Review Article

Current Nondopaminergic Therapeutic Options for Motor Symptoms of Parkinson's Disease

Juan-Juan Du, Sheng-Di Chen

Department of Neurology and Institute of Neurology, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

Abstract

Objective: The aim of this study was to summarize recent studies on nondopaminergic options for the treatment of motor symptoms in Parkinson's disease (PD).

Data Sources: Papers in English published in PubMed, Cochrane, and Ovid Nursing databases between January 1988 and November 2016 were searched using the following keywords: PD, nondopaminergic therapy, adenosine, glutamatergic, adrenergic, serotoninergic, histaminic, and iron chelator. We also reviewed the ongoing clinical trials in the website of clinicaltrials.gov.

Study Selection: Articles related to the nondopaminergic treatment of motor symptoms in PD were selected for this review.

Results: PD is conventionally treated with dopamine replacement strategies, which are effective in the early stages of PD. Long-term use of levodopa could result in motor complications. Recent studies revealed that nondopaminergic systems such as adenosine, glutamatergic, adrenergic, serotoninergic, histaminic, and iron chelator pathways could include potential therapeutic targets for motor symptoms, including motor fluctuations, levodopa-induced dyskinesia, and gait disorders. Some nondopaminergic drugs, such as istradefylline and amantadine, are currently used clinically, while most such drugs are in preclinical testing stages. Transitioning of these agents into clinically beneficial strategies requires reliable evaluation since several agents have failed to show consistent results despite positive findings at the preclinical level.

Conclusions: Targeting nondopaminergic transmission could improve some motor symptoms in PD, especially the discomfort of dyskinesia. Although nondopaminergic treatments show great potential in PD treatment as an adjunct therapy to levodopa, further investigation is required to ensure their success.

Key words: Dyskinesias; Motor Fluctuations; Nondopaminergic Options; Parkinson Disease

Introduction

Parkinson's disease (PD) is caused by neurodegeneration of nigrostriatal pathways and is characterized by a series of motor symptoms (bradykinesia, rigidity, postural instability, and static tremor), which are caused by progressive dopamine loss in the substantia nigra (SN) pars compacta. Dopamine replacement therapy, currently the most efficacious and gold standard treatment for PD, mainly comprises the use of the dopamine precursor levodopa (L-DOPA), dopamine agonists, monoamine oxidase B inhibitors, and catechol-O-methyltransferase inhibitors.[1] Long-term use of L-DOPA may result in several complications, including motor fluctuations and levodopa-induced dyskinesia (LID), which cause serious distress to patients. Moreover, symptoms that appear at the later stages of PD are often not responsive to dopaminergic treatments. The development of these symptoms could involve the degeneration of nondopaminergic systems, leading to PD.[2] The development of novel nondopaminergic treatments is therefore of great clinical interest. Continuous studies have shown that the mechanism of PD involves many nondopaminergic mechanisms including adenosine receptors (ARs), glutamatergic, adrenergic, serotoninergic, histaminic, and iron chelator pathways.[3-6] Targeting nondopaminergic systems could prove an effective

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.211555

Address for correspondence: Prof. Sheng-Di Chen, Department of Neurology and Institute of Neurology, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China
E-Mail: chen_sd@medmail.com.cn

Received: 01-05-2017 **Edited by:** Yuan-Yuan Ji

How to cite this article: Du JJ, Chen SD. Current Nondopaminergic Therapeutic Options for Motor Symptoms of Parkinson's Disease. Chin Med J 2017;130:1856-66.

alternative approach to enhance efficacy and improve motor complications in PD.[7] The aim of this article was to review currently available nondopaminergic therapeutic options, including clinically available options and those in clinical trials, for motor symptoms and motor complications in PD.

Search and Selection Criteria

Papers in English published in PubMed, Cochrane, and Ovid Nursing databases between January 1988 and November 2016 were searched using the following keywords: PD, nondopaminergic therapy, adenosine, glutamatergic, adrenergic, serotoninergic, histaminic, and iron chelator. We also reviewed the ongoing clinical trials in the website of clinicaltrials.gov. The classification of each nondopaminergic therapy is shown in Table 1.

Adenosine Options

Adenosine A2A receptor antagonists

ARs, which are seven-transmembrane G-protein-coupled receptors, are of four types, namely, A1, A2A, A2B, and A3.[8] Adenosine A2A receptors are abundantly located in γ-aminobutyric acid (GABA) ergic striatopallidal projection neurons and are closely associated with the indirect pathway of the basal ganglia system owing to the formation of receptor heteromers with the dopamine D2 receptors.[3] Blocking of A2A receptors contributes to dopamine D2 receptor function. In PD animal models, A2A receptor antagonists in the striatum inhibit the indirect pathway and reduce postsynaptic effects of dopamine depletion and thereby improve motor symptoms and decrease the speed of underlying neurodegeneration without inducing LID.[9] Moreover, A2A receptor antagonists can prolong the duration of dopaminergic action.[10] These findings strongly suggest that adenosine A2A antagonists could have clinical applications as adjunct therapies for patients with PD [Table 1].

Istradefylline, a selective adenosine A2A antagonist, recently licensed in Japan for clinical use as an adjunct treatment,[14,53] is capable of reducing off time in the management of motor complications in advanced PD.[12,15,54] However, treatment with istradefylline could result in adverse reactions, of which dyskinesia is the most common. Recently, a 52-week Phase III study in Japan showed that long-term administration of istradefylline (20 mg/d) was efficacious and caused an obvious reduction in off time despite mild-to-moderate dyskinesia.[54] However, there were controversial conclusions drawn on the benefits of istradefylline treatments in Phase II/III studies in the USA.[10,13,16,17] A Phase III study demonstrated that 10, 20, and 40 mg/d of istradefylline did not alter the duration of off time; only slight improvements in motor assessment were observed at 40 mg/d.[17] In contrast, positive results were described in other clinical trials in the preceding years.[10,13,16] The Food and Drug Administration approval was therefore not received. A subsequent 52-week Phase III trial to assess the effects of istradefylline in patients with moderate-to-severe PD is currently ongoing.[18] The improvement of motor function in early PD without provoking dyskinesia upon administration of istradefylline with low-dose dopaminergic drugs has been described in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated common marmosets.[55] Further istradefylline was reportedly safe and well tolerated as monotherapy for PD in a Phase II study, which showed great benefits based on the unified PD rating scale III (UPDRS III).[11]

Preladenant, another adenosine A2A antagonist, improved motor ability without worsening dyskinesia in rodent and primate models of PD.[56,57] A Phase II trial, assessing preladenant as an adjunct to levodopa in individuals with PD for 12 weeks, showed significant off time reduction upon treatment with 5 and 10 mg preladenant twice daily.[19] Moreover, preladenant was well tolerated. Another Phase II trial of long-term (36-week) preladenant treatment (5 mg twice a day) yielded similar findings.[20] However, in two Phase III and a Phase II trials, preladenant did not cause a clear reduction in off time compared with placebo,[21,22] and the failed results were attributed to inappropriate study design and execution. To the best of our knowledge, preladenant is no longer under study for the treatment of PD.

Tozadenant is another A2A antagonist that could alleviate motor fluctuation. The results of a small Phase IIa study suggested that tozadenant could cause an obvious decrease in thalamic cerebral blood flow following reduced pallidothalamic inhibition via the indirect pathway.[58] In a Phase IIb trial, tozadenant administered at 120 mg or 180 mg twice daily was generally effective in reducing off time.[23] A Phase III study is currently under way.[24] Combination treatments with tozadenant and other drugs have been tested in animal models. The A2A/NR2B receptor antagonist combination (tozadenant/radiprodil) could ameliorate motor symptoms without the side effects associated with dopaminergic treatment.[59] Other A2A antagonists that have progressed to Phase I clinical trials include ST1535, ST4206, ST3932, V81444, and PBF-509.[14]

A1/A2A receptor antagonists

Blocking of adenosine A1 receptors that are distributed throughout the cortex, hippocampus, and striatum has also resulted in motor activation in animal models.[60,61] Combined targeted blockage of A1 and A2A receptors could therefore synergistically provide a potential alternative to conventional PD treatments. Several novel adenosine A1/A2A antagonists that have been effective in treating motor deficits are based on the common structure of the synthesized 2-aminopyrimidine motif, with potent adenosine A1/A2A affinity.[62-66] Further studies on the physicochemical properties of these compounds are needed.

