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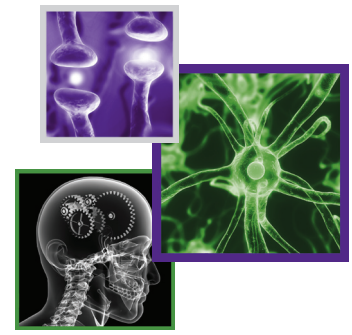
Neurodegenerative Disease Management



Nondopaminergic treatments for Parkinson's disease: current and future prospects

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Practice points

- Recent studies continue to expand the role of nondopaminergic pathways in Parkinson's disease (PD) pathophysiology.
- The nondopaminergic system includes glutamatergic, adrenergic, adenosine, serotonergic, histaminic, opioids and cholinergic pathways.
- Dysfunction in the nondopaminergic system may underlie motor and nonmotor symptoms of PD.
- Clinical trials testing novel nondopaminergic medications, as an adjunctive therapy to levodopa, have shown benefits in motor complications. However, to date, no nondopaminergic target is as effective as levodopa in improving motor symptoms of PD.
- Therapeutic options for nonmotor symptoms targeting the nondopaminergic system have also been investigated, particularly for cognition, sialorrhea and orthostatic hypotension.

Parkinson's disease is primarily caused by dysfunction of dopaminergic neurons, however, nondopaminergic (ND) systems are also involved. ND targets are potentially useful to reduce doses of levodopa or to treat nonlevodopa-responsive symptoms. Recent studies have investigated the role of ND drugs for motor and nonmotor symptoms. Adenosine A_{2A} receptor antagonists, mixed inhibitors of sodium/calcium channels and monoamine oxidase-B have recently been found to improve motor fluctuations. *N*-methyl-D-aspartate receptor antagonists and serotonin $5HT_{1B}$ receptor agonists demonstrated benefit in levodopa-induced dyskinesia. Conversely, studies using antiepileptic drugs and adrenoreceptor antagonist had conflicting results. Moreover, metabotropic glutamate receptor antagonists also failed to improve symptoms. The current review summarizes the most recent findings on ND drugs over the last 2 years.

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KEYWORDS

• motor and nonmotor symptoms • nondopaminergic treatment • Parkinson's disease

Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder manifesting with both motor and nonmotor symptoms, primarily secondary to degeneration of dopaminergic nigrostriatal pathway. Ongoing studies in animal models have shown new insights regarding the pathophysiology of PD, that continue to suggest that the nondopaminergic (ND) system is also affected [1,2] and may correlate with multiple PD symptoms. The ND system includes several neurotransmitter and neuromodulatory systems within the basal ganglia and related target areas, including glutamatergic,

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adrenergic, adenosine, serotonergic, histaminic, opioids and cholinergic pathways [3,4].

Dopaminergic medications are currently the most effective treatment for both motor and nonmotor symptoms, but may lead to complications such as motor fluctuations and levodopa-induced dyskinesia (LID). In addition, dopaminergic medication can also induce or aggravate nonmotor symptoms, which often manifest as nonmotor fluctuations related to OFF periods (transient worsening of symptoms due to oscillations in levodopa levels). Consequently, new therapeutic targets through alternative pathways, such as ND system, have been investigated and many are in the pipeline.

The goal of this article is to review advances in ND treatment in PD, for both motor **(Table 1)** and nonmotor symptoms **(Table 2)** over the last 2 years. Important ND targets that were previously evaluated are also mentioned if no further studies have been performed, using this target, in the past 2 years. The paper is divided into sections according to ND-specific pharmacological target; with coverage of all possible symptoms a single ND agent may treat. Readers are referred to **Tables 1 & 2** for categorization of targets according to symptoms.

Methods

• Search & selection criteria

We reviewed English-written papers published in PubMed between January 2014 and September 2015 using the keywords 'Parkinson's disease' and one of the following: 'adenosine', 'glutamate', 'serotonin', 'adrenergic', 'cholinesterase', 'botulinum toxin', 'histamine', 'antiepileptic' and 'opioid'. The yielded results were further filtered for Phase II/III clinical trials. We also reviewed the ongoing clinical trials using similar key words in the website Clinicaltrials.gov. The text is organized according to ND target, and the reader is referred to the tables for classification of each ND target according to clinical use. An extensive review of preclinical background and earlier studies is beyond the remit of this paper and readers are referred to referenced reviews in each section.

Nondopaminergic treatments

• Adenosine pathways

Adenosine A_{2A} receptor antagonists

Adenosine A_{2A} receptors are localized mainly within the striatum; activation causes stimulation of the indirect basal ganglia pathway, which modulates the output from globus pallidus internus (GPi) and substantia nigra (SN). Blockade of the adenosine A_{2A} receptor in striatopallidal neurons reduces postsynaptic effects of dopamine depletion, improving motor deficits in PD animal models without inducing LID [66,67]. Despite optimistic results in preclinical studies, clinical trials to date have shown variable efficacy to improve motor fluctuations [68].

Istradefylline was the first A_{2A} receptor antagonist evaluated as an adjunctive therapy with levodopa in PD patients with motor fluctuations **(Table 1)**. Several Phase III studies have already been conducted with generally positive results. The most recent study was in 373 PD patients over 12 weeks again showing significant reduction in OFF time with 20 mg/day (-0.99 h, $p < 0.003$) and 40 mg/day (-0.96 h; $p < 0.003$) compared with placebo (-0.23 h) [5]. An open-label phase [6] showed reduction in daily OFF time by -0.65 h in week 2. Dyskinesia was the most common side effect. Due to positive results, istradefylline was licensed in Japan in 2013. However, a US based Phase III study published in 2012 [69] failed to reach significance and as such, FDA approval was not given. A further multicenter Phase III trial is ongoing [7].

Preladenant is the second A_{2A} antagonist evaluated to treat motor fluctuations in PD **(Table 1)**. Initially, a Phase II study revealed reduction in mean daily OFF time with preladenant 5 mg (-1.0 h; $p = 0.0486$) and preladenant 10 mg (-1.2 h; $p = 0.019$) [70]. Two large Phase III trials, however, did not reach a significant difference in OFF time [8]. Development for PD has now ceased.

Tozadenant is the third A_{2A} antagonist aiming to treat motor fluctuations in PD **(Table 1)**. In a Phase IIb trial, the mean daily OFF time was significantly reduced in the tozadenant 120 mg group (-1.1 h; $p = 0.0039$) and the tozadenant 180 mg group (-1.2 h; $p = 0.0039$) [9]. The most common adverse events were dyskinesia, nausea and dizziness. A Phase III is currently active [10].

Caffeine is a nonselective adenosine antagonist recently investigated in a 6-week randomized controlled trial (RCT) using caffeine 100 mg twice daily for 3 weeks, then increasing to 200 mg twice daily for the next 3 weeks and matching placebo. Despite revealing nonsignificant reduction in Epworth Sleepiness Scale score for daytime somnolence or difference in motor fluctuations or dyskinesia, caffeine reduced the total UPDRS score (-4.69 points) and the

Table 1. Recent findings in nondopaminergic treatments for motor symptoms in Parkinson's disease.

