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REVIEW

Treatment of Parkinson's Disease: What's in the Non-dopaminergic Pipeline?

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Abstract Dopamine depletion resulting from degeneration of nigrostriatal dopaminergic neurons is the primary neurochemical basis of the motor symptoms of Parkinson's disease (PD). While dopaminergic replacement strategies are effective in ameliorating these symptoms early in the disease process, more advanced stages of PD are associated with the development of treatment-related motor complications and dopamine-resistant symptoms. Other neurotransmitter and neuromodulator systems are expressed in the basal ganglia and contribute to the extrapyramidal refinement of motor function. Furthermore, neuropathological studies suggest that they are also affected by the neurodegenerative process. These non-dopaminergic systems provide potential targets for treatment of motor fluctuations, levodopa-induced dyskinesias, and difficulty with gait and balance. This review summarizes recent advances in the clinical development of novel pharmacological approaches for treatment of PD motor symptoms. Although the non-dopaminergic pipeline has been slow to yield new drugs, further development will likely result in improved treatments for PD symptoms that are induced by or resistant to dopamine replacement.

Keywords Parkinson's disease · Non-dopaminergic · Dyskinesias · Motor fluctuations · Glutamate · Adenosine

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is characterized clinically by the classical motor symptoms of bradykinesia, rigidity, and resting tremor. These symptoms are primarily caused by the selective loss of dopaminergic neurons in the substantia nigra pars compacta, which results in decreased levels of dopamine in the striatum. Dopamine replacement strategies have been the mainstay of treatment for motor symptoms of PD, and nearly 50 years since its introduction, levodopa (the precursor of dopamine) remains the most effective treatment. However, despite its beneficial effects on motor function, dopaminergic therapy has significant limitations, making development of other therapeutic approaches targeting non-dopaminergic pathways a priority [1]. First, neither levodopa nor dopamine agonists have been demonstrated to slow the progression of nigrostriatal cell loss. Second, while initially successful in ameliorating motor symptoms, long-term treatment with levodopa is complicated by the onset of motor fluctuations (with alternating periods of mobility and relative immobility) and involuntary dyskinesias. Last, symptoms that develop at later stages of PD, both motor (e.g., postural instability and freezing of gait) and non-motor, are frequently not responsive to dopaminergic treatments. These symptoms are likely to be caused by the degeneration of neurons in other parts of the nervous system as a result of the same disease process that affects the nigrostriatal system [2].

In this review, we discuss potential non-dopaminergic approaches to treatment of PD symptoms. Multiple neurotransmitters are recognized to play a role in modulating the basal ganglia and other neural circuits thought to be involved in PD. We will focus primarily on neurotransmitter targets in which there have been therapeutic advances in targeting motor symptoms. Agents targeting non-dopaminergic pathways are also being actively explored for treatment of non-motor symptoms.

Neurotransmitter Diversity in the Basal Ganglia and Motor Control

To understand the potential use of pharmacologic agents targeting non-dopaminergic pathways, it is helpful to briefly

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review the role of these neurotransmitter systems in regulating motor function [3]. In the classic model of basal ganglia organization (Fig. 1), the cerebral cortex sends excitatory glutamatergic inputs to the striatum. Dopamine, via the nigrostriatal pathway, modulates these inputs, either through an excitatory effect on a subpopulation of striatal neurons that contain gamma-aminobutyric acid (GABA) and substance P (direct pathway), or through an inhibitory effect on a separate subpopulation of neurons that co-express GABA and enkephalin (indirect pathway). The effects on the direct and indirect pathways are mediated by dopamine binding to D1 and D2 receptors, respectively, both of which are highly expressed in the striatum (Fig. 2). In the direct pathway, striatal neurons send inhibitory GABAergic inputs directly to the output nuclei of the basal ganglia, the globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNr), which then send GABAergic fibers to ventral thalamic nuclei. In contrast, axons from striatofugal neurons in the indirect pathway form GABAergic synapses with cells in the globus pallidus pars externa, which then send GABAergic projections to the subthalamic nucleus (STN). The STN then uses glutamate to modulate basal ganglia output from the GPi/SNr. This classic model suggests that dopamine regulates basal ganglia activity by balancing opposing effects on the direct and indirect pathways. Loss of striatal dopamine in PD disrupts this balance, producing a hypokinetic (parkinsonian) state. In contrast, subsequent treatment with dopaminergic agents predisposes to hyperkinetic (dyskinesia) responses. While this model is