Nonspecific adenosine receptor antagonist

Caffeine is a nonspecific AR antagonist that has shown antiparkinsonian and neuroprotective effects in animal models of PD.[67,68] Caffeine could possibly increase excitatory activity in the striatopallidal area and inhibit astrocyte-induced

Table 1: Current nondopaminergic therapeutic options for motor symptoms in PD

Mechanism	Drugs	Stage	*n*	Dose	Duration	Results	Reference
Adenosine							
A2A receptor antagonist	Istradefylline	II	176	40 mg/d	12 weeks	Improvement in UPDRS III motor score	[11]
		II	363	20 or 40 mg/d	12 weeks	Reduction in off time	[12]
		II	196	40 mg/d	12 weeks	Reduction in off time	[10]
		II	395	20 or 60 mg/d	12 weeks	Reduction in off time	[13]
		III	373	20 or 40 mg/d	12 weeks	Reduction in off time	[14]
		III	308	20 or 40 mg/d	52 weeks	Sustained reduction in off time	[15]
		III	231	20 mg/d	12 weeks	Reduction in off time	[16]
		III	584	10, 20, or 40 mg/d	12 weeks	No reduction in off time, only improved motor score at 40 mg/d	[17]
		III		20 or 40 mg/d	12 weeks	Ongoing	[18]
	Preladenant	II	253	1, 2, 5, or 10 mg, bid	12 weeks	Reduction in off time	[19]
		II	106	5 mg, bid	36 weeks	Sustained reduction in off time	[20]
		II	450	2, 5, or 10 mg, bid	12 weeks	No reduction in off time	[21]
		III	778	2, 5, or 10 mg, bid	12 weeks	No obvious reduction in off time	[22]
		III	476	2 or 5 mg, bid	12 weeks	No obvious reduction in off time	[22]
	Tozadenant	II	420	60, 120, 180, or 240 mg, bid	12 weeks	Reduction in off time	[23]
		III	450	60 or 120 mg, bid	24 weeks	Ongoing	[24]
Nonspecific antagonist	Caffeine	III	119	200 mg, bid	5 years	Ongoing	[25]
Glutamate							
NMDA receptor antagonist	ADS-5102 (extended-release)	II	83	260, 340, or 420 mg/d	8 weeks	Reduction of LID, and increase in on time without troublesome LID	[26] (EASED study)
		III	77		13 weeks	Completed waiting for a result	[27] (EASE LID 3)
		III	126		25 weeks	Completed without results	[28] (EASE LID)
	Amantadine HCL (extended-release)	III	162	240 or 320 mg/d	16 weeks	Ongoing	[29] (ALLAY-LID I)
		III	162	240 or 320 mg/d	26 weeks	Ongoing	[30] (ALLAY-LID II)
	Mantadix	IV	80	200 mg/d	12 weeks	Reduction in severity of LID	[31]
	Memantine	III	15	20 mg/d	3 weeks	No significant change in LID	[32]
AMPA receptor antagonist	Perampanel	II	263	0.5, 1, 2 mg/d	12 weeks	No significant change in LID	[33]
		III	480	4 mg/d	18 weeks	No significant change in LID	[34]
		III	763	2 or 4 mg/d	30 weeks	No significant change in LID or off time	[35]
		III	751	2 or 4 mg/d	20 weeks	No significant change in LID or off time	[35]
	Topiramate	II	55		14 weeks	The trial testing topiramate combined with amantadine is ongoing	[36]
mGluR5 antagonist	Mavoglurant	II	31	50–300 mg/d	16 days	Reduction in severity of dyskinesia	[37]
		II	28	50–300 mg/d	16 days	Reduction in severity of dyskinesia	[37]
		II	197	20, 50, 100, 150, or 200 mg/d	13 weeks	Reduction in severity of dyskinesia without worsening underlying motor symptoms	[38]
		II	78	100 mg/d	12 weeks	No significant change in LID	[39]
		II	154	150 or 200 mg/d	12 weeks	No significant change in LID	[39]
		II	66		3.5 years	Completed without results	[40]

Contd...

Table 1: Contd...

Mechanism	Drugs	Stage	*n*	Dose	Duration	Results	Reference
	Dipraglurant	II	76	50–300 mg/d	4 weeks	Reduction in severity of LID	[41]
Adrenaline							
Noradrenergic reuptake inhibitor	Methylphenidate	IV	27	Up to 80 mg/d	24 weeks	Slight improvement in gait during off period	[42]
		IV	69	1 $mg \cdot kg^{-1} \cdot d^{-1}$	12 weeks	Improved gait hypokinesia and freezing	[43]
α2-adrenergic receptor antagonist	Fipamezole	II	180	90,180, or 270 mg/d	4 weeks	No significant change in LID	[44]
Serotonin							
α1 adrenergic receptor and 5-HT1A agonist	Buspirone	I	16	10 mg, tid	6 weeks	The trial testing buspirone combined with amantadine is ongoing	[45]
		III	100	10–30 mg/d	13 weeks	The trial for buspirone monotherapy is ongoing	[46]
Combined 5-HT1A and 5-HT1B agonist	Eltoprazine	II	22	2.5, 5, or 7.5 mg/d		Reduction in severity of dyskinesia	[47]
		II	60	2.5, 5, or 7.5 mg/d	3 weeks	Ongoing	[48]
Histamine							
Histamine H2 antagonist		II	7	80, 120, or 160	14 days	No significant change in LID	[49]
Iron chelator	Deferiprone	II	338	30 $mg \cdot kg^{-1} \cdot d^{-1}$	9 months	Ongoing	[50]
		II	140	300, 600, 900, or 1200 mg/d	9 months	Ongoing	[51]
c-Abl inhibitor	Nilotinib	I	12	150 or 300 mg/d	6 months	Beneficial effect on clinical motor outcome	[52]

c-Abl: c-Abelson tyrosine kinase; A2A: Adenosine 2A; NMDA: N-methyl-D-aspartate; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; UPDRS III: Unified Parkinson's disease rating scale III; LID: Levodopa-induced dyskinesia; PD: Parkinson's disease; 5-HT1A: 5-hydroxytryptamine-1A; mGluR5: Metabotropic glutamate receptor 5.

inflammation in PD.[69] A 4-year observational cohort study revealed that caffeine consumption played a pivotal role in reducing accrual of disability in PD.[70] However, there have been inconsistencies in the conclusions obtained from some clinical trials. A clinical study demonstrated that caffeine could reduce the likelihood of developing dyskinesia.[71] However, there were no significant changes in motor features except for reduced total UPDRS score and objective motor component in another randomized controlled trial.[72] A Phase III trial to evaluate the efficacy of caffeine in PD is currently ongoing.[25]

Glutamatergic Options

The role played by glutamate in the mechanism and progression of PD via various ionotropic and metabotropic receptor types in the basal ganglia motor loop has been extensively investigated. N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and metabotropic glutamate receptors (mGluRs) in particular have been extensively studied, not only to identify their role in the progression of PD but also as potential novel therapeutic options.[4,73] Overactivity of the corticostriatal glutamatergic pathways and disinhibition of the subthalamic nucleus (STN) exacerbate the pathogenesis of PD by further activating the indirect striatopallidal pathway by weakening of normal dopamine D2-like receptor-mediated inhibition.[73] Enhanced cell excitotoxicity to the SN also underpins the appearance of motor symptoms in PD. Increased glutamate transmission from corticostriatal projections by long-term volatile stimulation of dopamine receptors at the affected striatal synapses could play a key role in LID;[74] however, the mechanisms involved remain unclear [Table 1].

N-methyl-D-aspartate receptor antagonists

The appearance of LID is accompanied by the excessive activation of NMDA receptors, a type of inotropic glutamate receptor expressed in the striatum and STN.[75] Dopaminergic and glutamatergic receptors are located in mutual striatal projection spiny neurons. Activation of D1 receptors results in the phosphorylation of NMDA receptors (especially the NR2A and NR2B receptor subunits) via protein phosphatase-1 and Fyn protein tyrosine kinase and consequently triggers a rapid redistribution of NMDA receptors via trafficking from synaptic to extrasynaptic compartments.[76,77] Over time, this functional link between D1 and NMDA receptors results in a change of corticostriatal synaptic plasticity, known as long-term potentiation (LTP), which could promote the development of LID.[77,78]

Most conventional nonselective NMDA receptor antagonists, however, have been implicated in adverse effects including psychotomimetic effects, impairments of learning, memory, and dissociative anesthesia. Thus, more selective antagonists targeting specific subtypes of NMDA receptors, especially

NR2A and NR2B receptors that seem to be alternatively expressed in the striatum, have been explored.[73,78] A favorable antidyskinetic outcome was reported in a study using a NR2B-selective NMDA glutamate antagonist, CP-101, 606; however, adverse cognitive effects were observed.[79] The clinical efficacy of NR2B subtype-selective antagonists in alleviating PD symptoms could not be confirmed following a randomized controlled trial, which failed to show any motor improvements after treatment with the NR2B-selective antagonist MK-0657.[80] Studies on NR2A subunits revealed that a cell-permeable peptide blocking NR2A subunits caused a reduction of LID in parkinsonian rats.[81,82] Currently, nonselective NMDA antagonists are still preferred for clinical use.

