability <sup>a</sup>
Partial dopamine agonists	Aripiprazole <sup>105</sup>	Effective against LIDs, well tolerated
	Pardoprunox <sup>107,108</sup>	Effective against LIDs and improvement in UPDRS motor score
	Aplindore	NCT00623324 (completed, no published data available)
Monoamine oxidase-B inhibitors	Selegiline <sup>111,115,116</sup>	Controversial results concerning efficacy against LIDs
	Rasagiline <sup>112</sup>	Partially effective against LIDs
	Safinamide <sup>114</sup>	Improvement of LIDs
5HT agonists	Tandospirone <sup>118</sup>	No antidyskinetic effects, worsening of parkinsonism
	Sarizotane <sup>119,121,122</sup>	Controversial results concerning efficacy against LIDs, probably not effective
	Piclozotan	NCT00623363 (completed, no published data available)
Other treatments	Valproate <sup>125</sup>	No antidyskinetic effect
	Gabapentin <sup>126</sup>	No antidyskinetic effect
	Zonisamide <sup>127</sup>	Dose-dependent effectiveness against LIDs
	Levetiracetam <sup>128–130,133</sup>	Only mild antidyskinetic effect
	Topiramate	NCT00296959 (early termination due to slow recruitment)
	ACR325 (odopidine)	NCT01023282 (completed, but no published data are available)

**Notes:** \*Study redesigned due to tolerability issues; \*status verified on August 22, 2013.

**Abbreviations:** LIDs, levodopa-induced dyskinesias; PD, Parkinson's disease; NMDA, N-methyl-d-aspartate; mGluRs, metabotropic glutamate receptors; AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; 5HT, 5-hydroxytryptamine; UPDRS, Unified Parkinson's Disease Rating Scale.

Rating Scale >4) and received 100 mg safinamide, both motor fluctuations and LIDs were improved.<sup>114</sup>

On the other hand, the addition of an MAO-B inhibitor increases the availability of DA at the nigrostriatal synapse, and this could lead to an increased occurrence of LIDs. Shoulson et al tested individuals with PD, initially treated with deprenyl (selegiline) who in the progress of the disease had required levodopa. Continuing deprenyl was associated with increased incidences of dyskinesia in comparison to individuals who changed to a matching placebo under double-blind conditions.<sup>115</sup> The meta-analysis performed by Talati et al, which included the Shoulson et al study,

confirmed that coadministration of selegiline with levodopa increases the incidence of LID, despite the decreased need for levodopa.<sup>116</sup>

## 5-HT agonists

There is growing evidence that implicates the serotonergic system in the pathophysiology of LID;<sup>16,117</sup> however, the exact mechanism is still unknown. As mentioned above, it has been suggested that DAergic degeneration causes the raphestriatal serotonergic system to convert exogenous levodopa to DA that is released and acts as a “false neurotransmitter,” which in the absence of autoregulatory mechanisms proper

to DAergic transmission determines the expression of LIDs. However, in the clinical setting tandospirone failed to induce a clear antidyskinetic effect, and in addition it may worsen the antiparkinsonian effect of levodopa.<sup>118</sup> Similarly, sarizotan, a compound with full 5-HT<sub>1A</sub>-agonist properties and additional high affinity for D<sub>3</sub> and D<sub>4</sub> receptors, despite initial data showing promising antidyskinetic effects,<sup>119</sup> failed to improve dyskinesia significantly in two later double-blind, placebo-controlled, multicenter, multinational trials designed to assess its efficacy and safety in PD patients suffering from LIDs.<sup>120-122</sup>

Piclozotan, a 5-HT<sub>1A</sub>-receptor agonist, significantly reduced levodopa-induced forelimb hyperkinesias and improved motor complications in a rat model of advanced PD. A pilot study with primary outcome measure the “on” time without dyskinesia, testing also adverse effects and pharmacokinetic data of the drug, has been recently completed (NCT00623363).<sup>123</sup> No preliminary data are available so far.

Bezard et al tested the effects of eltoprazine, a mixed 5-HT<sub>1A/1B</sub>-receptor agonist, in LIDs in two experimental animal models of PD. The compound proved to be very effective in reducing LID, and was found to potentiate synergistically the antidyskinetic action of amantadine. However the administration of eltoprazine was associated with a worsening of the parkinsonian symptoms.<sup>124</sup> The study was based on previous data showing that a lesion in the serotonergic system or the administration of a 5-HT<sub>1A</sub> and a 5-HT<sub>1B</sub> agonist (and especially their coadministration) resulted in a spectacular decrease of LID. These intriguing results found recent confirmation in a clinical trial testing the antidyskinetic action of eltoprazine; however, to date no publication is available. According to the press release of the study, eltoprazine exhibited a statistically significant reduction in LID at the 5 mg dose ( $P=0.0007$ ) and the 7.5 mg dose ( $P=0.0467$ ), while no tolerability and safety issues have been raised ([http://www.psychogenics.com/pdf/Positive\\_Efficacy\\_Data\\_in\\_Levodopa\\_Induced\\_Dyskinesia.pdf](http://www.psychogenics.com/pdf/Positive_Efficacy_Data_in_Levodopa_Induced_Dyskinesia.pdf)).<sup>125</sup>