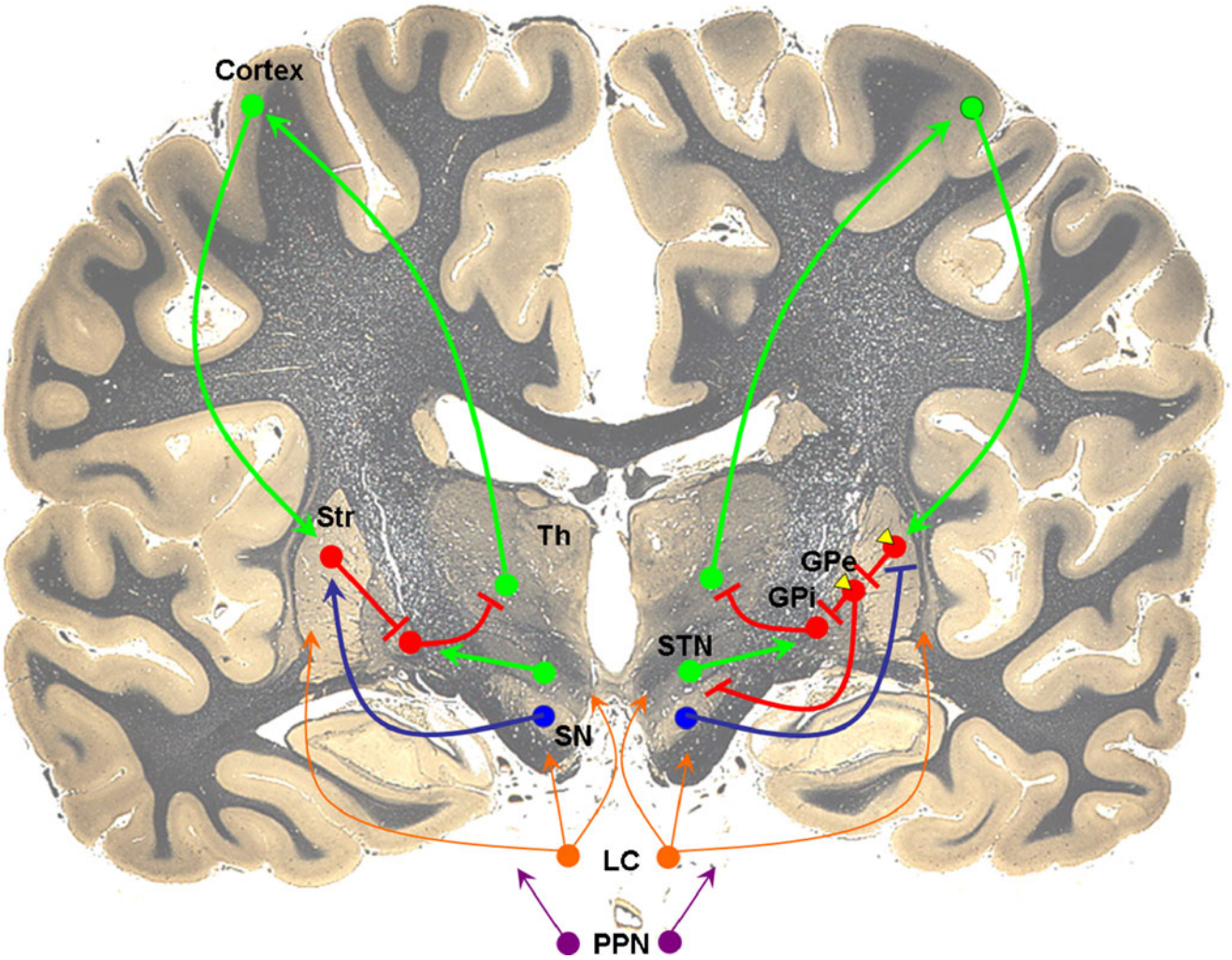

Fig. 1 Neurotransmitter systems involved in basal ganglia circuitry. Excitatory glutamatergic efferents (green) from cortex project to gamma-aminobutyric acid (GABA)ergic (red) striatal neurons. In the direct pathway (left), striatal neurons receive excitatory dopaminergic inputs (blue) from substantia nigra and project directly to globus pallidus interna (GPi). In the indirect pathway (right), dopamine inhibits striatal GABAergic output to the globus pallidus externa (GPe), which then projects to GPi. Adenosine A_{2A} receptors (yellow) are localized to dopamine D2 receptor-containing cells in the indirect pathway. Noradrenergic and cholinergic efferents from the locus coeruleus (orange) and pedunculopontine nucleus (purple), respectively, project widely to multiple brain regions, including cortex and basal ganglia. The coronal brain image is adapted with permission from http://www.brains.rad.msu.edu and http://brainmuseum.org, supported by the US National Science Foundation