There have been several reports on the antidyskinetic effects of amantadine, a nonselective NMDA receptor antagonist.[31,83,84] Amantadine has been approved for the treatment of LID despite its side effects such as confusion, constipation, and visual hallucinations. ADS-5102, a long-lasting sustained-release capsule of amantadine HCl, administered once daily at night, has been described in an 8-week Phase II study in patients with obvious dyskinesia.[26] The 340 mg/d dosage of amantadine caused significant improvement of dyskinesia versus placebo and increased "on" time without aggravating dyskinesia. Two Phase III trials by the same sponsor on the use of ADS-5102 for the treatment of LID were recently completed, and the results are awaited.[27,28] Two Phase III studies testing another long-lasting sustained-release formulation of amantadine for 16 and 26 weeks are currently ongoing.[29,30]

Memantine is another conventional nonselective NMDA antagonist used for the treatment of dementia. Unexpected improvements in LID and On-Off appearance in PD were recorded after administration of memantine in five cases.[85,86] Memantine could be effective against LID despite transient tolerance in 6-OHDA-lesioned rat models.[87] However, recent studies on memantine (20 mg) revealed no significant improvement in dyskinesia ratings. Further, no serious side effects were observed in a small crossover clinical study in 15 patients with PD.[32]

α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonists

AMPA receptors are ionotropic glutamate receptors expressed in the striatum and SN. The potential use of AMPA antagonists in the improvement of LID has been demonstrated in preclinical studies.[73,88] Perampanel, a selective AMPA receptor antagonist, however, failed to effect statistically significant improvement in motor symptoms and motor fluctuations of levodopa-treated patients with moderately advanced PD in clinical trials.[33-35] Topiramate is an antiepileptic drug that functions via inhibition of voltage-gated sodium and calcium currents. Topiramate is also a potent AMPA receptor antagonist and triggers AMPA receptor dephosphorylation. Studies in animal models have suggested applications for topiramate as a potential antidyskinetic treatment.[89,90] However, contrary to the results of preclinical studies, topiramate tended to worsen dyskinesia in patients with PD and was poorly tolerated.[91] The use of topiramate as an adjunct to amantadine is being evaluated in a Phase II trial.[36]

Metabotropic glutamate receptor antagonists

The mGluRs are eight G-protein-coupled receptors, consisting of three groups (Groups I, II, and III), which are localized in the basal ganglia. They are involved in synaptic transmission and plasticity in progression of LIDs.[92] Studies on Group I mGluRs, particularly subgroup mGluR5, showed that mGluR5 antagonists are highly efficient in ameliorating motor symptoms and LIDs in animal models.[93,94] Enhanced density of postsynaptic metabotropic glutamate 5 (mGlu5) receptor and specific combination with the striatum and posterior putamen observed in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned macaque models could contribute to the pathogenesis of LIDs in PD.[95-97] These results formed the basis of several clinical trials evaluating the potential of two mGlu5 receptor negative allosteric modulators (NAMs) — mavoglurant and dipraglurant. In previous studies, mavoglurant (AFQ056) demonstrated relevant antidyskinetic effects;[37,38] however, further clinical trials did not reveal obvious antidyskinetic efficacy.[40,98,99] A recent Phase II trial has been concluded without results being published.[40] Dipraglurant (ADX48621) is another mGluR5 antagonist that was proven to reduce LID in an MPTP-lesioned macaque model.[100] Results of a new Phase IIa study showed safety and well tolerability of dipraglurant.[41]

Activation of Group II mGluRs (mGluR2/3) could also be used to treat parkinsonian motor symptoms because of decreased excitatory glutamate transmission at corticostriatal synapses. However, there is no significant evidence from studies on animal models of PD that Group II mGluRs could reverse dyskinesia.[101,102] Group III mGluRs consist of mGlu4, 6, 7, and 8 receptors. Activation of mGlu4 receptors, especially localized at GABAergic and glutamatergic synapses in the indirect pathway of basal ganglia circuitry, was tested using positive allosteric modulators (PAMs) for reducing synapse transmission at GABAergic and glutamatergic synapses.[103] Several animal studies had revealed that mGlu4 PAMs (VU0364770, VU0400195, Lu AF21934, and VU0418506) have good efficacy in antiparkinsonian clinical use.[104-107]

Adrenergic Options

The degeneration of the locus coeruleus that can produce noradrenaline plays a major role in subcortical neuronal loss in PD.[108] Dramatic reductions in noradrenergic levels in the extensive brain regions, including the frontal cortex, striatum, hippocampus, and amygdala, have been detected in postmortem PD brains, and could contribute to motor dysfunction.[6] Noradrenaline deficiency is believed to

be involved in the pathogenesis of LID and freezing of gait (FOG).[109-111] However, the detailed mechanisms remain unclear. Growing evidence supports the development of strategies to enhance NE neurotransmission for the treatment of LID and FOG in animal models and clinical trials of PD [Table 1].[112]

Noradrenergic reuptake inhibitor

Methylphenidate is a central stimulant, conventionally used for treating attention-deficit hyperactivity disorder. It elevates noradrenaline and dopamine levels by inhibiting the presynaptic dopamine and noradrenaline transporters in the striatum and prefrontal cortex.[113] In a 3-month crossover study by Moreau *et al*.,[43] gait hypokinesia and freezing was improved in the methylphenidate group in 69 patients with advanced PD despite optimized dopamine treatment and subthalamic stimulation. Side effects were also reported in this group, including weight loss, increased heart rate, sleeplessness, and transient confusion. Further, dopamine transporter type 1-encoding gene (SLC6A3) variants played a vital role in the efficacy of methylphenidate treatment for gait disorders in the same population.[114] Another 6-month randomized trial (n = 27) did not show a significant improvement in gait,[42] although a double-blind assessment was also conducted. Thus, longer followed-up studies in patients with PD who have not received surgery are needed. A case report of isolated FOG in PKAN (pantothenate kinase-associated neurodegeneration) revealed dramatic responsiveness with an increased dosage of methylphenidate.[115] These findings suggest that the association between methylphenidate and FOG merits further exploration.

Adrenergic receptor antagonist

Fipamezole, an α2-adrenergic receptor antagonist, was previously reported to reduce LID and improve the quality of levodopa action in animal models.[116,117] In a 1-month crossover study,[44] conducted in the USA (n = 115) and India (n = 64), no significant outcome was reported, only a subgroup analysis of subjects in the USA revealed obvious LID reduction under fipamezole treatment, because of the difference in demographic characteristics between the USA and India.

Serotonergic Agents

In the brain, serotonergic receptors are localized in the raphe nuclei of the brainstem which provides 5-HT innervation to the entire brain. Depletion of serotonergic neurons and accumulation of lewy bodies in PD were observed in previous studies.[5] Abnormality in the serotonin system responsible for LID could be due to aberrant processing of exogenous levodopa and dysregulated dopamine release in striatal serotonergic terminals.[118] Furthermore, an increased serotonin-to-dopamine transporter binding ratio accelerates PD progression.[119] Several clinically available drugs have been assessed recently in this context [Table 1].