Motor symptom	Nondopaminergic treatment	Mechanism of action	Stage of development	Recent findings	Ref.
Motor fluctuations	Istradefylline	Adenosine A_{2A} receptor antagonist	Phase III ongoing Approved in Japan Under review at US FDA	Significant reduction in OFF time at 20 mg/day (-0.99 h) and 40 mg/day (-0.96 h) compared with placebo	[5–7]
	Preladenant		Phase III Development ceased	No significant difference compared with placebo in two clinical trials published this year	[8]
	Tozadenant		Phase III ongoing	Significant reduction of mean daily OFF time with tozadenant 120 mg (-1.1 h) and 180 mg (-1.2 h) compared with placebo	[9,10]
	Safinamide	Inhibition of sodium/calcium channels and MAO-B activity	Phase III Approved in Europe Under review at FDA	A 24-week RCT, demonstrated that safinamide, 50 and 100 mg/day significantly increased ON time without increasing dyskinesia. Subsequently, an 18-month study indicated no significant change in a DRS; while mean daily ON time without troublesome dyskinesia improved by 1.01 h (50 mg/day; p = 0.0031) and 1.18 h (100 mg/day; p = 0.0002). Recently, a 24-month study reported significant improvement in DRS score (p = 0.0488)	[11–13]
	Zonisamide		Currently available for epilepsy Phase III (PD) Approved for use in Japan	Change in the OFF time was -0.011 h/day for placebo, -0.436 h/day for zonisamide 25 mg, and -0.719 h/day for zonisamide 50 mg (p = 0.005). Zonisamide did not increase troublesome LID; however, the dose of levodopa in the trial is lower than commonly used in western populations	[14]
Levodopa-induced dyskinesia	ADS-5102 extended-release amantadine	NMDA antagonist	Phase III ongoing	Significant reduction of LID compared with placebo (27% reduction in UDysRS), as well as increased ON time without troublesome LID	[15] (EASED-Study)
	Amantadine HCl extended release	NMDA antagonist	Phase III ongoing	Ongoing Phase III: multicenter, double blind, randomized, placebo-control 16 week (ALLAY-LID I), and 26 week (ALLAY-LID II). Both studies testing two different doses 240 and 320 mg/day	[16] (ALLAY-LID I) [17] (ALLAY-LID II)
	Dextromethorphan/ Quinidine (AVP-923)	NMDA receptor antagonist Quinidine is a CYP2D6 inhibitor	Clinically available Phase II	Phase IIa completed, results are pending	[18]
	Memantine	NMDA receptor antagonist	Clinically available Phase III	No significant change in LID ratings, but 35% reduction in the percentage of time of the day spent with LID (self-administered diary)	[19]
	Topiramate	Blockade of voltage-gated sodium and calcium channels and enhancement of GABA effect	Clinically available Phase II	Significantly increased LID severity compared with placebo group and multiple side effects. A Phase II trial testing topiramate combined with amantadine is ongoing	[20,21]

Clinically available: but off-label use in this indication.

5-HT: Serotonin receptor; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; COMT: Catechol-*O*-methyltransferase; CYP2D6: Enzyme cytochrome P450 2D6; DRS: Dyskinesia Rating Scale; ESS: Epworth sleepiness scale; FoG: Freezing of gait; GABA: Gamma-aminobutyric acid; LID: Levodopa-induced dyskinesia; mAIMS: Modified abnormal involuntary movement score; MAO-B: Monoamine-B; mGluR5: Metabotropic glutamate receptors subtype 5; MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; nAChR: Nicotinic acetylcholine receptor; NMDA: *N*-methyl-D-aspartate receptors; PD: Parkinson's disease; UDysRS: Unified dyskinesia rating score; UPDRS-IV item 32: Unified Parkinson's disease rating score part IV item 32 – duration of dyskinesia.

Table 1. Recent findings in nondopaminergic treatments for motor symptoms in Parkinson's disease (cont.).

Motor symptom	Nondopaminergic treatment	Mechanism of action	Stage of development	Recent findings	Ref.
Levodopa-induced dyskinesia (cont.)	Mavoglurant (AFQ056)	mGluR5 antagonist	Phase II Development for PD ceased	Reduced Lang-Fahn Activities of Daily Living Dyskinesia score -4.6 compared with placebo -1.57, ($p = 0.021$). mAIMS also improved (-6.93) compared with placebo (-1.63), $p < 0.001$. Recently, a Phase II trial ($n = 154$) revealed no significant change on mAIMS	[22–24]
	Dipraglurant (ADX48621)	mGluR5 antagonist	Phase II No further studies in PD	Effective reduction in mAIMS at day 1 and 14, but no significant difference at study end (day 28)	[25]
	Buspirone	α1 adrenergic receptor and 5-HT_{1A} agonist	Clinically available Phase III ongoing	A Phase I study testing buspirone combined with amantadine and a Phase III trial (buspirone monotherapy) are currently active	[26,27]
	Eltoprazine	Combined 5-HT_{1A} and 5-HT_{1B} agonist	Clinically available Phase II trial ongoing	Eltoprazine 5 mg reduced the area under the curves of Clinical Dyskinesia Rating Scale (-1.02; $p = 0.004$) and Rush Dyskinesia Rating Scale (-0.15; $p = 0.003$)	[28,29]
	AQW051	Selective a α7- nAChR partial agonist	Phase II completed	Phase II randomized, double blind, placebo-controlled trial to assess safety, tolerability and efficacy of AQW051 in moderate-to-severe LID has been completed, but results are pending	[30]
	NP002	nAChR agonist	Phase II completed	Potential antidyskinetic role in PD patients. Phase II trial completed, but results are pending	[31,32]
Tremor	Botulinum toxin	Inhibition of acetylcholine release from nerve terminals	Clinically available Phase II trial ongoing	A 38-week open-label study assessed 28 PD patients receiving incobotulinumtoxinA (BoNT-A) at weeks 0, 16 and 32 in the upper limbs and revealed reduction in severity of rest tremor (UPDRS item 20) from 2.7 ± 0.6 at week 0 to 2.0 ± 0.8 at week 16 ($p = 0.006$) and to 2.1 ± 0.7 at week 32 ($p = 0.014$). Ten participants reported mild muscle weakness. Preliminary data of a Phase II trial (30 patients) revealed improvement in the UPDRS tremor scale after 4 weeks of BoNT-A injections ($p = 0.0007$) in eight patients	[33–35]
Gait disorders	Methylphenidate	Noradrenaline reuptake inhibitor	Phase IV Clinically available	Slight improvement in gait during OFF period, but did not change the FoG score. Reduced FoG and modest effect on apathy and attention in another trial	[36]
	Droxidopa	Artificial amino acid converted to norepinephrine	Phase II ongoing	Phase II, crossover study, assessing clinical benefit and safety of droxidopa 600 mg daily (11 weeks) for walking, freezing of gait and cognition is currently active	[37]

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Table 1. Recent findings in nondopaminergic treatments for motor symptoms in Parkinson's disease (cont.).