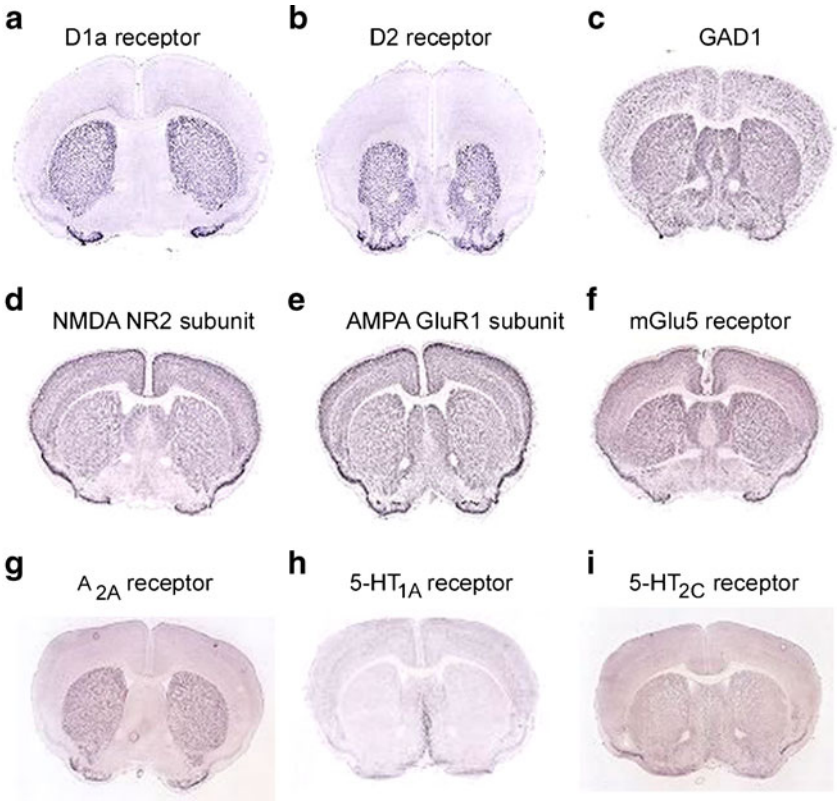

Fig. 2 Expression patterns of neurotransmitter systems in the rodent brain. Dopamine D1 and D2 receptors and adenosine A_{2A} receptors are localized and highly expressed in the striatum, while glutamic acid decarboxylase [GAD, present in gamma-aminobutryic acid (GABA)ergic neurons], N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA), and metabotropic glutamate receptor (mGlu5) subunits, and serotonin (5-HT) receptor subtypes are not concentrated in specific brain regions. In situ hybridization images are obtained from the Allen brain atlas (www.brain-map.org)

useful in accounting for some of the phenomenology associated with PD, basal ganglia circuitry is likely to be more complicated. For example, a recent rodent study suggests that both direct and indirect pathways are concurrently activated during initiation of action [4].

Glutamate receptors are expressed at high levels in the striatum. However, unlike dopamine receptors (which are highly enriched in the basal ganglia), they are present at high density throughout the brain (Fig. 2). GABA, which is synthesized from glutamate by the enzyme glutamic acid decarboxylase (GAD), is also expressed widely in the central nervous system (CNS). Given their primary role in basal ganglia circuitry, these neurotransmitter systems are potentially attractive targets to treat parkinsonian symptoms. However, their lack of regional specificity raises the potential challenge of side effects from actions on other brain regions.

Other neurotransmitters have also been implicated in the regulation of basal ganglia function. Adenosine is a purine nucleoside that acts to modulate synaptic function in the CNS. Its action is mediated by 4 G-protein-coupled receptor subtypes: A_1, A_{2A}, A_{2B}, and A_3. Of these, the A_{2A} receptor has received considerable attention as a potential treatment target because, like dopamine receptors, its expression is highly enriched in the striatum (Fig. 2) [5, 6]. Alterations in the serotonergic system have also been recognized in PD [7]. Of the 14 subtypes of serotonin (5-HT) receptors [8], multiple subtypes, including 5-HT_{1A} and 5-HT_{2C} receptors, are present in striatal neurons (Fig. 2). Serotonergic inputs from the raphe nuclei form widespread connections throughout the brain, including the substantia nigra, striatum, globus pallidus, STN, thalamus, and cortex.

Neuropathological studies have suggested that neurodegeneration in PD is not restricted to dopaminergic neurons and the basal ganglia. According to the Braak staging system [2], inclusion bodies containing α-synuclein are found in caudal brainstem nuclei (stage 1) prior to involvement of the substantia nigra (stage 3). At stage 2, 5-HT-producing raphe nuclei neurons are affected, as are projection neurons in the locus coeruleus that produce noradrenaline. At later stages (through stage 6), acetylcholine (ACh)-producing neurons in the pedunculopontine tegmental nucleus and neocortex also undergo degeneration. The diversity of affected neurotransmitter systems yields a number of symptoms that may only respond to adjunct non-dopaminergic therapies.

Symptomatic Treatment and Motor Fluctuations

The presence of multiple neurotransmitters modulating the basal ganglia circuitry that coordinates movement suggests that non-dopaminergic strategies may be helpful in treating motor symptoms. These approaches offer potential advantages, including providing antiparkinsonian benefits either as monotherapy or in combination with dopamine replacement,

allowing reduction in dose of dopaminergic agents to ameliorate treatment-related side effects, or directly reducing motor fluctuations and/or dyskinesias associated with chronic levodopa use.

Adenosine

Adenosine A_{2A} receptors are localized to dendrites, cell bodies, and axon terminals of GABAergic striatopallidal neurons of the indirect pathway, in close association with dopamine D_2 receptors [9–11]. By binding to A_{2A} receptors, adenosine activates striatopallidal neurons, opposing the inhibitory effects mediated by D2 receptor binding [12, 13]. These findings suggest that blockade of A_{2A} receptors should inhibit the excessive activity of the indirect pathway that results from dopamine depletion. Indeed, in rodent and non-human primate models of PD, A_{2A} antagonists consistently reversed parkinsonian deficits without development of tolerance to prolonged treatment [14]. The preclinical data have motivated multiple clinical trials investigating whether these agents are effective in treating PD symptoms (Table 1).

