Non-dopaminergic treatments in development for Parkinson's disease

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Non-dopaminergic treatments are increasingly being recognised as part of the therapeutic armamentarium for Parkinson's disease (PD). Clinical and pathological studies have shown that the disease extends beyond the substantia nigra pars compacta and involves various non-dopaminergic neurotransmitter systems that mediate both motor and non-motor symptoms that characterise PD. To date, several therapeutic strategies have been proposed to treat such symptoms. However, despite the significant morbidity associated with these symptoms, particularly non-motor symptoms, research into and drug development for problems such as mood and autonomic dysfunction remain scarce. Here, we review novel non-dopaminergic approaches that are in at least phase II clinical development for the treatment of PD.

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Introduction

Parkinson's disease (PD) is primarily a disorder of the nigrostriatal dopaminergic pathway that results in the cardinal motor symptoms of bradykinesia, tremor, and rigidity. However, the pathological changes in PD also involve various non-dopaminergic neurotransmitter systems, and these are also disturbed as a consequence of long-term levodopa therapy. Thus, cortical and brainstem acetylcholine, noradrenaline, serotonin, and other neurotransmitter systems probably mediate various non-motor symptoms as the disease progresses, including disturbances in cognition, mood, behaviour, sleep, and autonomic function. These symptoms are often resistant to dopamine-replacement therapies and modern surgical treatments, and contribute greatly to the disability of late-stage PD. In addition, glutamate, adenosine, serotonin, and other neurotransmitters are involved in control of motor symptoms and mediate problems such as dyskinesia that occur after long-term levodopa treatment.

Non-dopaminergic neurotransmitter systems within the brainstem might be affected before the onset of classic motor symptoms. Early recognition of pre-motor symptoms, such as sleep disturbances and bowel dysfunction, could provide an opportunity for the use of neuroprotective drugs that target both non-dopaminergic systems and dopaminergic cell death, since, to date, treatments that focus only on the latter have generally been unsuccessful. The need for a shift in focus from developing dopaminergic to non-dopaminergic therapies is important for the future management of PD.[1,2] We discuss potential novel therapeutic approaches to PD symptoms with a focus on non-dopaminergic therapies that are in at least phase II clinical development. Our purpose is not to cover all neurotransmitter systems known to be altered in PD, but only those in which there have been active recent therapeutic advances. For example, although much information is available on the endocannabinoid and opioid systems in PD, to our knowledge there are no new related compounds sufficiently advanced in their clinical development.

Non-dopaminergic therapies for non-motor symptoms

Non-motor symptoms in PD include neuropsychiatric symptoms, sleep disturbances, autonomic dysfunction, and pain or sensory problems.[3] Such symptoms are a frequent accompaniment to the motor disability with continuing disease progression.[4] Although several non-dopaminergic systems within the brainstem and cortex are involved in PD, specific clinicopathological correlation for such features remains uncertain, and despite the increasing recognition of these problems, specific pharmacological therapies that target the relevant non-dopaminergic neurotransmitter system are limited. Our goal for this section is to review novel non-dopaminergic treatments that are under development for non-motor symptoms. Many other symptoms, such as primary sensory complaints including pain, remain poorly understood and need further research.

Psychiatric problems

Mood disturbances

Anxiety and depression are extremely common in PD and frequently coexist. Both might respond to dopaminergic therapies, and anxiety in particular can be experienced when the motor effects of levodopa have worn off (ie, during an "off period"). However, successful management of these mood disorders often requires treatments in addition to dopaminergic agents, which suggests that non-dopaminergic neurotransmitters are involved. The dorsal raphe nucleus and locus coeruleus are both affected in PD, resulting in serotonergic and noradrenergic dysfunction.[5–7] However, direct evidence that a disturbance of serotonergic neurotransmission contributes to depression or anxiety in PD is lacking due to limited correlation with mood symptoms in several clinico-pathological studies and confounding effects of serotonin 5-HT receptor downregulation with repeated use of serotonergic drugs.[8–10] In addition, in an acute tryptophan depletion study,[11] no effect on mood in PD patients with depression was shown, in contrast to the classic mood-lowering effects of acute tryptophan depletion seen in non-PD patients at risk of depression; therefore, this study

further suggested that serotonin might contribute less to PD depression than previously thought.[11] Thus, enhancing serotonin concentrations with selective serotonin reuptake inhibitors (SSRIs) might not, in fact, be the most effective treatment for mood disorders in PD. Indeed, many patients with PD have depression even on conventional antidepressant therapy,[12] suggesting that the pathophysiology of depression in PD might be different from that in patients without PD. Because the age of onset is older, the pathophysiology of anxiety in PD might also differ from that occurring in the non-PD population.[13]