Motor symptom	Nondopaminergic treatment	Mechanism of action	Stage of development	Recent findings	Ref.
Motor symptoms (total UPDRS)	Caffeine	Nonselective adenosine antagonist	Clinically available Phase III ongoing	6-week randomized controlled trial with caffeine 200 mg b.i.d. with primary end point for excessive daytime sleepiness was nonsignificant, but total UPDRS score; (-4.69 points) and motor III component (-3.15 points) was significantly reduced compared with placebo. A Phase III trial assessing motor and nonmotor symptoms (caffeine 200 mg twice daily) is ongoing	[38,39]

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objective motor component (-3.15 points) [38]. A Phase III RCT assessing motor and nonmotor symptoms in PD patients on caffeine 200 mg twice daily compared with placebo is ongoing **(Table 1)** [39].

Comments

Adenosine A_{2A} antagonists are potentially useful adjuncts for wearing off, and appear to have similar benefit to the other clinically available drugs, such as monoamine oxidase-B inhibitors (MAOB-I) and catechol-*O*-methyltransferase inhibitors (COMT-I). Thus, all such drugs can increase daily ON time by about 1 h. Tolerability is good, although, as with MAOB-I and COMT-I, worsening of peak dose dyskinesia may limit clinical utility in some patients. The variability in efficacy between the three A_{2A} antagonists evaluated so far may relate to biological differences in binding potential to A_{2A} receptors and different half-life of the drugs, as well as variability in placebo effects in Phase III trials which potentially mask a true clinical benefit [71].

• Glutamatergic pathways

There is extensive evidence implicating glutamate in the pathophysiology of PD via multiple receptor subtypes, including *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and metabotropic glutamate receptors (mGluR). Most studies have focused on motor circuits. Overactivity of the corticostriatal glutamatergic pathways, as well as excessive inhibitory output through overactivity of the direct pathway (GPi and SN pars reticulata), disinhibiting the subthalamic nucleus (STN) and increasing glutamate release are key features underlying the pathophysiology of LID [72]. The role of glutamate in nonmotor PD symptoms such as cognition have recently been evaluated [73].

N-methyl-D-aspartate receptor antagonists

Overactive glutamate transmission in LID is partly due to increased activity of NMDA receptors, a subtype of inotropic glutamate receptors localized in the striatum and STN [4]. Chronic levodopa leads to altered distribution and consequent increased activation of striatal dopaminergic D1/D3 receptors within the striatum. Activation of dopamine D1 receptors results in enhanced phosphorylation of NMDA glutamate receptor subunits, and consequent hyperactivation of signaling pathways including sequential

Table 2. Recent findings in nondopaminergic treatments for nonmotor symptoms in Parkinson's disease.

Nonmotor symptoms	Nondopaminergic treatment	Mechanism of action	Stage of development	Recent findings	Ref.
Neuropsychiatric symptoms (depression, anxiety, apathy, psychosis)	Pimavanserin	$5HT_{2A}$ inverse agonist	Phase III Under review at US FDA	Significantly reduced PD-psychosis over 6 weeks: -5.79 decrease in SAPS-PD scores compared with -2.73 for placebo (difference -3.06, 95% CI: -4.91 to -1.20; p = 0.001)	[40]
	Rivastigmine	Cholinesterase inhibitor	Clinically available Phase IV ongoing	Ongoing study to reduce development of visual hallucinations in nondemented PD	[41]
ICD	Naltrexone	Opioid antagonist	Clinically available Phase IV	Naltrexone 50–100 mg/day over 8 weeks in PD patients with ICD showed nonsignificant reduction in ICD severity using clinical global impression scale	[42]
Orthostatic hypotension	Midodrine	α1-adrenoceptor agonist	Clinically available Phase II Crossover trial ongoing	Use in PD has not yet been validated in clinical trials. Crossover trial is ongoing: Midodrine 2.5–5 mg given three-times a day for 2 weeks in PD patients	[43,44]
	Droxidopa	Artificial amino acid converted to norepinephrine	Phase III FDA approved	Increase standing systolic blood pressure. Only short-term benefit reported in clinical trials	[45,46]
	Pyridostigmine	Peripheral inhibitor of acetylcholinesterase	Clinically available Phase II ongoing	Symptomatic management of OH. RCT Phase II is ongoing and will assess noninferiority of the effect of pyridostigmine compared with fludrocortisone for 14 days of active treatment in each group	[43,47,48]
Sialorrhea	Glycopyrrolate	Anticholinergic	Clinically available Phase II ongoing	Mean sialorrhea score improved from 4.6 with placebo to 3.8 with glycopyrrolate 1 mg three-times daily for 4 weeks. Phase II assessing glycopyrrolate 1.5 mg three-times daily for 90 days is ongoing	[49,50]
	Botulinum toxin	Inhibition of acetylcholine release from nerve terminals	Clinically available 2 Phase III trials ongoing	A/Abo 250 U or B/Rima 2500 U injections in PD were effective in 89% of treatments. The overall mean duration was 87 days similar for both serotypes (p = 0.392). Injection-related adverse effects complicated 1.5% of treatments (pain at injection sites, subcutaneous hematoma and mouth bleeding). No patients reported dysphagia or facial weakness	[51–53]

Clinically available: but off-label use in this indication.

A/Abo: Abobotulinumtoxin A; B/Rima: Rimabotulinumtoxinb B/Rima; ADL: Activities of daily living; ICD: Impulse control disorder; MCI: Mild cognitive impairment; MMSE: Mini-mental state examination; MOCA: Montreal cognitive assessment; OH: Orthostatic hypotension; PD: Parkinson's disease; PDD: Parkinson's disease dementia; RCT: Randomized controlled trial; SAPS-PD: Parkinson's disease-adapted scale for assessment of positive symptoms.

Table 2. Recent findings in nondopaminergic treatments for nonmotor symptoms in Parkinson's disease (cont.).

Nonmotor symptoms	Nondopaminergic treatment	Mechanism of action	Stage of development	Recent findings	Ref.
Mild cognitive impairment	Memantine	NMDA receptor antagonist	Clinically available Phase III	Memantine 20 mg/day improved choice reaction time, immediate and delayed word recognition	[54]
	Rivastigmine	Cholinesterase inhibitor	Clinically available Phase III	28 PD patients with MCI treated with rivastigmine (patch) 9.5 mg/day (4.6 mg/day during the initial 4 weeks); however, only a trend toward improved global rating of cognition was seen versus placebo after 24 weeks	[55]
PD dementia	Donepezil	Cholinesterase inhibitor	Currently available Phase II ongoing	Phase II study ongoing comparing donepezil 23 mg versus 10 mg once a day	[56]
	Rivastigmine	Cholinesterase inhibitor	Currently available	Rivastigmine 3 mg orally twice daily for 12 months showed higher MOCA and reduced number of falls compared with placebo	[57]
	SYN120	Dual 5-HT_6/5-HT_{2A} antagonist	Phase II ongoing	A Phase II in PDD patients treated with a stable dose of cholinesterase inhibitor is ongoing	[58,59]
Overactive bladder	Botulinum toxin	Inhibition of acetylcholine release from nerve terminals	Currently available 2 Phase IV trials are ongoing	Level A recommendation – effective for overactive bladder. There are 2 Phase IV trials currently active for neurogenic bladder in PD patients	[60,61]
Pain	Oxycodone-Naloxone	Opioid analgesic (oxycodone) with opioid receptor antagonist (naloxone)	Clinically available Phase II ongoing	No significant difference compared with placebo. Reduced pain scores in a smaller trial (fewer side effects)	[62–64]
	Botulinum toxin	Inhibition of acetylcholine release from nerve terminals	Clinically available Phase IV ongoing	A double-blind randomized crossover study is currently ongoing (onabotulinum toxin A)	[65]

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phosphorylation of secondary messengers. This functional link between dopamine D1 and NMDA neurotransmission leads to a form of synaptic plasticity similar to long-term potentiation (LTP) underlying learning and memory; thus in the striatum in LID, excessive LTP may contribute to the development of motor fluctuations [74].