Among A_{2A} antagonists that have been investigated clinically, istradefylline (KW-6002) has been studied most extensively. In a phase II randomized clinical trial, istradefylline did not improve motor function when used as monotherapy [15]. However, multiple phase II clinical trials in levodopa-treated PD patients with motor fluctuations demonstrated a significant reduction in off time [16–20]. Several of these trials demonstrated an increase in on time with dyskinesias, although they were not troublesome and did not impair mobility [17–19]. A long-term, open-label study showed persistent improvement in off time over a 52-week treatment period, suggesting a sustained symptomatic benefit [21]. However, despite the initial optimism based on the early studies, subsequent phase III clinical trials have yielded conflicting results. Two studies demonstrated a significant reduction in daily off time with an increased incidence of dyskinesias [22, 23], but istradefylline did not affect off time in another trial [24]. In the latter study, motor function in the on state was improved compared with placebo, and a large placebo response may account for the negative effect on off time [24]. Although the US Food and Drug Administration issued a not approvable letter for istradefylline based on available data in 2008 [25], the drug was later approved for use in Japan as adjunctive treatment for PD [26], and phase III clinical development recently resumed in North America [27].

More recently, preladenant, a second-generation A_{2A} antagonist with higher affinity and greater selectivity, had been moving through the therapeutic pipeline. In a phase II, dose-finding, 12-week randomized, placebo-controlled trial, preladenant at a dose of 5 mg and 10 mg twice daily was well-tolerated and reduced off time without increasing on time with troublesome dyskinesias [28]. In a 36-week open-label extension study, the drug similarly provided a reduction in off time, but with an increased incidence of dyskinesias (33 % *vs* 9 % in the randomized study) [29]. Three separate phase III randomized, controlled clinical trials have been ongoing, 2 assessing preladenant when added to levodopa in patient with moderate-to-severe PD, and another as monotherapy in early PD. Results have not been presented or published, but a press release from the manufacturer [30] indicated that initial review did not show evidence of efficacy; as a result, extension studies were discontinued and there are no plans to pursue regulatory filings.

A phase IIb randomized clinical trial investigating the safety and efficacy of the A_{2A} antagonist tozadenant (SYN115) to treat end-of-dose wearing off in 420 patients with moderate-to-severe PD patients has been completed, and a preliminary communication reported good tolerability and significant reduction in off time [31]. A previous smaller clinical study of tozadenant in PD patients provided functional magnetic resonance imaging evidence that the drug enters the CNS and engages its putative target of striatopallidal adenosine A_{2A} receptors to reduce the inhibitory influence of the indirect pathway on motor function [32].

Lastly, it is worth noting that the non-specific adenosine receptor antagonist caffeine, likely acting by blocking striatal A_{2A} receptors [33], has recently demonstrated evidence of significant antiparkinsonian actions in a randomized clinical trial. Although the study by Postuma et al. [34] was designed primarily to investigate potential alerting effects, they observed a reduction in Unified Parkinson's Disease Rating Scale score comparable to that with more specific A_{2A} antagonists and are now pursuing a long-term phase III study to investigate potential disease-modifying benefits, as well as to possibly confirm short-term motor benefits. Convergent epidemiological and laboratory animal data also support the neuroprotective potential of A_{2A} antagonists, including caffeine, in PD [35]. Similarly, clinical, pathological, imaging, and laboratory findings have suggested these agents may help prevent the development of dyskinesias in PD [36–39].

GABA: Glutamic Acid Decarboxylase Gene Therapy

In PD, loss of dopaminergic neurons in the nigrostriatal pathway and reduction of striatal dopamine levels results in disinhibition of the subthalamic nucleus that causes parkinsonian symptoms. The enzyme GAD converts glutamate into GABA, the major inhibitory neurotransmitter in the brain. GAD gene transfer using an adeno-associated virus (AAV) has been explored as an approach

Table 1 Non-dopaminergic therapies for motor symptoms of Parkinson's disease: Results from clinical trials