Buspirone is a combined 5-hydroxytryptamine-1A (5-HT1A) and α1 adrenergic receptor agonist with antidyskinetic potential.[120] Results of a dose-finding study suggested the suitability of buspirone for use as antidyskinetic agent in PD.[118] A Phase I study assessing the efficacy of buspirone (in combination with amantadine) and a Phase III (monotherapy) are actively ongoing.[45,46]

Eltoprazine is a mixed 5-HT1B and 5-HT1A agonist, which exerts antidyskinetic effects by reducing striatal glutamate transmission.[121,122] Eltoprazine (5 mg/d) showed antidyskinetic effects without reducing normal motor responses to levodopa,[47] through the restoration of LTP and synaptic depotentiation in a subset of striatal spiny projection neurons.[123] However, in another rat model study, reduced levodopa-induced mobility was observed despite the antidyskinesia properties of eltoprazine.[122] A combination of eltoprazine and preladenant reduced dyskinesia and maintained the full therapeutic effects of a low dose of levodopa.[124] A Phase II study is currently active.[48]

A retrospective investigation on the effects of selective serotonin reuptake inhibitors (SSRIs) during dopaminergic treatment revealed that SSRIs did not prevent dyskinesias. However, SSRI exposure could delay onset of dyskinesia and reduce the severity, suggesting potential anti-PD applications for the serotonergic system in the future.[125]

Histamine Pathways

Histamine receptors are classified into four subtypes (H1, H2, H3, and H4). H2 receptors are mainly distributed in basal ganglia, particularly in the major input nucleus of the striatum indicating that histamine can affect direct pathways.[126] In addition, cholinergic interneurons activated in LID were attenuated by inhibition of H2 histaminergic transmission in mouse models.[127] Furthermore, histamine modulates the microglial activity in PD, which is accompanied by microglia-induced neuroinflammation.[128] Famotidine, a selective histamine H2 antagonist, could enhance the antiparkinsonian effects and duration of levodopa action in a macaque model.[129] However, a Phase II trial evaluating famotidine 80, 120, 160 mg/d failed to demonstrate efficacy in reducing dyskinesia severity [Table 1].[49]

Iron Chelators

A normal SN has a higher density of iron linked to ferritin and neuromelanin.[130] Maintenance of iron homeostasis is important and involves several mechanisms. Mismanagement of iron homeostasis may lead to various neurological injuries observed in PD.[131] Brain iron deposition could contribute to oxidative stress response in the SN and therefore exacerbate dopamine neuron degeneration.[132] Iron chelators likely protect against reduction in striatal dopamine by combining with iron in the SN. This dopaminergic neuroprotection was proved in animal models, wherein the iron chelator desferrioxamine ameliorated iron accumulation.[133-135] Desferrioxamine has long been clinically available. However, its obstruction of the blood–brain barrier has restricted its use in neurodegenerative disorders.[136] The

chelator deferiprone has an advantage over desferrioxamine, a 12-month study in patients with early-stage PD revealed a meaningful reduction in iron levels and improvement in motor symptoms,[137] and several Phase II clinical trials evaluating deferiprone are ongoing [Table 1].[50,51]

C-Abelson Tyrosine Kinase Inhibitor

C-Abelson tyrosine kinase (c-Abl) is activated in the brain of patients with PD. Nilotinib, the c-Abl inhibitor, is clinically used for chronic myelogenous leukemia treatment. Recent studies revealed that nilotinib could degrade autophagy of α-synuclein, leading to protection of SN neurons and amelioration of motor symptoms.[138,139] A new 6-month Phase I trial (n = 12) showed that nilotinib had beneficial effects on clinical motor outcome and changed cerebrospinal fluid biomarkers which indicated reduction of toxicity to the brain.[52] However, this small proof-of-concept study lacked a placebo group, and further studies with a greater sample size and control group are needed [Table 1].

Conclusions

Targeting nondopaminergic transmission could improve some motor symptoms in PD, especially the discomfort of dyskinesia. Some nondopaminergic drugs, such as istradefylline and amantadine, are currently used clinically, while most such drugs are in preclinical testing stages. Transitioning of these agents into clinically beneficial strategies requires reliable evaluation since several agents have failed to show consistent results despite positive findings at the preclinical level. In conclusion, although nondopaminergic treatments show great potential in PD treatment as an adjunct therapy to levodopa, further investigation is required to ensure their success.

Financial support and sponsorship

This work was supported by grants from the National Natural Science Foundation of China (No. 81371407 and No. 81430022).

Conflicts of interest

There are no conflicts of interest.

References

1. Jankovic J. Parkinson's disease therapy: Treatment of early and late disease. Chin Med J 2001;114:227-34.
2. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197-211. doi: 10.1016/S0197-4580(02)00065-9.
3. Schiffmann SN, Fisone G, Moresco R, Cunha RA, Ferré S. Adenosine A2A receptors and basal ganglia physiology. Prog Neurobiol 2007;83:277-92. doi: 10.1016/j.pneurobio.2007.05.001.
4. Blandini F, Porter RH, Greenamyre JT. Glutamate and Parkinson's disease. Mol Neurobiol 1996;12:73-94. doi: 10.1007/bf02740748.
5. Huot P, Fox SH, Brotchie JM. The serotonergic system in Parkinson's disease. Prog Neurobiol 2011;95:163-212. doi: 10.1016/j.pneurobio.2011.08.004.
6. Buddhala C, Loftin SK, Kuley BM, Cairns NJ, Campbell MC, Perlmutter JS, *et al.* Dopaminergic, serotonergic, and noradrenergic deficits in Parkinson disease. Ann Clin Transl Neurol 2015;2:949-59. doi: 10.1002/acn3.246.
7. Jenner P. Treatment of the later stages of Parkinson's disease-pharmacological approaches now and in the future. Transl Neurodegener 2015;4:3. doi: 10.1186/2047-9158-4-3.
8. Klinger M, Freissmuth M, Nanoff C. Adenosine receptors: G protein-mediated signalling and the role of accessory proteins. Cell Signal 2002;14:99-108. doi: 10.1016/S0898-6568(01)00235-2.
9. Schwarzschild MA, Agnati L, Fuxe K, Chen JF, Morelli M. Targeting adenosine A2A receptors in Parkinson's disease. Trends Neurosci 2006;29:647-54. doi: 10.1016/j.tins.2006.09.004.
10. LeWitt PA, Guttman M, Tetrud JW, Tuite PJ, Mori A, Chaikin P, *et al.* Adenosine A2A receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: A double-blind, randomized, multicenter clinical trial (6002-US-005). Ann Neurol 2008;63:295-302. doi: 10.1002/ana.21315.
11. Fernandez HH, Greeley DR, Zweig RM, Wojcieszek J, Mori A, Sussman NM; US Study Group. Istradefylline as monotherapy for Parkinson disease: Results of the 6002-US-051 trial. Parkinsonism Relat Disord 2010;16:16-20. doi: 10.1016/j.parkreldis.2009.06.008.
12. Mizuno Y, Hasegawa K, Kondo T, Kuno S, Yamamoto M; Japanese Istradefylline Study Group. Clinical efficacy of istradefylline (KW-6002) in Parkinson's disease: A randomized, controlled study. Mov Disord 2010;25:1437-43. doi: 10.1002/mds.23107.
13. Stacy M, Silver D, Mendis T, Sutton J, Mori A, Chaikin P, *et al.* A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease. Neurology 2008;70:2233-40. doi: 10.1212/01.wnl.0000313834.22171.17.
14. Pinna A. Adenosine A2A receptor antagonists in Parkinson's disease: Progress in clinical trials from the newly approved istradefylline to drugs in early development and those already discontinued. CNS Drugs 2014;28:455-74. doi: 10.1007/s40263-014-0161-7.
15. Mizuno Y, Kondo T; Japanese Istradefylline Study Group. Adenosine A2A receptor antagonist istradefylline reduces daily OFF time in Parkinson's disease. Mov Disord 2013;28:1138-41. doi: 10.1002/mds.25418.
16. Hauser RA, Shulman LM, Trugman JM, Roberts JW, Mori A, Ballerini R, *et al.* Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. Mov Disord 2008;23:2177-85. doi: 10.1002/mds.22095.
17. Pourcher E, Fernandez HH, Stacy M, Mori A, Ballerini R, Chaikin P. Istradefylline for Parkinson's disease patients experiencing motor fluctuations: Results of the KW-6002-US-018 study. Parkinsonism Relat Disord 2012;18:178-84. doi: 10.1016/j.parkreldis.2011.09.023.
18. A 12-week Randomized Study to Evaluate Oral Istradefylline in Subjects With Moderate to Severe Parkinson's Disease [NCT01968031]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Oct 20].
19. Hauser RA, Cantillon M, Pourcher E, Micheli F, Mok V, Onofrj M, *et al.* Preladenant in patients with Parkinson's disease and motor fluctuations: A phase 2, double-blind, randomised trial. Lancet Neurol 2011;10:221-9. doi: 10.1016/s1474-4422(11)70012-6.
20. Factor SA, Wolski K, Togasaki DM, Huyck S, Cantillon M, Ho TW, *et al.* Long-term safety and efficacy of preladenant in subjects with fluctuating Parkinson's disease. Mov Disord 2013;28:817-20. doi: 10.1002/mds.25395.
21. Hattori N, Kikuchi M, Adachi N, Hewitt D, Huyck S, Saito T. Adjunctive preladenant: A placebo-controlled, dose-finding study in Japanese patients with Parkinson's disease. Parkinsonism Relat Disord 2016;32:73-79. doi: 10.1016/j.parkreldis.2016.08.020.
22. Hauser RA, Stocchi F, Rascol O, Huyck SB, Capece R, Ho TW, *et al.* Preladenant as an adjunctive therapy with levodopa in parkinson disease: Two randomized clinical trials and lessons learned. JAMA Neurol 2015;72:1491-500. doi: 10.1001/jamaneurol.2015.2268.
23. Hauser RA, Olanow CW, Kieburtz KD, Pourcher E, Docu-Axelerad A, Lew M, *et al.* Tozadenant (SYN115) in patients with Parkinson's disease who have motor fluctuations on levodopa: A phase 2b, double-blind, randomised trial. Lancet Neurol 2014;13:767-76. doi: 10.1016/s1474-4422(14)70148-6.
24. Safety and Efficacy Study of Tozadenant to Treat End of Dose Wearing