Nonselective antagonism of NMDA receptors in nonbasal ganglia areas, however, has been implicated in side effects; and thus more selective targeting of subtypes of NMDA receptor, in particular the NR2B subtype that appear to be selectively localized within the striatum, have been investigated in preclinical studies with efficacy in LID [72]. However, to date, few clinically available subtype-selective NMDA receptor antagonists have been available for evaluation, to determine whether this approach translates into better clinical efficacy in PD patients. Nonselective NMDA antagonists thus remain the drug target available for clinical use.

Amantadine is a nonselective NMDA antagonist currently in clinical use to treat LID **(Table 1)** [75]. However, side effects can occur including confusion and visual hallucinations (VH). A longer acting preparation has been suggested to improve side effects profile by reducing nighttime drug levels. ADS-5102 is a long-acting, formulation of amantadine HCl extended release administered as a capsule once daily before bedtime. ADS-5102 has been shown to achieve high plasma amantadine concentrations in the early morning that are sustained throughout the afternoon and are lower in the evening. A Phase II/III study assessed 83 PD patients receiving ADS-5102 for 8 weeks and reported significant reduction of dyskinesia compared with placebo (27% reduction in Unified Dyskinesia Rating Scale – UDysRS, $p = 0.005$), as well as increased ON time without troublesome dyskinesia [15]. The most common side effect was constipation. A Phase III trial is ongoing [76]. Another long-acting formulation of Amantadine HCl extended release is also being evaluated in two Phase III RCTs during 16 weeks (ALLAY-LID I) [16] and 26 weeks (ALLAY-LID II) [17]. Amantadine formulation is a tablet administered as a single dose daily in the morning so that amantadine concentrations are maintained throughout the day.

Dextromethorphan is another NMDA receptor antagonist that has been combined with quinidine, a CYP2D6 inhibitor responsible for reducing and stabilizing the metabolism of dextromethorphan into a single drug preparation. This combination of dextromethorphan combined with quinidine (AVP923) is clinically available in the USA for treatment of pseudobulbar affect [77]. Due to the clinical availability of this agent, and earlier studies showing efficacy, a small Phase IIa study in PD to treat LID is ongoing **(Table 1)** [18,78].

Memantine, another clinically available nonselective NMDA antagonist, has been previously evaluated for PD motor symptoms without benefit. This agent was originally developed as an alternative NMDA antagonist due to the properties of uncompetitive binding with a lower affinity and more rapid off-rate kinetics at the NMDA receptor with theoretical better tolerability. Recently, in a small crossover trial ($n = 15$) memantine (20 mg) for 3 weeks revealed no change in dyskinesia ratings. Memantine was well tolerated and six patients reported nonspecific symptoms including tiredness and vertigo. No serious adverse events occurred [19].

Glutamate neurotoxicity via NMDA receptors is also thought to underlie dementia, and memantine is approved and in clinical use for treatment of Alzheimer's disease (AD). NMDA receptor antagonists have thus been evaluated for cognitive impairment in PD. Memantine has been evaluated in two prior RCTs and demonstrated efficacy in Dementia with Lewy Bodies (DLB) and possibly in PD dementia (PDD), with generally good tolerability [79]. Further studies have investigated the role of memantine in mild cognitive impairment (MCI) and a recent 24-week trial of memantine (20 mg/day) showed improvement in choice reaction time, immediate and delayed word recognition **(Table 2)** [54].

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

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are another subtype of inotropic glutamate receptor and are expressed at relevant excitatory synapses within the SN pars compacta, SN pars reticulata and striatum. Although AMPA antagonists have shown limited benefit as monotherapy for symptomatic relief in PD, preclinical studies suggest possible potentiation of the effects of levodopa and also improvement in LID [72]. Talampanel previously showed improvement in motor symptoms in PD animal models [80]. However, three Phase II trials were never published [81–83]. Perampanel is a selective, noncompetitive AMPA

receptor antagonist developed to treat epilepsy. Perampanel failed to improve motor fluctuations and LID in clinical trials [84,85] and development for PD has now ceased.

Topiramate is another antiepileptic drug with several mechanism of action including inhibition of voltage-gated sodium and calcium channels, reduction of glutamate-related excitatory neurotransmission via AMPA receptors and enhancement of GABA effect. Previous studies have shown that topiramate significantly reduced LID in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP-lesioned) animal models [86,87]. Contrary to preclinical studies, a recent crossover trial in 15 PD patients using topiramate 100 mg/day showed significant increase in dyskinesia severity and medication was poorly tolerated (dry mouth and hallucinations) **(Table 1)** [20]. A Phase II trial assessing topiramate combined to amantadine is listed as currently active, but no recent data have been reported [21].

Metabotropic glutamate receptor antagonist

Modulating excessive glutamate neurotransmission via mGluRs has been proposed to be potentially effective at reducing LID in PD, with a wider therapeutic index. Metabotropic glutamate receptors (mGluRs) are divided into subtypes according to receptor structure and activity [73]. Thus preclinical evidence demonstrates that group I mGluR antagonism and groups II and III mGluR activation improves motor symptoms and decreases LID in PD animal models [73,88].

Mavoglurant (AFQ056) is a selective mGluR5 inhibitor. Three previous studies revealed mild improvement in dyskinesia **(Table 1)** [22,23]. Open-label Phase II results are pending [89]. Recently, a Phase II trial (n = 154) revealed no significant change on mAIMS [24]. Development for PD has ceased due to lack of efficacy [90].

Dipraglurant (ADX48621) is another selective mGluR5 antagonist. Results of a Phase IIa study [25] published in abstract form showed reduction in mAIMS (peak dose) at day 1 ($p = 0.042$) and 14 ($p = 0.034$), but no significant difference was detected at study end point (day 28) **(Table 1)**. Currently, there are no known plans for future studies in PD.

Comments

Glutamate antagonists continue to be an important ND target, due to the integral component that the glutamate system plays in PD. Amantadine is the only clinically available glutamate antagonist that can reduce LID, but side effects, including hallucinations, means tolerability can be poor. The longer acting version in development appears to be equally effective, and is thought to reduce nighttime complications. Amantadine, however, has other ND actions including muscarinic antagonist activity, which can also induce other side effects such as constipation. The effectiveness of metabotropic glutamate receptors, with potentially better tolerability, has not yet been proven despite good preclinical data, and development of this class appears to have stalled. The other inotropic glutamate target, AMPA receptor antagonists, although theoretically useful, in complementing both NMDA and mGluR5 activity, has generally shown very poor efficacy and tolerability.