Mechanism	Drug	Phase	Use	n	Dose	Duration	Primary Outcome	Result	Ref
SYMPTOMATIC TREATMENT AND MOTOR FLUCTUATIONS									
Adenosine									
A_{2A} antagonist	Istradefylline (KW-6002)	II	Mono	176	40 mg/day	12 weeks	Change from baseline in UPDRS motor score	Negative	[15]
			Adjunct	15	40 or 80 mg/day	6 weeks	Duration of L-dopa effect	Positive	[16]
			Adjunct	83	5/10/20 or 10/20/40 mg/day	12 weeks	Reduction in off time	Positive	[17]
			Adjunct	395	20 and 60 mg/day	12 weeks	Reduction in off time	Positive	[18]
			Adjunct	196	40 mg/day	12 weeks	Reduction in off time	Positive	[19]
			Adjunct	363	20 or 40 mg/day	12 weeks	Reduction in off time	Positive	[20]
		III	Adjunct	231	20 mg/day	12 weeks	Reduction in off time	Positive	[22]
			Adjunct	373	20 or 40 mg/day	12 weeks	Reduction in off time	Positive	[23]
			Adjunct	584	10, 20, or 40 mg/day	12 weeks	Reduction in off time	Negative	[24]
	Preladenant	II	Adjunct	253	1, 2, 5, or 10 twice daily	12 weeks	Reduction in off time	Positive (for 5, 10 mg doses)	[28]
	Tozadenant	II	Adjunct	420	60, 120, 180, or 240 mg twice daily	12 weeks	Reduction in off time	Positive (for 120, 180 mg doses)	[31]
GABA									
GAD gene therapy	AAV2–GAD	II	Adjunct	45	Bilateral AAV2–GAD delivery	6 months	Change from baseline in off state UPDRS motor score	Positive	[42]
Serotonin									
5-HT_{1A} agonist	Pardoprunox	II	Mono	139	9-45 mg/day	3 weeks	Change from baseline in UPDRS motor score	Positive	[49]
		III	Mono	468	6, 12, or 12–42 mg/day	24 weeks	Change from baseline in UPDRS motor score	Positive (high dropout rate)	[50]
			Mono	334	12–42 mg/day (*vs* pramipexole)	24 weeks	Change from baseline in UPDRS motor score	Positive (high dropout rate)	[50]
		III	Adjunct	295	12–42 mg/day	12 weeks	Reduction in off time	Positive (high dropout rate)	[51]
LEVODOPA-INDUCED DYSKINESIAS									
Glutamate									
NMDA receptor antagonist	Traxoprodil (CP-101,606)	II	Adjunct	12	Low, high-dose infusion	Single dose	Change in Dyskinesia Rating Scale score	Positive (dose-related side effects)	[71]
	Memantine	II	Adjunct	12	30 mg/day	2 week treatment	Change in dyskinesia score after single levodopa challenge	Negative	[72]
AMPA receptor antagonist	Perampanel	III	Adjunct	763	2 or 4 mg/day	30 weeks	Reduction in off time and severity of dyskinesias (UPDRS IV)	Negative	[82]
			Adjunct	751	2 or 4 mg/day	20 weeks	Reduction in off time and severity of dyskinesias (UPDRS IV)	Negative	[82]
mGluR5 negative allosteric modulator	Mavoglurant (AFQ056)	II	Adjunct	31	50–300 mg/day	16 days	Change in LFADLDS	Positive	[95]
			Adjunct	28	50–300 mg/day	16 days	Change in mAIMS score	Positive	[95]
			Adjunct	197	20, 50, 100, 150, or 200 mg/day	13 weeks	Change in mAIMS score	Positive (for 200 mg dose)	[96]
	Dipraglurant (ADX48261)	II	Adjunct	76	Dose titration to 300 mg/day	4 weeks	Change in mAIMS score	Positive (on Days 1, 14)	[99]

Table 1 (continued)

Mechanism	Drug	Phase	Use	n	Dose	Duration	Primary Outcome	Result	Ref
Noradrenaline									
α2 Adrenergic receptor antagonist	Fipamezole	II	Adjunct	179	90, 180, or 270 mg/day	4 weeks	Change in levodopa-induced dyskinesia scale	Negative	[109]
Serotonin									
5-HT_{1A} receptor agonist	Sarizotan	II	Adjunct	398	2, 4, or 10 mg/day	12 weeks	Change in diary-based *on* time without dyskinesias	Negative	[110]
GAIT AND BALANCE									
Cholinesterase inhibitor	Donepezil	IV	Adjunct	23	5–10 mg/day	6 weeks	Reduction in fall frequency	Positive	[119]
Noradrenergic reuptake inhibitor	Methylphenidate	IV	Adjunct (+ STN DBS)	69	1 mg/kg/day	90 days	Change in number of steps in stand-walk-sit test	Positive	[125]
			Adjunct	23	Up to 80 mg/day	12 weeks; 3-week washout	Change in gait composite score	Negative	[126]
NMDA receptor antagonist	Memantine	IV	Adjunct	25	20 mg/day	90 days	Change in stride length	Negative	[127]

GABA = gamma-aminobutyric acid; GAD = glutamic acid decarboxylase; 5-HT = serotonin; NMDA = *N*-methyl-D-aspartate; AMPA = alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid; mGlu = metabotropic glutamate; AAV = adeno-associated virus; STN = subthalamic nucleus; DBS = deep brain stimulation; UPDRS = Unified Parkinson Disease Rating Scale; LFADLDS = Lang-Fahn Activities of Daily Living Dyskinesia Scale; mAIMS, modified Abnormal Involuntary Movement Scale

to convert STN neurons from being excitatory to inhibitory [40]. In an initial phase I, open-label study, 12 patients with advanced PD were followed for 12 months after unilateral injection of AAV–GAD into the STN. Improvements in contralateral on and off motor function were observed 3 months after the injection and persisted for 12 months [41]. In a phase II double-blind, randomized trial comparing bilateral delivery of AAV2–GAD to sham surgery, patients receiving active gene therapy demonstrated a significant improvement in motor Unified Parkinson's Disease Rating Scale score in the off state, but not the on state, at 6 months [42]. Despite these initial promising proof-of-principle findings for non-dopaminergic modulation of STN neurotransmission and for gene therapy in PD, the long-term follow-up study has been terminated owing to financial reasons [43] and there are no plans for phase III studies.