Desite this, the current management of depression and anxiety in PD involves the use of conventional treatments that enhance serotonergic neurotransmission, such as SSRIs or tricyclic antidepressants. Although in clinical practice many patients with PD do experience a significant improvement in mood symptoms with these agents (whatever the exact mechanism of action), the true effectiveness in PD has not been established owing to the limited numbers of available randomised controlled trials (RCTs).[12,14] Several RCTs assessing serotonin involvement in depression in PD are now in progress at phase III or IV level, and are generally assessing the benefit of established antidepressants, such as SSRIs (table 1).

The role of noradrenergic dysfunction in PD patients with depression is supported by a recent PET study that

	Mechanism of action	Clinical studies	Comments
Depression and anxiety			
Paroxetine	SSRI	Phase II completed (no results published); paroxetine compared with nortriptyline and placebo[15]	Comparative effects between different potential antidepressants are difficult owing to variable primary outcome measures; in addition, rating depression in PD involves use of non-PD-validated scales[16]
Sertraline	SSRI	Phase IV, single-blind completed; 50 mg sertraline had non-significant effect compared with amitryptiline (25 mg) over 3 months (n=31)[17]	..
Atomoxetine	SSRI and SNRI	Phase IV study underway[18]	..
Duloxetine	SSRI and SNRI	Phase IV (open-label) study underway[19]	..
Venlafaxine	SSRI and SNRI	Phase III compared with paroxetine underway[20]	..
Desipramine	SNRI	Phase IV completed; significant improvement compared with citalopram and placebo (n=48)[21]	Adverse effects more common with desipramine; efficacy not clear owing to short duration (4 weeks) of study
Psychosis and visual hallucinations			
Pimavanserin (ACP-103)	5-HT_{2A} inverse agonist	Phase II completed; trend towards improvement in psychosis (n=60);[22] phase III study underway[23,24]	No reported worsening of PD motor symptoms in phase II study
Cognition			
Memantine	NMDA receptor antagonist	Phase III/IV trials underway in USA and Europe; 20 mg daily for 24 weeks[25,26]	Tolerability of memantine is possibly better than for other NMDA receptor antagonists because agent enters the receptor-associated ion channel preferentially when it is excessively open, and has a fast rate of dissociation, so there is less interference with normal synaptic transmission
Rivastigmine patch	Cholinesterase inhibitor	Phase III compared with rivastigmine capsule (76 weeks) underway[27]	Also comparing effects on PD motor scores (potential side-effect is to worsen PD tremor); in AD, the rivastigmine patch was associated with less nausea
Safinamide	MAO-B inhibitor, dopamine and noradrenaline reuptake inhibitor, Na^+/Ca^{2+} channel blocker, and glutamate release inhibitor	Phase III study underway[28]	Effect of safinamide on cognition is a secondary outcome of the phase III study, in which the main focus is motor symptoms; safinamide has several potential mechanisms of action; the proposed effect on cognition is unclear
Behavioural problems (impulse control disorders)			
Acamprosate (calcium acetyl-homotaurine)	Reduces glutamate-mediated transmission	Phase II study underway (for compulsive behaviour and cravings)[29]	..
Excessive daytime sleepiness			
Caffeine	Non-specific adenosine antagonist	Phase III study underway[30]	..
BF 2.649	Histamine H_3 inverse agonist	Phase II study underway[31]	..
Orthostatic hypotension			
L-threo-3,4-dihydroxyphenylserine	An artificial amino acid that is decarboxylated to noradrenaline by aromatic L-amino acid decarboxylase	Phase IIb study completed (orphan drug status, Jan, 2007); phase III study underway[32]	Potential interaction with peripheral decarboxylase inhibitors carbidopa and benserazid in levodopa formulations might limit efficacy in levodopa-treated PD
Urge incontinence			
Solifenacin succinate	Muscarinic antagonist	Phase IV study[33]	Study on hold; large multicentre study planned

All clinical studies are randomised controlled trials (RCTs), unless otherwise stated. Further information is available at ClinicalTrials.gov (http://www.clinicaltrials.gov/). MAO-B=monoamine oxidase B. SSRI=selective serotonin reuptake inhibitor. SNRI=selective noradrenaline reuptake inhibitor.