The rationale for NMDA antagonist use in PDD has been that cognitive function due to altered NMDA transmission underlying LTP is also implicated in PD as well as non-PD dementias such as AD. However, to date, there is little direct evidence of this process in PDD and the varied cognitive profile of PDD versus AD, may underlie differences in pathophysiology and hence treatment strategies. In fact a recent meta-analysis reviewed ten trials of agents for PD dementia using memantine and cholinesterase inhibitors and showed overall small global efficacy; however, only the cholinesterase inhibitors significantly improved Mini-Mental State Examination (MMSE) [91] suggesting the pathophysiology of PDD is more cholinergic than glutamatergic. In clinical practice, triggering hallucinations are also of concern in the PD population with glutamate agents.

Mixed monoamine-B & glutamate release inhibitors

The clinical use of MAOB-I, selegiline and rasagiline in PD is well known to enhance the duration of action of levodopa, and thus to improve wearing-off. Clinical use of MAOB-I, can, however, often increase peak-dose LID. Safinamide is a reversible and highly selective MAOB-I, with additional properties including sodium channel antagonism and N-type calcium channel modulator with consequent inhibition of excessive glutamate release. Theoretically, the action of safinamide was to improve duration of levodopa action, without increased risk of LID due to the glutamate antagonistic properties. A 24-week RCT, demonstrated that safinamide,

50 and 100 mg/day significantly increased ON time without increasing dyskinesia (Table 1) [11]. Subsequently, an 18-month study indicated no significant change in a Dyskinesia Rating Scale (DRS; the primary end point); while secondary end points of mean daily ON time without troublesome dyskinesia improved by 1.01 h (50 mg/day; p = 0.0031) and 1.18 h (100 mg/day; p = 0.0002) [12]. Recently, a 24-month treatment study reported that safinamide 100 mg/day significantly improved the DRS score (p = 0.0488) [13]. Safinamide was recently licensed for use in PD in the European Union.

A similar agent, zonisamide was originally developed as an antiepileptic, but also has multiple mechanism of action such as inhibition of sodium/calcium channels, monoamine-B (MAO-B) activity and GABA transmission. In a recent trial, daily OFF time reduced significantly (-0.719 h) in zonisamide 50 mg/day group (p = 0.005) (Table 1) [14]. Dyskinesia duration decreased in placebo group at week 12 (-0.027 h/day) and increased 0.197 h/day (p = 0.103) for zonisamide 25 mg, and 0.138 h/day (p = 0.235) for zonisamide 50 mg. Further analysis revealed that zonisamide did not increase troublesome dyskinesia, however, the dose of levodopa in the trial is lower than commonly used in western populations. Zonisamide is licensed for treatment of motor fluctuations in Japan; further global licensing is unlikely.

Comments

Safinamide and zonisamide both appear to reduce wearing-off in PD, but the ability to do this without exacerbating peak dose LID is not yet clear. The current clinical availability of safinamide will enable real-world experience to show whether the theoretical benefit is present in day-to-day practice.

• Serotonin pathways

Serotonin (5HT) receptors are located in the raphe nuclei of the brainstem and are involved in several basic brain functions including cognition, emotion, circadian rhythms as well as motor behavior [92]. Serotonergic neuronal loss and presence of Lewy bodies in the raphe nuclei has been described in PD as well as changes in cortical $5HT_2$ receptors implicating 5HT dysfunction in mood and psychosis in PD [2,92,93]. Dysfunction in the serotonin system may play a role in LID, as 5HT loss is less than dopamine loss. In addition, ectopic levodopa converted to dopamine, with resultant unregulated dopamine release, can occur from remaining 5HT terminals [94,95]. Listed below are several clinically available drugs with 5HT binding properties that have been recently evaluated for a range of clinical indications in PD, including PD psychosis, LID, anxiety and depression.

Clozapine is a dibenzodiazepine with antiserotoninergic properties (5-$HT_{2A/2C}$ receptor antagonist) [96] that is not only a very effective drug for the treatment of neuropsychiatric symptoms in PD [97] due to a lack of PD motor side effects, but also a potential therapeutic tool for LID [3,96]. The practical issue limiting clozapine use is mandatory blood monitoring due to low risk of agranulocytosis. A recent new selective $5HT_{2A}$ inverse agonist, pimavanserin, has shown success in a single Phase III RCT in reducing hallucinations in PD, without worsening PD motor symptoms, and no requirement for blood monitoring (Table 2) [40].

Buspirone is a mixed α1 adrenergic receptor and 5-HT_{1A} agonist with potential antidyskinetic role in animal models [98]. A single acute dose study showed possible benefit in PD patients with LID (Table 1) [99]. A Phase I evaluating the efficacy of buspirone in combination with amantadine and a Phase III trial (buspirone monotherapy) are currently active [26,27].

Eltoprazine is a combined 5-HT_{1A} and 5-HT_{1B} agonist, originally developed to treat aggressive behavior. An antidyskinetic role in PD animal models has been recently proposed [100]. In a Phase IIa study (n = 22) eltoprazine 5 mg improved LID measured by the area under the curves of Clinical Dyskinesia Rating Scale (-1.02; p = 0.004) and Rush Dyskinesia Rating Scale (-0.15; p = 0.003) (Table 1) [28]. Nausea and dizziness were the most common side effects. Another Phase II trial is currently active [29].

Extending the hypothesis that $5HT_{1a}$ receptor agonists may reduce LID, a recent study suggested that PD patients exposed to selective serotonin reuptake inhibitors (SSRIs) may have delayed onset of LID [101]. Forty-nine patients received SSRIs concomitant to levodopa for at least 2 years (mean exposure 5.1 ± 4.1 years); 86 were never treated with antidepressants. Patients were exposed to sertraline, fluoxetine, paroxetine, citalopram and escitalopram. No significant difference between the groups was observed (p = 0.897) in the prevalence of LID. However, patients exposed to SSRIs developed LID later compared with nonexposed group

(6.48 vs 5.70 years between PD diagnosis and LID onset; p = 0.020). The median dyskinesia severity score was 0 in the exposed group versus 1 in nonexposed patients (p = 0.025).

Serotonin is also implicated in cognitive function and ligands binding to several 5HT receptors have been proposed as potential therapeutic targets in AD [58]. SYN120 is a dual 5-HT_6/5-HT_2 antagonist evaluated in AD; and a Phase IIa is currently recruiting PD patients with dementia **(Table 2)** [59].

Comments

The serotonergic system continues to be investigated for both motor and nonmotor PD symptoms. In reducing LID, $5HT_{1A}$ agonists have had mixed benefits with prior drugs such as sarizotan, a mixed $5HT_{1A}$ agonist and possible dopamine D_4 antagonist, failing to show significant benefit compared with a marked placebo effect, and also having issues with worsening of PD motor symptoms [102]. Despite this, recent studies continue to evaluate clinically available $5HT_{1A}$ agonists due to the theoretical ability to reduce release of dopamine from aberrant 5HT terminals. Buspirone and eltoprazine may be useful.