## Other treatments

A therapeutic class of agents that has been intensively tested for the efficacy against LIDs despite having a very different pharmacological profile is anticonvulsants. One of the very first studies to test the antidyskinetic effects of anticonvulsants came from Price et al, who tested sodium valproate for the treatment of LIDs in a double-blind crossover trial with matched placebo and found no significant effect.<sup>126</sup> In the next two decades, several other antiepileptic agents were

tested regarding the effectiveness against motor fluctuations in PD. Gabapentin failed to improve LIDs.<sup>127</sup> Zonisamide significantly improved PD symptoms, but the positive effect on LID was not consistently documented (improvement only in the 50 mg group, but not in the 25 mg and 100 mg groups versus placebo has been reported).<sup>128</sup> Similarly, levetiracetam, despite existing data suggesting the opposite,<sup>129</sup> seems to have only mild antidyskinetic effects<sup>130,131</sup> in a wide range of doses. In an MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-lesioned marmoset model of PD, treatment with topiramate, a Glu antagonist, significantly improved LID without affecting the antiparkinsonian action of levodopa, thus making topiramate a potentially attractive therapeutic approach for LIDs. However, the only clinical crossover trial to assess the antidyskinetic properties of topiramate in patients with PD and LID was terminated due to slow recruitment, and no data have been published to date (NCT00296959).<sup>132</sup> Dopidines are a new pharmacological class of agents that act primarily on DA D<sub>2</sub> receptors in a dual way (agonist or antagonist), and therefore they are known as DA stabilizers. Pridopidine, the most widely used compound, was found to be effective as a psychomotor stabilizer, and in clinical studies improved motor function in patients with Huntington’s disease.

Based on unpublished preclinical data and positive Phase I results (<https://newsclient.omxgroup.com/cdsPublic/viewDisclosure.action?disclosureId=368187&messageId=439581>), a clinical study has been initiated, with safety and tolerability being the primary outcome and the effect of ACR325 (odopidine) on established LIDs the secondary outcome of the study. The trial has been completed, but no published data are available (NCT01023282).<sup>133</sup>

## Conclusion

The management of LID has proved to be a challenging issue in the field of PD treatment. The appearance of LID is not only an unfortunate emergence in the course of PD, having serious negative effects on the quality of the patient’s life, but also limits the use of levodopa, the most effective agent so far for the symptomatic control of the disease.

Levodopa induces priming actions due to chronic pulsatile DAergic stimulation, and this is the reason that research interest has been focused, in the last few decades, on agents that could provide more continuous DAergic stimulation. However, this strategy appeared to have several limitations, and the control of LID remained an unsolved problem. Recent findings regarding the pathophysiology of LIDs turned scientific interest towards non-DAergic pathways as



possible targets for modulating the emergence of LIDs. The results from numerous neuroimaging and pharmacological studies in animals plus postmortem findings were in some cases impressive, and a number of compounds have been further tested in humans. Several studies reported positive results, most notably those using mGluR antagonists and partial DA agonists. However, the majority of the pharmacological agents failed to confirm previously reported safety, tolerability, and effectiveness, a typical example being the antagonists of NMDA and AMPA Glu receptors.

Given the effectiveness (though limited) of amantadine against LID, the positive preclinical data, and the undisputed involvement of NMDA receptors in the pathophysiology of levodopa-induced motor complications, NMDA-receptor antagonists entered the clinical setting as a very promising group of agents for the treatment of LIDs. However, the classical agents that block NMDA receptors in a nonspecific way (remacemide and dextromethorphan) proved to be ineffective in improving LIDs. Similarly, the highly promising results from selected AMPA-receptor antagonists were not confirmed in the clinical setting. The reason for this discrepancy is unknown. Given the structural differences and the degree of complexity between human and rodent brains, one might expect differences in effectiveness and the adverse effects. Moreover, the high prevalence of adverse effects might be associated with the abundance of NMDA receptors in other brain areas, which are not directly involved in motor functions in PD. However, a significant number of clinical trials were based on preclinical data on primates, where this obvious explanation would lose much of its strength. The time the animals were killed during the priming phase (“on” or “off” state) and the lack of a behavioral correlate could also explain discrepancies between clinical data and postmortem findings in animal models.<sup>134</sup>

NMDA receptors consist of several receptor subunits. Studies in experimental models demonstrated that the expression and development of LIDs are associated with changes in selected NMDA subunits, mostly NR2A and NR2B, with the ratio between these two in the molecular composition of NMDA receptors playing a crucial role in the occurrence of LIDs (reviewed in Huot et al).<sup>135</sup> So far, the results from clinical trials using selective NMDA-receptor antagonists, despite positive preclinical data, have been limited and not that exciting. Differences between toxin-induced parkinsonism in animals and idiopathic PD, as well as differences in the doses of the administered agents, could only partially explain this discrepancy. In the future, determining the specific role of each receptor subunit in the establishment

of LID could provide additional information concerning its pathophysiology and facilitate the development of an agent with better selectivity and improved safety.

In conclusion, no truly innovative therapies have come to light in recent years, and treatment options against LIDs remain limited. Maybe what is missing are more sophisticated agents capable of acting in a specific way on several pathways involved in the expression of LID, thus causing a synergistic antidyskinetic effect. However, the recent widening of research focus on non-DAergic pathways in itself is an innovative step towards novel therapeutic approaches, which will hopefully soon lead to more fruitful results regarding this disabling effect of levodopa treatment.

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