Table 1: **Non-dopaminergic treatments for non-motor symptoms in PD**

used ^{11}C-RTI-32,[34] which binds to dopamine and noradrenergic reuptake sites. The study showed reduced binding in the locus coeruleus and limbic system (amygdala, thalamus, and anterior cingulate, areas that receive noradrenergic innervation) compared with non-depressed patients with PD.[34] Some antidepressants, which are undergoing investigation for depression and anxiety in PD, are also selective noradrenergic reuptake inhibitors (eg, duloxetine, venlafaxine, and desipramine; table 1).

Visual hallucinations and psychotic symptoms

Well formed, complex, visual hallucinations are characteristic of idiopathic PD, and up to 50% of patients could be affected at some point in the disease.[35] In some individuals, visual hallucinations can be stable, non-distressing, and might not require treatment. However, in others visual hallucinations can become frightening and additional psychotic symptoms can occur, including persecutory paranoid delusions, with loss of insight. The cause of psychotic symptoms in PD is probably multifactorial, involving interplay between pathological processes and dopaminergic medications. Serotonin is thought to be involved in the pathogenesis of visual hallucinations as suggested by the finding of increased 5-HT$_2$ receptors in the temporal cortex of PD patients with visual hallucinations compared with non-hallucinators;[36] this area is shown to be selectively affected by Lewy body disease in PD patients with visual hallucinations.[37] Current treatment options for psychosis in PD include the atypical antipsychotic drugs clozapine and quetiapine.[38] These drugs are mixed dopamine D$_2$ and 5-HT$_{2A/2C}$ receptor antagonists. Patients with PD respond to doses of as little as 10 times less than the doses required by patients with schizophrenia. At these doses, there is high occupancy of 5-HT$_{2A}$ receptors but low dopamine D$_2$ occupancy,[39] further supporting a role for 5-HT$_{2A}$ receptors. A 5-HT$_{2A}$ receptor inverse agonist, pimavanserin (ACP-103), is in clinical development for visual hallucinations in PD (table 1).

Cognitive dysfunction

Dementia and lesser degrees of cognitive impairment are common in advancing PD.[4] The pathological substrate of PD dementia (PDD) most often involves widespread cortical Lewy bodies and neuronal loss, but in particular there is an extensive involvement of the basal forebrain cholinergic system.[40] The current therapeutic options for cognitive impairment in PD include the cholinesterase inhibitors rivastigmine, donepezil, and galantamine,[38] although only rivastigmine is licensed for this indication. Visual hallucinations are commonly associated with dementia and, in this setting, can improve with use of cholinesterase inhibitors.[41] However, these agents can potentially worsen tremor because they non-selectively activate cholinergic receptors, including those in the striatum. Comparative prospective clinical trials have not been done to determine the relative benefit of cholinesterase inhibitors, but retrospective comparisons suggest no difference in efficacy.[42] A patch formulation of rivastigmine is currently being compared with oral rivastigmine in PDD in an open-label study (table 1). To date, we are unsure which subtypes of acetylcholine receptors mediate the cognitive benefit,[43] and future development of selective cholinergic drugs is limited. Studies using agents that target nicotinic acetylcholine receptors, such as the nicotinic receptor agonist SIB-1508Y, have, to date, shown no cognitive enhancing effects and poor tolerability.[44]

An alternative agent that might be useful in PDD is the uncompetitive (channel-blocking) NMDA antagonist memantine. This agent has efficacy in dementia due to Alzheimer's disease,[45] possibly by blocking chronic, mildly overactive glutamatergic activity that leads to neuronal damage and impaired synaptic plasticity and learning.[46] Memantine is licensed for use in Alzheimer's disease in the USA and Europe. Clinical trials of memantine in PDD are underway. The combination of cholinesterase inhibitors with memantine, as used in Alzheimer's disease,[47] also needs to be assessed in PDD.

Safinamide, originally developed as an antiepileptic drug, is in development for various indications in PD, including cognition (table 1). This agent has multiple proposed mechanisms of action, including inhibition of monoamine-oxidase B (MAO-B) and glutamate release.[48] Preliminary reports on a subgroup of patients suggest that safinamide might improve executive function and working memory in patients with early PD who are on dopamine agonists.[49] In phase III studies on the effects of safinamide on motor function in early and advanced PD, cognitive function tests are planned as secondary outcomes (table 1).