Serotonin

In PD, serotonergic neurons in the raphe nuclei degenerate, leading to a reduction in 5-HT levels [7]. Loss of 5-HT is thought to contribute to both motor and non-motor symptoms. In preclinical models, several 5-HT_{1A} receptor agonists have shown efficacy in improving motor activity and reducing dyskinesias. However, interpretation of these results is complicated in that these agents can also interact with other receptors. In levodopa-treated parkinsonian rats, the partial 5-HT_{1A} receptor agonist piclozotan improved motor function [44]. A randomized pilot study using piclozotan in a small number of PD patients on levodopa was also reported to show improvements in off and on time without dyskinesias [45, 46]. However, results have been published only in abstract form and additional trials have not been registered.

Pardoprunox (SLV308) is a full 5-HT_{1A} agonist that also has partial dopamine D2/D3 agonist properties. As monotherapy in animal models it reduced parkinsonian symptoms and induced only mild dyskinesias [47, 48]. In a double-blind study of pardoprunox in early PD, treatment resulted in improvement in motor function and activities of daily living [49]. Two large, randomized, phase III dose-finding trials also showed significant improvement in motor function, although dropout rates were high owing to treatment-emergent adverse events (e.g., nausea, somnolence, and dizziness) at higher doses [50]. As adjunctive therapy to levodopa, pardoprunox reduced off time and improved on time without troublesome dyskinesias in a phase III study [51]. However, a high dropout rate was similarly noted with the selected dose range, and the most recent registered clinical trial of pardoprunox was terminated "due to strategic considerations" [52].

Levodopa-induced Dyskinesias

Repeated administration of levodopa results in the development of motor complications, including involuntary dyskinesias. Age of PD onset, disease severity, and high levodopa dose are risk factors for the development of levodopa-induced dyskinesias (LID). Based on a literature review, the rate of development of dyskinesias has been reported to be about 35–40 % by 4–6 years of treatment, and nearly 90 % within a decade [53]. The mean time to onset of dyskinesias in a recent community-based study was 6.6 years [54]. LID can be clinically expressed in a variety of ways, occurring when levodopa effects are maximal (peak-dose dyskinesias, generally choreiform, but may be dystonic), with rising or falling levels of medication (diphasic dyskinesias), or at low levels of levodopa (off-period dystonia) [55, 56].

Evidence from postmortem and pharmacological preclinical studies supports a role for multiple non-dopaminergic systems in the development of LID [57–59]. These studies have led to exploratory trials investigating drugs targeting other neurotransmitters as adjunctive therapy with the goal of decreasing LID without compromising motor function.

Glutamate

Glutamate is the most abundant excitatory neurotransmitter in the brain and is directly involved in activating basal ganglia motor circuits. Loss of nigrostriatal dopamine input is believed to induce changes in synaptic connectivity in the striatum [60]. Repeated exposure to dopaminergic drugs, particularly in a hypodopaminergic parkinsonian state, results in maladaptive plasticity in glutamatergic synapses that contributes to the expression of dyskinesias [57, 61, 62].

Glutamate signaling in the CNS is mediated by a variety of receptors, including ionotropic receptors (those that directly conduct ion flow in response to glutamate binding) and metabotropic receptors (those whose actions are mediated via intracellular signaling pathways). Among ionotropic receptors, *N*-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA) receptors have been most extensively studied for a possible role in LID [59, 63].

Changes in NMDA receptor levels, phosphorylation state, and cellular distribution have been identified in the dyskinetic state in animal models [59]. Highlighting the complexity of antidyskinetic strategies targeting these receptors, preclinical studies using NMDA antagonists directed at specific receptor subunits in nonhuman primate models have yielded conflicting results. In one study, a negative allosteric modulator (Co-101,244/PD-174,494) acting on NR2B receptors decreased LID, while antagonists with increased specificity for NR1A/NR2A receptors exacerbated dyskinesias [64]. In contrast, another NR2B-specific antagonist (traxoprodil, CP-101,606) increased severity of dyskinesias in levodopa-treated animals [65].

As clinical support for a role for NMDA receptor modulation as an approach to treat LID, the nonselective NMDA antagonist amantadine is currently the only accepted treatment for dyskinesia in PD [66]. It has been recommended by the American Academy of Neurology for the treatment of dyskinesias (level C evidence) [67], and has also been suggested to be efficacious in treatment of LID in an evidence-based review by the Movement Disorders Society [68]. In a recent double-blind, randomized, placebo-controlled cross-over study of 36 patients with PD and dyskinesias, 64 % of patients showed improvement in LID [69]. Treatment with amantadine can also be limited by neuropsychiatric and other side effects. Remacemide, another nonselective NMDA antagonist, did not show a significant benefit in reducing dyskinesias in a randomized, controlled trial [70]. Hence, there is a need to develop better NMDA receptor antagonists with antidyskinetic properties.