Off in Parkinson's Patients Using Levodopa [NCT02453386]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Oct 20].
25. Caffeine as a Therapy for Parkinson's Disease[NCT01738178]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Oct 20].
26. Pahwa R, Tanner CM, Hauser RA, Sethi K, Isaacson S, Truong D, *et al.* Amantadine extended release for levodopa-induced dyskinesia in Parkinson's disease (EASED Study). Mov Disord 2015;30:788-95. doi: 10.1002/mds.26159.
27. Efficacy and Safety Study of ADS-5102 in PD Patients With Levodopa-Induced Dyskinesia (EASE LID 3)[NCT02274766]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Oct 22].
28. ADS-5102 for the Treatment of Levodopa Induced Dyskinesia (EASE LID Study) (EASE LID)[NCT02136914]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Oct 22].
29. Efficacy and Safety of Amantadine HCl Extended Release Tablets to Treat Parkinson's Disease Patients With Levodopa Induced Dyskinesia. (ALLAY-LID I).[NCT02153645]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Oct 22].
30. Efficacy and Safety of Amantadine HCl Extended Release Tablets in Parkinson's Disease Subjects with Levodopa-induced Dyskinesias (ALLAY-LID II). [NCT02153632]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Oct 24].
31. Friedman JH. Withdrawing amantadine in dyskinetic patients with Parkinson disease: The AMANDYSK trial. Neurology 2014 9;83:1035-6. doi: 10.1212/01.wnl.0000454037.22235.5e.
32. Wictorin K, Widner H. Memantine and reduced time with dyskinesia in Parkinson's Disease. Acta Neurol Scand 2016;133:355-60. doi: 10.1111/ane.12468.
33. Eggert K, Squillacote D, Barone P, Dodel R, Katzenschlager R, Emre M, *et al.* Safety and efficacy of perampanel in advanced Parkinson's disease: A randomized, placebo-controlled study. Mov Disord 2010;25:896-905. doi: 10.1002/mds.22974.
34. Rascol O, Barone P, Behari M, Emre M, Giladi N, Olanow CW, *et al.* Perampanel in Parkinson disease fluctuations: A double-blind randomized trial with placebo and entacapone. Clin Neuropharmacol 2012;35:15-20. doi: 10.1097/WNF.0b013e318241520b.
35. Lees A, Fahn S, Eggert KM, Jankovic J, Lang A, Micheli F, *et al.* Perampanel, an AMPA antagonist, found to have no benefit in reducing "off" time in Parkinson's disease. Mov Disord 2012;27:284-8. doi: 10.1002/mds.23983.
36. Topiramate as an Adjunct to Amantadine in the Treatment of Dyskinesia in Parkinson's Disease (TOP-DYSK)[NCT01789047]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Nov 05].
37. Berg D, Godau J, Trenkwalder C, Eggert K, Csoti I, Storch A, *et al.* AFQ056 treatment of levodopa-induced dyskinesias: Results of 2 randomized controlled trials. Mov Disord 2011;26:1243-50. doi: 10.1002/mds.23616.
38. Stocchi F, Rascol O, Destee A, Hattori N, Hauser RA, Lang AE, *et al.* AFQ056 in Parkinson patients with levodopa-induced dyskinesia: 13-week, randomized, dose-finding study. Mov Disord 2013;28:1838-46. doi: 10.1002/mds.25561.
39. Trenkwalder C, Stocchi F, Poewe W, Dronamraju N, Kenney C, Shah A, *et al.* Mavoglurant in Parkinson's patients with l-Dopa-induced dyskinesias: Two randomized phase 2 studies. Mov Disord 2016;31:1054-8. doi: 10.1002/mds.26585.
40. Open Label, Safety, Tolerability and Efficacy of AFQ056 in Parkinson's Patients With L-dopa Induced Dyskinesias [NCT01173731]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Nov 06].
41. Tison F, Keywood C, Wakefield M, Durif F, Corvol JC, Eggert K, *et al.* A phase 2a trial of the novel mglur5-negative allosteric modulator dipraglurant for levodopa-induced dyskinesia in parkinson's disease. Mov Disord 2016;31:1373-80. doi: 10.1002/mds.26659.
42. Foley PB. Methylphenidate for gait impairment in Parkinson disease: A randomized clinical trial. Neurology 2011;77:e140. doi: 10.1212/WNL.0b013e318239c081.
43. Moreau C, Delval A, Defebvre L, Dujardin K, Duhamel A, Petyt G, *et al.* Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: A multicentre, parallel, randomised, placebo-controlled trial. Lancet Neurol 2012;11:589-96. doi: 10.1016/s1474-4422(12)70106-0.
44. Lewitt PA, Hauser RA, Lu M, Nicholas AP, Weiner W, Coppard N, *et al.* Randomized clinical trial of fipamezole for dyskinesia in Parkinson disease (FJORD study). Neurology 2012;79:163-9. doi: 10.1212/WNL.0b013e31825f0451.
45. Buspirone, in Combination With Amantadine, for the Treatment of Levodopa-induced Dyskinesia [NCT02589340]. Available from: https://www.clinicaltrials.gov1. [Last accessed on 2016 Nov 21].
46. Buspirone Treatment of Iatrogenic Dyskinesias in Advanced Parkinson' Disease [NCT02617017]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Nov 21].
47. Svenningsson P, Rosenblad C, Af Edholm Arvidsson K, Wictorin K, Keywood C, Shankar B, *et al.* Eltoprazine counteracts l-DOPA-induced dyskinesias in Parkinson's disease: A dose-finding study. Brain 2015;138(Pt 4):963-73. doi: 10.1093/brain/awu409.
48. A Study of Efficacy and Safety of Eltoprazine HCl for Treating Levodopa-induced Dyskinesia in Parkinson's Disease Patients [NCT02439125]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Dec 05].
49. Mestre TA, Shah BB, Connolly BS, Camila A, Amaal AD, Richard W, *et al*. Famotidine, a histamine h2 receptor antagonist, does not reduce levodopa-induced dyskinesia in parkinson's disease: A proof-of-concept study. Mov Dis Clin Pract 2014;1:219-24. doi: 10.1002/mdc3.12061.
50. Conservative Iron Chelation as a Disease-modifying Strategy in Parkinson's Disease (FAIRPARKII) [NCT02655315]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Dec 05].
51. Study of Parkinson's Early Stage With Deferiprone (SKY) [NCT02728843]. Available from: https://www.clinicaltrials.gov. [Last accessed on 2016 Dec 06].
52. Pagan F, Hebron M, Valadez EH, Torres-Yaghi Y, Huang X, Mills RR, *et al.* Nilotinib effects in parkinson's disease and dementia with lewy bodies. J Parkinsons Dis 2016;6:503-17. doi: 10.3233/jpd-160867.
53. Dungo R, Deeks ED. Istradefylline: First global approval. Drugs 2013;73:875-82. doi: 10.1007/s40265-013-0066-7.
54. Kondo T, Mizuno Y; Japanese Istradefylline Study Group. A long-term study of istradefylline safety and efficacy in patients with Parkinson disease. Clin Neuropharmacol 2015;38:41-6. doi: 10.1097/WNF.0000000000000073.
55. Uchida S, Soshiroda K, Okita E, Kawai-Uchida M, Mori A, Jenner P, *et al.* The adenosine A2A receptor antagonist, istradefylline enhances anti-parkinsonian activity induced by combined treatment with low doses of L-DOPA and dopamine agonists in MPTP-treated common marmosets. Eur J Pharmacol 2015;766:25-30. doi: 10.1016/j.ejphar.2015.09.028.
56. Hodgson RA, Bertorelli R, Varty GB, Lachowicz JE, Forlani A, Fredduzzi S, *et al.* Characterization of the potent and highly selective A2A receptor antagonists preladenant and SCH 412348 [7-[2-[4-2,4-difluorophenyl]-1-piperazinyl] ethyl]-2-(2-furanyl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c] pyrimidin-5-amine] in rodent models of movement disorders and depression. J Pharmacol Exp Ther 2009;330:294-303. doi: 10.1124/jpet.108.149617.
57. Hodgson RA, Bedard PJ, Varty GB, Kazdoba TM, Di Paolo T, Grzelak ME, *et al.* Preladenant, a selective A(2A) receptor antagonist, is active in primate models of movement disorders. Exp Neurol 2010;225:384-90. doi: 10.1016/j.expneurol.2010.07.011.
58. Black KJ, Koller JM, Campbell MC, Gusnard DA, Bandak SI. Quantification of indirect pathway inhibition by the adenosine A2a antagonist SYN115 in Parkinson disease. J Neurosci 2010;30:16284-92. doi: 10.1523/jneurosci.2590-10.2010.
59. Michel A, Downey P, Van Damme X, De Wolf C, Schwarting R, Scheller D. Behavioural assessment of the A2a/NR2B combination in the unilateral 6-OHDA-lesioned rat model: A new method to examine the therapeutic potential of non-dopaminergic drugs. PLoS One 2015;10:e0135949. doi: 10.1371/journal.pone.0135949.