Current treatments for anxiety and depression in PD continue to rely on classical 5HT reuptake inhibitors (SSRIs) and 5HT antagonists (tricyclics), and thus one serotonergic drug such as $5HT_{1A}$ agonist, could theoretically help both motor (LID) and nonmotor (anxiety) symptoms in a PD patient. Another potential 'multi-use' drug is the atypical antipsychotic drug, clozapine that at low doses is a $5HT_{2A/2C}$ antagonist, and can reduce PD psychosis, as well as LID, and also tremor, without worsening PD motor symptoms (unlike other antipsychotics). The newly developed $5HT_{2A}$ inverse agonist, pimavanserin, appears promising for use in PD psychosis. However, relative clinical efficacy compared with the currently clinically used drugs (quetiapine and clozapine) remains unknown.

• Adrenergic pathway

Extensive noradrenergic denervation in the frontal cortex, cerebellum, striatum, thalamus and hypothalamus along with Lewy bodies in the axons of noradrenergic neurons of the locus coeruleus have been described in PD brains [93]. Thus the adrenergic system may have a role in the pathophysiology of several PD symptoms, including autonomic failure and gait; in addition, α_2-adrenoreceptors in striatal GABAergic neurons have also been suggested as a potential therapeutic target for LID [103].

Adrenergic receptor agonists

Treatment of symptomatic neurogenic orthostatic hypotension (OH) currently relies on nonpharmacological approaches including additional fluids and salt supplementation, compression stockings and reduction of antihypertensive drugs. Pharmacological management of OH aims to increase standing blood pressure in PD patients, however, due to lack of level 1 RCT specifically in this population, general pressor agents, such as adrenergic receptor agonists, are commonly used [43].

Midodrine is a directly acting α1-adrenoceptor agonist with short action duration (2–4 h). It has been extensively and successfully used for symptomatic neurogenic OH for more than 20 years, even though use in PD has not yet been validated in clinical trials **(Table 2)** [43]. A crossover study is currently active [44].

Droxidopa (L-threo-3,4-dihydroxyphenylserine) is an artificial amino acid converted both peripherally and centrally into norepinephrine [104]. FDA recently approved the use of droxidopa for the treatment of symptomatic OH **(Table 2)**. The main studies included Phase III trial (n = 162, mixed population with OH, n = 35 had PD) revealed mild, short-term (1 week) improvement in total score and subscores of OH questionnaire [45]. Mean standing systolic blood pressure (SBP) increased by 11.2 versus 3.9 mm Hg (droxidopa vs placebo; p < 0.001). The adverse events were headache and dizziness. A recent Phase III trial in PD only showed improvement in OH questionnaire and with mean increase in SBP at week 1 of 6.4 mmHg for droxidopa compared with 0.7 mmHg in placebo (p = 0.032) [46]. A Phase III trial is currently active and will assess benefit and safety of Droxidopa 600 mg/day for both freezing of gait (FoG) and cognition in PD [37].

Noradrenergic reuptake inhibitor

Methylphenidate is a known stimulant that blocks both dopamine and noradrenaline reuptake through inhibition of the presynaptic dopamine transporter in the striatum and prefrontal cortex [105]. Recent studies have shown a possible benefit for gait and FoG in PD patients **(Table 1)**. The mechanism of action is unclear but theoretically degeneration of locus coeruleus brainstem

noradrenergic circuits may affect gait and balance, as well as enhanced noradrenaline cortical activation, with enhanced attention, having an indirect effect on preventing falls. A 6-month crossover study (n = 27) revealed slight improvement in the gait score during OFF period, but did not improve the FoG score or UPDRS motor score [36]. In a 3-month trial in 69 PD patients with severe gait problems despite the optimization of drugs and subthalamic stimulation parameters, FoG was less frequent in the methylphenidate group during ON or OFF conditions [106]. Improvement in apathy and modest effects in attention were seen [106].

α_2-adrenergic receptor antagonist

Fipamezole is an α_2-adrenoceptor antagonist that has been shown to suppress LID in PD animal models [107]. A trial conducted in the USA (115 PD patients) and India (64 PD patients) showed no statistically significant results, however, a subgroup analysis of US patients only reported significant LID reduction in LID scale compared with placebo (-1.9 points; p = 0.047) [108]. Nausea and transient blood pressure elevation were the most reported adverse events. To date, no newer α_2-adrenoceptor antagonists have been evaluated in PD.

Comments

The noradrenergic system is implicated in autonomic function and thus targeting adrenergic receptors appears to have potential to improve symptomatic OH in PD. The issue of supine hypertension, however, still remains a potential side effect. The role of the noradrenergic system in motor function to date remains less clear. Although preclinical studies have suggested reduced LID with α_2-adrenoceptor antagonists, clinical studies have not yet shown convincing results. Interesting observations with methylphenidate and ongoing studies with droxidopa suggest that enhanced adrenergic function may help gait, again it is unclear how, above general increased alerting effects and thus improved attention.

• Cholinergic pathways

The cholinergic system is also affected in PD. In particular pathological studies from patients with PD and dementia (PDD) have shown greater loss of cortical cholinergic function compared with AD [109]. In addition, there is a suggestion that cholinesterase inhibitors are particularly useful in PDD patients with visual hallucinations, to reduce such psychotic symptoms. Preclinical studies have also shown that central cholinergic nicotinic receptors are implicated in basal ganglia motor function and LID. Autonomic failure is a common clinical issue in PD, and thus peripheral cholinergic muscarinic receptors in the parasympathetic system can be targeted to reduce bladder overactivity, constipation as well as reducing saliva to reduce drooling in PD.

Cholinesterase inhibitors

Donepezil is an acetylcholinesterase inhibitor that showed benefit originally in AD, and is now used clinically in PD for treating cognitive impairment. Previous RCT of donepezil (5 or 10 mg) in PDD demonstrated improvement in executive function and attention despite no significant benefit in activities of daily living [110]. The current dose range is 5–10 mg. However, higher doses (once daily sustained-release 23 mg) have been used in moderate-to-severe AD [111]. A Phase II trial of donepezil 23 versus 10 mg donepezil in PDD is ongoing [56].

Rivastigmine is another cholinesterase inhibitor that is used clinically in PDD **(Table 2)**. Oral and patch preparations are available with efficacy and better tolerability using the patch [91,112]. A recent trial in 176 PD patients evaluating rivastigmine 3 mg twice daily for 12 months showed higher MoCA scores (p = 0.002) and reduced the number and the incidence of falls (p < 0.01) compared with placebo [57]. Rivastigmine has also been evaluated in 28 PD patients with MCI treated with rivastigmine (patch) 9.5 mg/day (4.6 mg/day during the initial 4 weeks); however, only a trend toward improved global rating of cognition was seen versus placebo after 24 weeks [55]. A Phase IV trial assessing rivastigmine 6 mg twice daily (orally) for 24 months is also underway in nondemented PD patients to determine if early treatment delays the progression of minor VH to major VH [41].

Pyridostigmine is a peripheral inhibitor of acetylcholinesterase used for treatment of OH **(Table 2)**, however; literature in PD is scarce [47]. A Phase II crossover trial is currently ongoing comparing pyridostigmine versus fludrocortisone [48].