To date, several small pilot studies have been conducted investigating other NMDA receptor blockers in PD. Traxoprodil, an antagonist selective for NR2B subunits, reduced the maximum severity of acute LID by approximately 30 % in response to a 2-h levodopa infusion in 12 PD patients with motor fluctuations and dyskinesias, but did not improve parkinsonism and caused dose-related neuropsychiatric side effects [71]. However, memantine, an NMDA receptor antagonist approved for treatment of dementia, did not improve dyskinesias in a small cross-over study [72], although there are case studies reporting a positive response [73–75]. An early small, double-blind, cross-over study suggested that the NMDA antagonist dextromethorphan may be effective in reducing LID [76]. AVP-923, a combination agent combining dextromethorphan and quinidine that has been approved for treatment of pseudobulbar affect [77], is currently being studied to assess its efficacy in reducing dyskinesias in a small phase IIa study [78]. Interestingly, recent preclinical data suggests that the potential antidyskinetic effect may be mediated by indirect 5-HT_{1A} agonism rather than through an NMDA antagonist effect [79].

The role of AMPA receptors in the development of LID has received less attention, although the AMPA antagonists talampanel (LY-300,164) [80] and topiramate [81] reduced LID in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primates. To date, 2 phase III human clinical trials using the AMPA antagonist perampanel as potential treatment for PD motor fluctuations have been published, but the drug did not show benefit either in reducing dyskinesias or "off" time [82]. Two small phase II studies investigating talampanel as an antidyskinetic agent have been completed, but results have not been published [83, 84].

Currently, metabotropic glutamate (mGlu) receptors are receiving significant attention as potential therapeutic targets [85, 86]. In particular, mGlu5 receptors are highly expressed

in the striatum and globus pallidus. Expression of mGlu5 is upregulated in MPTP-lesioned primates treated with levodopa, and this increase is associated with the development of LID [87]. Administration of mGlu5 antagonists has been shown to attenuate abnormal involuntary movements in rodent models [88, 89] and LIDs in primates [90–93].

Negative allosteric modulators (NAM) of G-protein-coupled receptors target binding sites distinct from the active site and inhibit the response to endogenous ligand. Drugs targeting allosteric sites may provide greater receptor selectivity and potentially decrease adverse side effects [94]. Clinically, the selective mGlu5 NAM mavoglurant (AFQ056) was demonstrated to show a significant antidyskinetic effect in 2 small phase II randomized clinical trials [95]. Findings from a larger dose-finding study of 197 patients with PD and dyskinesias provided further evidence of anti-dyskinetic benefit without worsening of parkinsonism [96]. A phase II study exploring the efficacy and safety of a modified release form was also recently completed [97]. Another mGlu5 NAM, dipraglurant (ADX48261), has similarly been under investigation as a putative antidyskinetic agent [98]. Although not yet published, preliminary results presented in abstract form suggest a significant reduction in peak dose LIDs without affecting levodopa efficacy [99]. Together, these results suggest that mGlu5 antagonists offer promise for the treatment of LID.

Noradrenaline

Noradrenaline exerts its action by binding to G-protein-coupled adrenergic receptors, which are expressed in the striatum, STN, and substantia nigra [100]. Of particular interest are $\alpha 2$ adrenergic receptors, which may act to modulate GABA [101, 102] and dopamine release [103]. In pharmacological studies using primate models, $\alpha 2$ antagonists have been shown to reduce LID [104, 105], possibly through preferential effects on the direct pathway [57]. These preclinical findings have motivated clinical trials exploring these agents as potential antidyskinetic therapies.

Pilot studies using idazoxan yielded conflicting results [106, 107], and this drug is no longer in clinical development for PD. Currently, the selective $\alpha_{2A/2C}$ receptor antagonist fipamezole is being studied for LID. An initial small pilot study demonstrated good tolerability and suppression of LID without exacerbating parkinsonian symptoms [108]. In a phase II study conducted in the USA and India, fipamezole failed to show a statistically significant reduction in dyskinesias [109]. However, separate outcome analysis of the US patients did show a benefit at the highest dose used; it has been proposed that this differential result may be owing to heterogeneity between the US and Indian study populations. An additional clinical trial may be helpful to determine whether fipamezole is indeed useful for treatment of LID.

Serotonin

Serotonin has also been implicated to play a role in LID, and 5-HT_{1A} receptor agonists and 5-HT_{2A} receptor antagonists have been explored as promising antidyskinetic agents. In a large phase IIb study, sarizotan, a full 5-HT_{1A} agonist with additional affinity for dopamine D3/D4 receptors, did not show benefit in increasing on time without dyskinesias, and resulted in increased off time at higher doses [110]. Eltoprazine, a mixed 5-$HT_{1A/1B}$ receptor agonist, is effective in suppressing LID in animal models [111]. A small, human, randomized clinical trial has been completed in Sweden, but results have not yet been published [112]. It has been proposed that drugs aimed at reducing LID by modulating serotonergic function may need to demonstrate anatomic selectivity, as well as receptor selectivity [113].