60. Antoniou K, Papadopoulou-Daifoti Z, Hyphantis T, Papathanasiou G, Bekris E, Marselos M, *et al.* A detailed behavioral analysis of the acute motor effects of caffeine in the rat: Involvement of adenosine A1 and A2A receptors. Psychopharmacology (Berl) 2005;183:154-62. doi: 10.1007/s00213-005-0173-6.
61. Trevitt J, Vallance C, Harris A, Goode T. Adenosine antagonists reverse the cataleptic effects of haloperidol: Implications for the treatment of Parkinson's disease. Pharmacol Biochem Behav 2009;92:521-7. doi: 10.1016/j.pbb.2009.02.001.
62. Atack JR, Shook BC, Rassnick S, Jackson PF, Rhodes K, Drinkenburg WH, *et al.* JNJ-40255293, a novel adenosine A2A/A1 antagonist with efficacy in preclinical models of Parkinson's disease. ACS Chem Neurosci 2014;5:1005-19. doi: 10.1021/cn5001606.
63. Robinson SJ, Petzer JP, Rousseau AL, Terre'Blanche G, Petzer A, LourensAC.Carbamatesubstituted2-amino-4,6-diphenylpyrimidines as adenosine receptor antagonists. Bioorg Med Chem Lett 2016 1;26:734-8. doi: 10.1016/j.bmcl.2016.01.004.
64. Shook BC, Rassnick S, Chakravarty D, Wallace N, Ault M, Crooke J, *et al.* Optimization of arylindenopyrimidines as potent adenosine A(2A)/A(1) antagonists. Bioorg Med Chem Lett 2010 1;20:2868-71. doi: 10.1016/j.bmcl.2010.03.024.
65. Shook BC, Rassnick S, Hall D, Rupert KC, Heintzelman GR, Hansen K, *et al.* Methylene amine substituted arylindenopyrimidines as potent adenosine A(2A)/A(1) antagonists. Bioorg Med Chem Lett 2010 1;20:2864-7. doi: 10.1016/j.bmcl.2010.03.042.
66. Shook BC, Rassnick S, Osborne MC, Davis S, Westover L, Boulet J, *et al. In vivo* characterization of a dual adenosine A2A/A1 receptor antagonist in animal models of Parkinson's disease. J Med Chem 2010;53:8104-15. doi: 10.1021/jm100971t.
67. Rivera-Oliver M, Díaz-Ríos M. Using caffeine and other adenosine receptor antagonists and agonists as therapeutic tools against neurodegenerative diseases: A review. Life Sci 2014;101:1-9. doi: 10.1016/j.lfs.2014.01.083.
68. Bagga P, Chugani AN, Patel AB. Neuroprotective effects of caffeine in MPTP model of Parkinson's disease: A(13)C NMR study. Neurochem Int 2016;92:25-34. doi: 10.1016/j.neuint.2015.11.006.
69. Roshan MH, Tambo A, Pace NP. Potential role of caffeine in the treatment of Parkinson's disease. Open Neurol J 2016;10:42-58. doi: 10.2174/1874205X01610010042.
70. Moccia M, Erro R, Picillo M, Vitale C, Longo K, Amboni M, *et al.* Caffeine consumption and the 4-year progression of *de novo* Parkinson's disease. Parkinsonism Relat Disord 2016;32:116-119. doi: 10.1016/j.parkreldis.2016.08.005.
71. Wills AM, Eberly S, Tennis M, Lang AE, Messing S, Togasaki D, *et al.* Caffeine consumption and risk of dyskinesia in CALM-PD. Mov Disord 2013;28:380-3. doi: 10.1002/mds.25319.
72. Postuma RB, Lang AE, Munhoz RP, Charland K, Pelletier A, Moscovich M, *et al.* Caffeine for treatment of Parkinson disease: A randomized controlled trial. Neurology 2012;79:651-8. doi: 10.1212/WNL.0b013e318263570d.
73. Duty S. Targeting glutamate receptors to tackle the pathogenesis, clinical symptoms and levodopa-induced dyskinesia associated with Parkinson's disease. CNS Drugs 2012;26:1017-32. doi: 10.1007/s40263-012-0016-z.
74. Blandini F, Armentero MT. New pharmacological avenues for the treatment of L-DOPA-induced dyskinesias in Parkinson's disease: Targeting glutamate and adenosine receptors. Expert Opin Investig Drugs 2012;21:153-68. doi: 10.1517/13543784.2012.651457.
75. Hallett PJ, Dunah AW, Ravenscroft P, Zhou S, Bezard E, Crossman AR, *et al.* Alterations of striatal NMDA receptor subunits associated with the development of dyskinesia in the MPTP-lesioned primate model of Parkinson's disease. Neuropharmacology 2005;48:503-16. doi: 10.1016/j.neuropharm.2004.11.008.
76. Dunah AW, Sirianni AC, Fienberg AA, Bastia E, Schwarzschild MA, Standaert DG. Dopamine D1-dependent trafficking of striatal N-methyl-D-aspartate glutamate receptors requires Fyn protein tyrosine kinase but not DARPP-32. Mol Pharmacol 2004;65:121-9. doi: 10.1124/mol.65.1.121.
77. Calabresi P, Di Filippo M, Ghiglieri V, Tambasco N, Picconi B. Levodopa-induced dyskinesias in patients with Parkinson's disease: Filling the bench-to-bedside gap. Lancet Neurol 2010;9:1106-17. doi: 10.1016/s1474-4422(10)70218-0.
78. Vastagh C, Gardoni F, Bagetta V, Stanic J, Zianni E, Giampà C, *et al.* N-methyl-D-aspartate (NMDA) receptor composition modulates dendritic spine morphology in striatal medium spiny neurons. J Biol Chem 2012;287:18103-14. doi: 10.1074/jbc.M112.347427.
79. Nutt JG, Gunzler SA, Kirchhoff T, Hogarth P, Weaver JL, Krams M, *et al.* Effects of a NR2B selective NMDA glutamate antagonist, CP-101,606, on dyskinesia and Parkinsonism. Mov Disord 2008;23:1860-6. doi: 10.1002/mds.22169.
80. Addy C, Assaid C, Hreniuk D, Stroh M, Xu Y, Herring WJ, *et al.* Single-dose administration of MK-0657, an NR2B-selective NMDA antagonist, does not result in clinically meaningful improvement in motor function in patients with moderate Parkinson's disease. J Clin Pharmacol 2009;49:856-64. doi: 10.1177/0091270009336735.
81. Gardoni F, Sgobio C, Pendolino V, Calabresi P, Di Luca M, Picconi B. Targeting NR2A-containing NMDA receptors reduces L-DOPA-induced dyskinesias. Neurobiol Aging 2012;33:2138-44. doi: 10.1016/j.neurobiolaging.2011.06.019.
82. Mellone M, Stanic J, Hernandez LF, Iglesias E, Zianni E, Longhi A, *et al.* NMDA receptor GluN2A/GluN2B subunit ratio as synaptic trait of levodopa-induced dyskinesias: From experimental models to patients. Front Cell Neurosci 2015;9:245. doi: 10.3389/fncel.2015.00245.
83. Wolf E, Seppi K, Katzenschlager R, Hochschorner G, Ransmayr G, Schwingenschuh P, *et al.* Long-term antidyskinetic efficacy of amantadine in Parkinson's disease. Mov Disord 2010;25:1357-63. doi: 10.1002/mds.23034.
84. Pilleri M, Antonini A. Therapeutic strategies to prevent and manage dyskinesias in Parkinson's disease. Expert Opin Drug Saf 2015;14:281-94. doi: 10.1517/14740338.2015.988137.
85. Vidal EI, Fukushima FB, Valle AP, Villas Boas PJ. Unexpected improvement in levodopa-induced dyskinesia and on-off phenomena after introduction of memantine for treatment of Parkinson's disease dementia. J Am Geriatr Soc 2013;61:170-2. doi: 10.1111/jgs.12058.
86. Varanese S, Howard J, Di Rocco A. NMDA antagonist memantine improves levodopa-induced dyskinesias and "on-off" phenomena in Parkinson's disease. Mov Disord 2010;25:508-10. doi: 10.1002/mds.22917.
87. Tronci E, Fidalgo C, Zianni E, Collu M, Stancampiano R, Morelli M, *et al.* Effect of memantine on L-DOPA-induced dyskinesia in the 6-OHDA-lesioned rat model of Parkinson's disease. Neuroscience 2014;265:245-52. doi: 10.1016/j.neuroscience.2014.01.042.
88. Marin C, Jiménez A, Bonastre M, Vila M, Agid Y, Hirsch EC, *et al.* LY293558, an AMPA glutamate receptor antagonist, prevents and reverses levodopa-induced motor alterations in Parkinsonian rats. Synapse 2001;42:40-7. doi: 10.1002/syn.1097.
89. Kobylecki C, Hill MP, Crossman AR, Ravenscroft P. Synergistic antidyskinetic effects of topiramate and amantadine in animal models of Parkinson's disease. Mov Disord 2011;26:2354-63. doi: 10.1002/mds.23867.
90. Silverdale MA, Nicholson SL, Crossman AR, Brotchie JM. Topiramate reduces levodopa-induced dyskinesia in the MPTP-lesioned marmoset model of Parkinson's disease. Mov Disord 2005;20:403-9. doi: 10.1002/mds.20345.
91. Kobylecki C, Burn DJ, Kass-Iliyya L, Kellett MW, Crossman AR, Silverdale MA. Randomized clinical trial of topiramate for levodopa-induced dyskinesia in Parkinson's disease. Parkinsonism Relat Disord 2014;20:452-5. doi: 10.1016/j.parkreldis.2014.01.016.
92. Amalric M. Targeting metabotropic glutamate receptors (mGluRs) in Parkinson's disease. Curr Opin Pharmacol 2015;20:29-34. doi: 10.1016/j.coph.2014.11.001.
93. Gasparini F, Di Paolo T, Gomez-Mancilla B. Metabotropic glutamate receptors for Parkinson's disease therapy. Parkinsons Dis 2013;2013:196028. doi: 10.1155/2013/196028.
94. Hovelsø N, Sotty F, Montezinho LP, Pinheiro PS, Herrik KF, Mørk A. Therapeutic potential of metabotropic glutamate receptor modulators. Curr Neuropharmacol 2012;10:12-48. doi: 10.2174/157015912799362805.
95. Ouattara B, Grégoire L, Morissette M, Gasparini F, Vranesic I, Bilbe G, *et al.* Metabotropic glutamate receptor type 5 in levodopa-induced motor complications. Neurobiol Aging