Muscarinic receptor antagonists

Muscarinic cholinergic antagonists have been used in the treatment of PD for decades, Recent

evidence-based medicine reviews considered trihexyphenidyl and benztropine likely efficacious for PD tremor [75]. However, side effect profile of oral anticholinergic has limited use for tremor as well as other indications. Thus topical/local applications have been evaluated for reducing saliva in sialorrhea.

Glycopyrrolate is a muscarinic competitive antagonist currently used to reduce salivation **(Table 2)**. Glycopyrrolate 1 mg three-times per day (TID) for 4 weeks in 23 PD patients improved mean sialorrhea score from 4.6 with placebo to 3.8 with glycopyrrolate (mean difference 0.8; p = 0.011) [49]. A Phase II trial is ongoing evaluating 0.5 mg t.i.d. for 4 days, followed by an increase to 1.0 mg t.i.d. for 4 days and to 1.5 mg t.i.d. at day 8 (target dose) for a longer period of 90 days [50].

Tropicamide is a short-acting muscarinic receptor antagonist with pharmacodynamics similar to atropine, but fewer side effects. A recent pilot study tested a slowly dissolving, mucoadhesive intra-oral thin film containing tropicamide (NH004) and reported a visual analog scale (VAS) reduction of -0.55, -1.08, -1.53 and -0.81 for placebo and 0.3, 1 and 3 mg tropicamide, respectively (p = 0.6) [113]. No adverse effects were detected.

Nicotinic receptor agonists

The role of nicotine in PD has been of interest for many years due to the epidemiological observations that PD is less likely in individuals who are smokers. Clinical studies evaluating nonselective nicotinic agents, however, have been poorly tolerated and shown no clinical benefit in PD. More recently preclinical data have shown certain subtypes of nicotinic receptors (nAchR) maybe implicated in PD and LID. AQW051 is a selective a α7-nAChR partial agonist and studies in PD animal models have shown no worsening in motor symptoms, reduced dyskinesia score and extended levodopa antiparkinsonian response in MPTP-lesioned monkey [114]. Phase II trial results are pending **(Table 1)** [30]. NP002 (nicotine tablets) is another nAChR agonist with potential antidyskinetic role in PD patients [31,115]. Results of a small Phase II trial were never published [32].

Botulinum toxin

Botulinum toxin (BoNT) also decreases cholinergic action, by reducing release of acetylcholine in muscle terminal endplates. Focally injected BoNT is currently used in PD patients and is the most effective treatment for focal dystonia, blepharospasm and eyelid apraxia (level A recommendation) [60]. Despite this no RCTs have been reported evaluating use specifically in PD.

There have been several studies investigating BoNT injections for PD tremors **(Table 1)**. A 38-week open-label study assessed 28 PD patients receiving incobotulinumtoxinA (BoNT-A) at weeks 0, 16 and 32 in the upper limbs and revealed reduction in severity of rest tremor (UPDRS item 20) from 2.7 ± 0.6 at week 0 to 2.0 ± 0.8 at week 16 (p = 0.006) and to 2.1 ± 0.7 at week 32 (p = 0.014) [33]. Ten participants reported mild muscle weakness according to self-reporting Likert scale following the third treatment, which did not interfere with performing activities of daily living. Preliminary data of a Phase II trial (30 patients) revealed improvement in the UPDRS tremor scale after 4 weeks of BoNT-A injections (p = 0.0007) in 8 patients [34]. A Phase II trial is ongoing [35].

BoNT injections are established as effective treatment for overactive bladder in PD and hyperhidrosis (level A recommendation) **(Table 2)** [60]. There are two active Phase IV trials testing BoNT injections for neurogenic bladder in PD [61].

A Phase IV trial is ongoing to assess the efficacy and safety of BoNT (onabotulinum toxin A) for limb pain **(Table 2)**. Injections target painful muscles (upper or lower limbs) and are compared with placebo injections [65].

BoNT injections are effective for sialorrhea in PD patients **(Table 2)** [60,116,117]. A recent trial followed for 8 years 32 amyotrophic lateral sclerosis (ALS) and 33 PD patients with severe sialorrhea receiving at least two ultrasound-guided intrasalivary glands abobotulinumtoxin A (A/Abo) 250 U or rimabotulinumtoxinB (B/Rima) 2500 U injections [51]. Compared with baseline, A/Abo and B/Rima induced a clear benefit in 89% of treatments and PD patients had a longer duration of benefit (p < 0.001). The overall mean duration was 87 days similar for both serotypes (p = 0.392). BoNT did not lose efficacy over time in up to 8 years of repeated treatments and authors observed failures in 11% of treatments. Injection-related adverse effects complicated 1.5% of treatments, unrelated to BoNT serotype: pain at injection sites (0.6%), subcutaneous hematoma (0.3%) and mouth bleeding (0.6%). No patients reported dysphagia or facial weakness. Two Phase III trials are currently active [52,53].

Comments

The concern with manipulation of the cholinergic system in PD is balancing benefit with side effects. Muscarinic cholinergic antagonists are very effective treatments for PD tremor, but with significant side effects that limit use, including dry mouth, aggravating constipation and causing hallucinations, confusion and drowsiness. Cholinesterase inhibitors by enhancing central cholinergic function may reduce cognitive issues and visual hallucinations but can conversely increase PD tremor. Oral and sublingual muscarinic antagonists used to treat sialorrhea, should thus theoretically act locally within the parasympathetic system of the salivary glands and not cross the blood–brain barrier. Reducing peripheral muscarinic neurotransmitter release with injection of botulinum toxins, that will not induce central side effects, has been used successfully for several symptoms of PD. The newer selective nicotinic agonists studied for potential to reduce LID are thought to have less side effects than nicotine, due to selective basal ganglia targeting but further studies are needed.

• Histamine pathways

Histamine pathways have also been implicated in the motor function. Histaminic receptors are divided in four subtypes (H_1-H_4) and H_2 is highly expressed in the basal ganglia including striatum, GP and SN and involved in the GABAergic striatopallidal and striatonigral pathways [118,119]. Famotidine is a clinically available histaminic receptor antagonist that has shown antidyskinetic properties in MPTP animal models [118]. Recently, a Phase IIa (n = 7) study using famotidine 80, 120 and 160 mg/day revealed no significant change in UDysRS part III or UPDRS part III. There were no significant adverse events [120]. To date, no further studies evaluating histamine targets are ongoing.

• Anti-epileptics

Levetiracetam is a synaptic vesicle glycoprotein (SV2A) modulator and largely used for epilepsy treatment. Previously, levetiracetam (60 mg/kg) has shown significantly antidyskinetic efficacy in the MPTP-treated macaque [121]. A crossover trial assessed levetiracetam 1000 mg/day for treatment of LID in 38 PD patients and reported a reduction in ON period with LID (assessed by patient diaries) by 37 min (p = 0.02) at 500 mg/day and 75 min (p = 0.002) at 1000 mg/day [122]. However, another crossover trial analyzed 16 PD patients on levetiracetam 2000 mg/day with hourly-videotaped LID assessments scored by the Goetz method and hourly UPDRS motor subscale demonstrating slightly less LID on placebo (p = 0.26) including patient diary records (p = 0.10) [123]. Additionally, UPDRS motor subscale worsened on levetiracetam, but with borderline statistical significance (p = 0.05).