Gait and Balance

Postural instability and gait difficulty are cardinal features of idiopathic PD, but typically do not cause prominent functional disability until later stages of disease. In particular, patients at more advanced stages of PD may become unable to initiate locomotion and develop freezing of gait (FOG) [114]. FOG is often associated with gait imbalance and can result in falls [115]. In some cases, FOG may respond to dopaminergic therapy at earlier stages [116]; however, PD-associated gait disorders may become progressively resistant to dopamine replacement or can be unresponsive from the start. Neurodegeneration in non-dopaminergic brainstem structures may contribute directly to this lack of response [117]. Cholinergic neurons in the pedunculopontine tegmental nucleus (PPN) and the prefrontal and frontal cortex are thought to be involved in gait control. Noradrenaline-producing cells in the locus coeruleus are also severely affected in PD. As a result of striatal dopamine depletion, excessive glutamatergic activity at projections from STN to PPN may also contribute to locomotor dysfunction. Interest in the role of PPN in PD gait disorders has been supported by the finding that low-frequency deep brain stimulation may reduce falls and FOG, either alone or in combination with high-frequency STN stimulation [118].

Strategies to increase ACh transmission have been used to target gait and balance symptoms unrelated to FOG. A small, randomized, placebo-controlled, crossover study in PD patients with falls showed that the centrally-acting cholinesterase inhibitor donepezil reduced falls by approximately half [119]. A single-center study in the UK is similarly exploring the effects of rivastigmine on gait and balance [120]. In the striatum, nicotinic ACh receptors are located presynaptically, and include subtypes $\alpha 4\beta 2$, $\alpha 6\beta 2$, and $\alpha 7$ receptors. A single-site study investigating the use of varenicline, a partial

α4β2 and full α7 agonist used as an aid for smoking cessation, to improve balance is ongoing [121].

Methylphenidate is an amphetamine-like stimulant that inhibits presynaptic noradrenaline and dopamine transporters. Three small pilot studies using different dosing protocols demonstrated improvement in various gait measures, including gait speed and freezing [122–124]. Two subsequent randomized studies have been completed and reported conflicting results. In a study of 69 PD patients treated with STN–DBS, methylphenidate treatment improved the number of steps in the stand-walk-sit test; the treated group experienced significantly more adverse events [125]. However, another trial of 23 patients did not show any improvement in a gait composite score of stride length and velocity [126].

A recent study of 25 patients explored the use of the NMDA receptor antagonist memantine as treatment for axial symptoms of PD. Although the treated group showed improvement in axial motor symptoms and dyskinesias, no improvement was noted in stride length [127]. Similarly, a randomized, double-blind, placebo-controlled crossover trial of the non-specific NMDA antagonist amantadine failed to show benefit against FOG resistant to dopaminergic therapy [128].

Conclusions

Dopamine deficiency due to degeneration of the nigrostriatal pathway is the primary cause of motor symptoms in PD. Nevertheless, multiple other neurotransmitter systems play an important role in modulating basal ganglia function and motor control. Targeting these systems, in particular, offers potential approaches to treating motor complications of dopamine replacement and symptoms that are resistant to dopaminergic therapy. At first glance, candidate non-dopaminergic agents would appear to be the proverbial "low-hanging" fruit in the PD pipeline. Receptors for neurotransmitters, including adenosine, GABA, serotonin, glutamate, and noradrenaline, have been well characterized biochemically with extensive knowledge of their neuroanatomic distribution and intracellular signaling pathways. Moreover, preclinical studies in rodent and nonhuman primate models have demonstrated effectiveness in reducing parkinsonian symptoms.

Based on the promise of the animal studies and early phase clinical studies, a number of randomized clinical trials directed at a variety of neurotransmitter targets have been completed [129]. Unfortunately, no compound specifically targeting non-dopaminergic pathways has yet received broad regulatory approval of an indication for use in the therapeutic armamentarium for PD. Drawing on previous studies, a potential hurdle may be finding agents that show high receptor specificity and also target specific brain regions. For example, the presence of multiple glutamate and serotonin receptor subtypes offers the potential for designing drugs that act on one, or a narrow, subset of receptors. However, the widespread distribution of these receptors throughout the CNS poses the challenge of finding doses that do not cause limiting side effects through action at undesired neuroanatomic sites.

Adenosine A_{2A} receptors have been an attractive potential target, as they are highly enriched in the striatum. Phase III studies investigating 2 A_{2A} antagonists, istradefylline and preladenant, have been conducted, and while phase II studies have consistently shown benefit in reducing motor fluctuations, the large phase III studies have yielded conflicting results, slowing progression through the therapeutic pipeline. These discrepancies raise questions about the design of clinical trials addressing motor fluctuations. Determination of on/off fluctuations relies on patient diaries, which may be subject to variability despite appropriate training. Also, while there are multiple dyskinesia rating scales [130], the clinical variability in the types of dyskinesias and their timing offers challenges in quantifying response to treatment. There is similarly a need to define the most appropriate outcome measures for trials focusing on PD gait symptoms. The recent approval of istradefylline in Japan [26] will hopefully provide additional experience about the effect of A_{2A} antagonists as adjunctive therapy. Additional phase III studies with mGlu5 receptor antagonists will be necessary to confirm the initial promising results from phase I/II studies.

Given the complexity of the pharmacology of dopamine-induced and dopamine-refractory PD symptoms, it may be necessary to target multiple non-dopaminergic systems in order to optimize clinical response while minimizing side effects from any particular pathway. This presents obvious obstacles to clinical trial design. However, despite the challenges thus far, ongoing development of these strategies remains a critical and hopeful pursuit toward improved treatment of PD.

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