2011;32:1286-95. doi: 10.1016/j.neurobiolaging.2009.07.014.
96. Samadi P, Grégoire L, Morissette M, Calon F, Hadj Tahar A, Dridi M, *et al.* mGluR5 metabotropic glutamate receptors and dyskinesias in MPTP monkeys. Neurobiol Aging 2008;29:1040-51. doi: 10.1016/j.neurobiolaging.2007.02.005.
97. Sanchez-Pernaute R, Wang JQ, Kuruppu D, Cao L, Tueckmantel W, Kozikowski A, *et al.* Enhanced binding of metabotropic glutamate receptor type 5 (mGluR5) PET tracers in the brain of parkinsonian primates. Neuroimage 2008;42:248-51. doi: 10.1016/j.neuroimage.2008.04.170.
98. Petrov D, Pedros I, de Lemos ML, Pallàs M, Canudas AM, Lazarowski A, *et al.* Mavoglurant as a treatment for Parkinson's disease. Expert Opin Investig Drugs 2014;23:1165-79. doi: 10.1517/13543784.2014.931370.
99. Rascol O, Fox S, Gasparini F, Kenney C, Di Paolo T, Gomez-Mancilla B. Use of metabotropic glutamate 5-receptor antagonists for treatment of levodopa-induced dyskinesias. Parkinsonism Relat Disord 2014;20:947-56. doi: 10.1016/j.parkreldis.2014.05.003.
100. Bezard E, Pioli EY, Li Q, Girard F, Mutel V, Keywood C, *et al.* The mGluR5 negative allosteric modulator dipraglurant reduces dyskinesia in the MPTP macaque model. Mov Disord 2014;29:1074-9. doi: 10.1002/mds.25920.
101. Rylander D, Recchia A, Mela F, Dekundy A, Danysz W, Cenci MA. Pharmacological modulation of glutamate transmission in a rat model of L-DOPA-induced dyskinesia: Effects on motor behavior and striatal nuclear signaling. J Pharmacol Exp Ther 2009;330:227-35. doi: 10.1124/jpet.108.150425.
102. Samadi P, Grégoire L, Morissette M, Calon F, Hadj Tahar A, Bélanger N, *et al.* Basal ganglia group II metabotropic glutamate receptors specific binding in non-human primate model of L-Dopa-induced dyskinesias. Neuropharmacology 2008;54:258-68. doi: 10.1016/j.neuropharm.2007.08.009.
103. Duty S. Therapeutic potential of targeting group III metabotropic glutamate receptors in the treatment of Parkinson's disease. Br J Pharmacol 2010;161:271-87. doi: 10.1111/j.1476-5381.2010.00882.x.
104. Bennouar KE, Uberti MA, Melon C, Bacolod MD, Jimenez HN, Cajina M, *et al.* Synergy between L-DOPA and a novel positive allosteric modulator of metabotropic glutamate receptor 4: Implications for Parkinson's disease treatment and dyskinesia. Neuropharmacology 2013;66:158-69. doi: 10.1016/j.neuropharm.2012.03.022.
105. Iderberg H, Maslava N, Thompson AD, Bubser M, Niswender CM, Hopkins CR, *et al.* Pharmacological stimulation of metabotropic glutamate receptor type 4 in a rat model of Parkinson's disease and L-DOPA-induced dyskinesia: Comparison between a positive allosteric modulator and an orthosteric agonist. Neuropharmacology 2015;95:121-9. doi: 10.1016/j.neuropharm.2015.02.023.
106. Jones CK, Engers DW, Thompson AD, Field JR, Blobaum AL, Lindsley SR, *et al*. Discovery, synthesis, and structure-activity relationship development of a series of N-4-(2,5-dioxopyrrolidin-1-yl) phenylpicolinamides (VU0400195, ML182): Characterization of a novel positive allosteric modulator of the metabotropic glutamate receptor 4 (mGlu (4)) with oral efficacy in an antiparkinsonian animal model. J Med Chem 2011;54:7639-47. doi: 10.1021/jm200956q.
107. Engers DW, Blobaum AL, Gogliotti RD, Cheung YY, Salovich JM, Garcia-Barrantes PM, *et al.* Discovery, synthesis, and preclinical characterization of N-(3-Chloro-4-fluorophenyl)-1H-pyrazolo[4,3-b] pyridin-3-amine (VU0418506), a novel positive allosteric modulator of the metabotropic glutamate receptor 4 (mGlu4). ACS Chem Neurosci 2016;7:1192-200. doi: 10.1021/acschemneuro.6b00035.
108. Zarow C, Lyness SA, Mortimer JA, Chui HC. Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. Arch Neurol 2003;60:337-41. doi: 10.1001/archneur.60.3.337.
109. Wang Y, Wang HS, Wang T, Huang C, Liu J. L-DOPA-induced dyskinesia in a rat model of Parkinson's disease is associated with the fluctuational release of norepinephrine in the sensorimotor striatum. J Neurosci Res 2014;92:1733-45. doi: 10.1002/jnr.23439.
110. Shin E, Rogers JT, Devoto P, Björklund A, Carta M. Noradrenaline neuron degeneration contributes to motor impairments and development of L-DOPA-induced dyskinesia in a rat model of Parkinson's disease. Exp Neurol 2014;257:25-38. doi: 10.1016/j.expneurol.2014.04.011.
111. Lewitt PA. Norepinephrine: The next therapeutics frontier for Parkinson's disease. Transl Neurodegener 2012;1:4. doi: 10.1186/2047-9158-1-4.
112. Espay AJ, LeWitt PA, Kaufmann H. Norepinephrine deficiency in Parkinson's disease: The case for noradrenergic enhancement. Mov Disord 2014;29:1710-9. doi: 10.1002/mds.26048.
113. Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, *et al.* Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. Am J Psychiatry 1998;155:1325-31. doi: 10.1176/ajp.155.10.1325.
114. Moreau C, Meguig S, Corvol JC, Labreuche J, Vasseur F, Duhamel A, *et al.* Polymorphism of the dopamine transporter type 1 gene modifies the treatment response in Parkinson's disease. Brain 2015;138(Pt 5):1271-83. doi: 10.1093/brain/awv063.
115. Kwon KY, Lee HM, Kim M, Kang SH, Koh SB. Long-lasting isolated freezing of gait with good response to methylphenidate: A patient with pantothenate kinase-associated neurodegeneration. Parkinsonism Relat Disord 2015;21:671-2. doi: 10.1016/j.parkreldis.2015.04.003.
116. Johnston TH, Fox SH, Piggott MJ, Savola JM, Brotchie JM. The alpha2 adrenergic antagonist fipamezole improves quality of levodopa action in Parkinsonian primates. Mov Disord 2010;25:2084-93. doi: 10.1002/mds.23172.
117. Savola JM, Hill M, Engstrom M, Merivuori H, Wurster S, McGuire SG, *et al.* Fipamezole (JP-1730) is a potent alpha2 adrenergic receptor antagonist that reduces levodopa-induced dyskinesia in the MPTP-lesioned primate model of Parkinson's disease. Mov Disord 2003;18:872-83. doi: 10.1002/mds.10464.
118. Politis M, Wu K, Loane C, Brooks DJ, Kiferle L, Turkheimer FE, *et al.* Serotonergic mechanisms responsible for levodopa-induced dyskinesias in Parkinson's disease patients. J Clin Invest 2014;124:1340-9. doi: 10.1172/jci71640.
119. Roussakis AA, Politis M, Towey D, Piccini P. Serotonin-to-dopamine transporter ratios in Parkinson disease: Relevance for dyskinesias. Neurology 2016;86:1152-8. doi: 10.1212/wnl.0000000000002494.
120. Eskow KL, Gupta V, Alam S, Park JY, Bishop C. The partial 5-HT(1A) agonist buspirone reduces the expression and development of l-DOPA-induced dyskinesia in rats and improves l-DOPA efficacy. Pharmacol Biochem Behav 2007;87:306-14. doi: 10.1016/j.pbb.2007.05.002.
121. Paolone G, Brugnoli A, Arcuri L, Mercatelli D, Morari M. Eltoprazine prevents levodopa-induced dyskinesias by reducing striatal glutamate and direct pathway activity. Mov Disord 2015;30:1728-38. doi: 10.1002/mds.26326.
122. Tronci E, Fidalgo C, Stancampiano R, Carta M. Effect of selective and non-selective serotonin receptor activation on L-DOPA-induced therapeutic efficacy and dyskinesia in parkinsonian rats. Behav Brain Res 2015;292:300-4. doi: 10.1016/j.bbr.2015.06.034.
123. Ghiglieri V, Mineo D, Vannelli A, Cacace F, Mancini M, Pendolino V, *et al.* Modulation of serotonergic transmission by eltoprazine in L-DOPA-induced dyskinesia: Behavioral, molecular, and synaptic mechanisms. Neurobiol Dis 2016;86:140-53. doi: 10.1016/j.nbd.2015.11.022.
124. Pinna A, Ko WK, Costa G, Tronci E, Fidalgo C, Simola N, *et al.* Antidyskinetic effect of A2A and 5HT1A/1B receptor ligands in two animal models of Parkinson's disease. Mov Disord 2016;31:501-11. doi: 10.1002/mds.26475.
125. Mazzucchi S, Frosini D, Ripoli A, Nicoletti V, Linsalata G, Bonuccelli U, *et al.* Serotonergic antidepressant drugs and L-dopa-induced dyskinesias in Parkinson's disease. Acta Neurol Scand 2015;131:191-5. doi: 10.1111/ane.12314.
126. Bolam JP, Ellender TJ. Histamine and the striatum. Neuropharmacology 2016;106:74-84. doi: 10.1016/j.neuropharm.2015.08.013.
127. Lim SA, Xia R, Ding Y, Won L, Ray WJ, Hitchcock SA, *et al.* Enhanced histamine H2 excitation of striatal cholinergic interneurons in L-DOPA-induced dyskinesia. Neurobiol Dis 2015;76:67-76. doi: 10.1016/j.nbd.2015.01.003.