Comments

Using clinically available drugs is of benefit in translational studies in PD due to reduced time to reach clinical use. Several such anti-epileptic drugs, due to the respective pharmacological profiles, have been evaluated in PD. However, to date, results have been disappointing. Thus levetiracetam, perampanel and topiramate failed to significantly improve symptoms in PD. Tolerability was also an issue, reflecting the variable sensitivity to such agents in epilepsy and PD patients.

• Opioids

Opioids and opioid receptors play a role in the pathophysiology of LID, however; clinical studies in PD patients with LID have been disappointing due to lack of clinically available subtype-selective opioid receptor binding drugs [124].

Opioids are well known to be involved in pain and studies have investigated opioids for treatment of nonmotor symptoms in PD, particularly pain. PD-related pain has a complex physiopathology including peripheral mechanism and also changes in pain processing. Patients may experience musculoskeletal, central or visceral and limb pain. Given the lack of RCTs specifically assessing pain management in this population, two recent studies have investigated clinically available general analgesics such as opioids, in PD patients.

Oxycodone-naloxone prolonged release is a combination of oxycodone (opioid analgesic) with naloxone (opioid receptor antagonist) to reduce constipation. A Phase II trial revealed no significant difference in pain score compared with placebo after 16 weeks (difference -0.6; p = 0.058) **(Table 2)** [62]. Side effects were nausea and constipation. A smaller trial (n = 16) showed reduced pain scores with fewer side effects [63]. A Phase II/III is currently active [64].

Another use of opioid-binding agents in PD has been to extend the use of clinically available nonselective opioid antagonist, naltrexone used

in treatment of addiction, into the PD field. Thus a recent RCT evaluated 50–100 mg/day naltrexone in 50 PD patients with impulsive compulsive disorders (ICDs) over 8 weeks and showed nonsignificant reduction in ICD severity using clinical global impressions scale ($p = 0.5$) [42].

Conclusion

In summary, ND medications have been extensively investigated lately with significant advances. Adenosine A_{2A} antagonists seem to be potentially useful adjuncts for wearing off and have shown benefit compared with controls in RCTs. Glutamate antagonists such as amantadine can reduce LID, but side effects are still a concern. Metabotropic glutamate receptor antagonists failed to show clear clinical improvement and, therefore, development appears to have ceased. AMPA receptor antagonists had very poor efficacy and tolerability. Moreover, antiepileptics such as topiramate and levetiracetam failed to reduce LID in PD patients. The clinically available serotonergic anxiolytics, buspirone and eltoprazine, may have use in reducing LID but further studies in PD are needed.

Concomitantly, additional studies have investigated ND medications as therapeutic options for nonmotor symptoms. NMDA antagonist such as memantine, despite being efficacious for AD, has shown limited benefit for PDD. Serotonergic medications have been investigated for PD psychosis, most recently pimavanserin, a $5HT_{2A}$ inverse agonist, has demonstrated potential for reducing hallucinations. Adrenergic medications including droxidopa may be a therapeutic option for OH according to recent studies, but benefit is short term, and comparison with other agents not yet known. Cholinergic medications such as muscarinic receptor antagonists (glycopyrrolate and tropicamide) can reduce sialorrhea, without causing central side effects. The newer nicotinic agonists due to selective targeting are expected to cause fewer side effects, however, this drug target is still under development. BoNT remains a very effective treatment for sialorrhea, bladder overactivity, focal dystonia and blepharospasm. In addition, BoNT has shown a potential therapeutic benefit for parkinsonian tremor in recent studies. Opioids agonists (oxycodone) revealed modest benefit for pain control with significant side effects and opioid antagonist (naloxone) did not demonstrate benefit for impulsive compulsive disorders.

Future perspective

The ND system continues to be recognized as a potential therapeutic target for motor and increasingly, nonmotor symptoms in PD. Most trials in Phase II or III have focused predominantly on the management of motor fluctuations and LID, where ND drugs are used as adjunctive therapy to extend the duration of action, and allow reduction in doses of levodopa. Thus adenosine A_{2A} antagonists along with mixed MAO-B and glutamate release inhibitors (safinamide and zonisamide) seem to be potentially useful adjuncts for motor fluctuations and have shown significant benefit. The 'real-world' use of such drugs will determine how useful such targets are in comparison to currently available drugs for wearing off (e.g., dopamine agonists, MAOB-I and COMT-I). Head-to head RCTs of efficacy as add-on therapy for motor fluctuations between these drugs are unlikely to occur; thus evidence of relative efficacy will have to be determined retrospectively. Due to different mechanisms of action, in theory, addition of an adenosine A_{2A} antagonist should be useful in a patient already taking an MAOB-I and COMT-I. Tolerability with these newer agents appears overall good. The risk of triggering or exacerbating LID appears common with all agents that are add-on for wearing off and strategies to reduce peak-dose levels of dopamine (e.g., decrease levodopa doses) may be the key to overall benefit.

In terms of LID management, glutamate antagonism still appears the most effective option. The longer acting amantadine preparations may help reduce nighttime side effects, but all other known side effects with immediate release amantadine (e.g., livido reticularis, leg edema, anticholinergic issues) will still likely occur even with this preparation. The lack of clinical efficacy with metabotropic glutamate receptor antagonists has been disappointing and remains unclear. Other ND drugs for LID that show potential include $5HT_{1A}$ agonists to reduce ectopic dopamine release. Clinically available serotonergic drugs, buspirone and eltoprazine, have shown promising results, but longer duration studies in PD are needed.

Historically, translational studies evaluating new ND drugs for LID have been difficult, with good preclinical efficacy rarely replicated at the clinical level. There are many reasons that this may have occurred; including inherent differences in animal models from PD patients and

issues with trial design, for example, large placebo effects masking potential efficacy and variability in outcome measures of LID in patients. Efforts to address these issues are ongoing (e.g., new preclinical models of PD [125]) and development of more reliable measure of LID, with hopefully improved drug development.

More importantly, nonmotor symptoms play a significant role in the quality of life of PD, requiring new therapeutic approaches. ND drugs have emerged as relevant alternatives for the management of several nonmotor features, particularly due to a poor response to dopaminergic therapy. Control of PD psychosis is particularly challenging without worsening PD motor symptoms. Thus pimavanserin ($5HT_{2A}$ inverse agonist) has potential to control psychosis and hallucinations without the risk of agranulocytosis caused by clozapine.

In most other clinical situations ND drugs for controlling nondopaminergic symptoms have not been developed purely for PD, but rather used clinically available drugs from the non-PD field. Recent successful examples have included cholinesterase inhibitors for PDD, botulinum toxin for drooling, adrenergic agents for OH. Such approaches assume the same, or similar, pathophysiology underlying the nonmotor symptoms in PD as in non-PD. This may be true to a certain extent but differences clearly exist in some key symptoms, for example, mood disorders and cognitive profiles, that reflect the specific pathology of PD. The last few years have seen an increase in research into the pathophysiology of nonmotor issues in PD, but the field still lacks behind knowledge of motor symptoms, and as such, drug development including ND drugs specifically for PD is lacking.

In conclusion, ND medications continue to be extensively investigated and remain promising therapeutic options for both motor and nonmotor symptoms in PD.

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