128. Rocha SM, Saraiva T, Cristóvão AC, Ferreira R, Santos T, Esteves M, *et al.* Histamine induces microglia activation and dopaminergic neuronal toxicity via H1 receptor activation. J Neuroinflammation 2016;13:137. doi: 10.1186/s12974-016-0600-0.
129. Johnston TH, van der Meij A, Brotchie JM, Fox SH. Effect of histamine H2 receptor antagonism on levodopa-induced dyskinesia in the MPTP-macaque model of Parkinson's disease. Mov Disord 2010;25:1379-90. doi: 10.1002/mds.23069.
130. Li X, Jankovic J, Le W. Iron chelation and neuroprotection in neurodegenerative diseases. J Neural Transm (Vienna) 2011;118:473-7. doi: 10.1007/s00702-010-0518-0.
131. Zucca FA, Segura-Aguilar J, Ferrari E, Muñoz P, Paris I, Sulzer D, *et al.* Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. Prog Neurobiol 2015. pii: S0301-008200101-X. doi: 10.1016/j.pneurobio.2015.09.012.
132. Weinreb O, Mandel S, Youdim MB, Amit T. Targeting dysregulation of brain iron homeostasis in Parkinson's disease by iron chelators. Free Radic Biol Med 2013;62:52-64. doi: 10.1016/j.freeradbiomed.2013.01.017.
133. Haleagrahara N, Siew CJ, Ponnusamy K. Effect of quercetin and desferrioxamine on 6-hydroxydopamine (6-OHDA) induced neurotoxicity in striatum of rats. J Toxicol Sci 2013;38:25-33. doi: 10.2131/jts.38.25.
134. Lv H, Liu J, Wang L, Zhang H, Yu S, Li Z, *et al.* Ameliorating effects of combined curcumin and desferrioxamine on 6-OHDA-induced rat mode of Parkinson's disease. Cell Biochem Biophys 2014;70:1433-8. doi: 10.1007/s12013-014-0077-3.
135. Xiong P, Chen X, Guo C, Zhang N, Ma B. Baicalin and deferoxamine alleviate iron accumulation in different brain regions of Parkinson's disease rats. Neural Regen Res 2012;7:2092-8. doi: 10.3969/j.issn.1673-5374.2012.27.002.
136. Stayte S, Vissel B. Advances in non-dopaminergic treatments for Parkinson's disease. Front Neurosci 2014;8:113. doi: 10.3389/fnins.2014.00113.
137. Devos D, Moreau C, Devedjian JC, Kluza J, Petrault M, Laloux C, *et al.* Targeting chelatable iron as a therapeutic modality in Parkinson's disease. Antioxid Redox Signal 2014;21:195-210. doi: 10.1089/ars.2013.5593.
138. Hebron ML, Lonskaya I, Moussa CE. Nilotinib reverses loss of dopamine neurons and improves motor behavior via autophagic degradation of a-synuclein in Parkinson's disease models. Hum Mol Genet 2013;22:3315-28. doi: 10.1093/hmg/ddt192.
139. Karuppagounder SS, Brahmachari S, Lee Y, Dawson VL, Dawson TM, Ko HS. The c-Abl inhibitor, nilotinib, protects dopaminergic neurons in a preclinical animal model of Parkinson's disease. Sci Rep 2014;4:4874. doi: 10.1038/srep04874.