Behavioural disorders

Patients with PD can experience various behavioural problems as a consequence of dopaminergic medications, including impulse control disorders, such as pathological gambling, shopping, eating, and hypersexuality,[50] and abnormal excessive motor behaviours ranging from purposeless fiddling to complex stereotypic activities, known as "punding".[51] These problems have been particularly associated with dopamine agonists, but also with levodopa. The symptoms might resolve on reducing or discontinuing the dopamine agonists,[52] although they can persist in some patients. The pathogenesis of these problems probably involves a combination of abnormal dopaminergic stimulation within the ventral striatum with underlying individual susceptibilities including a previous history of chronic alcohol use or gambling.[53,54] There is evidence from the non-PD literature that increased glutamatergic neurotransmission might be involved in impulse control disorders.[55] An RCT of acamprosate, a GABA and taurine analogue that reduces glutamate-mediated neurotransmission licensed for use

in chronic alcohol use,[54] is underway in PD for compulsive behaviours and cravings (table 1).

Sleep disturbances

Excessive daytime sleepiness

The cause of excessive daytime sleepiness in PD is multifactorial, and includes disease-related factors such as primary dysfunction of the sleep–wake cycle due to brainstem and hypothalamic pathological changes, sleep disorders, and sedative side-effects of PD medications.[56] Recent studies have reported a loss of hypocretin, a hypothalamic peptide hormone involved in arousal systems, in PD.[57] Adenosine is a neurotransmitter implicated in sleep promotion,[58] and stimulation of adenosine A_1 receptors inhibits hypocretin neurons.[59] Thus, adenosine A_1 antagonists might increase wakefulness in PD, although, to date, no selective adenosine A_1 antagonists are available for clinical use. The adenosine A_{2A} receptor has also been implicated in sleep.[60] Selective adenosine A_{2A} antagonists are in development for motor features of PD, as discussed below. However, none of these studies has specifically measured excessive daytime sleepiness as an outcome measure. Caffeine, a non-selective adenosine antagonist, is currently being assessed in a phase II study in PD patients with excessive daytime sleepiness (table 1).

The histamine system is also involved in the sleep–wake cycle. Histamine neurons project from the tuberomammillary nucleus of the posterior hypothalamus to many brain regions and are tonically active during wakefulness.[61] Histamine H_3 receptors are autoreceptors located on histaminergic terminals within the CNS that modulate histamine release. Thus, reducing H_3 receptor activity increases histamine release with resultant activation of postsynaptic H_1 receptors and improvements in vigilance, cognition, and sleep–wake regulation.[62] The wake-promoting drug modafinil, which possibly affects histamine release in the hypothalamus,[63] is currently used as an option to treat excessive daytime sleepiness in patients with PD.[64] BF 2.649 is a selective histamine H_3 inverse agonist that enhances histaminergic transmission in the brain and increases wakefulness.[65] A phase II study is in progress to assess its effects on excessive daytime sleepiness in PD (table 1).

Autonomic dysfunction

Orthostatic hypotension

Orthostatic hypotension in PD is due to loss of post-ganglionic sympathetic neurons with impaired release of noradrenaline and baroreflex–cardiac vagal failure.[66] The symptoms include postural lightheadedness with fainting or worsening of gait and balance. Drugs currently used to treat orthostatic hypotension in PD include midodrine, a sympathomimetic, and fludrocortisone, a mineralocorticoid. Supine hypertension is a potential side-effect of both of these approaches.[67] The acetylcholinesterase inhibitor pyridostigmine bromide has been suggested to reduce orthostatic hypotension with less effect on supine hypertension, although evidence is limited.[67] L-threo-3,4-dihydroxyphenylserine (L-threo-DOPS) is a synthetic amino acid precursor of noradrenaline that is available in Japan for freezing of gait in PD (see below) and orthostatic hypotension in autonomic failure.[68] L-threo-DOPS has orphan drug status in the USA for orthostatic hypotension in autonomic failure, and a phase III RCT study is underway in North America to assess L-threo-DOPS in several disorders including PD (table 1). Of note, few RCTs of treatment for orthostatic hypotension have been undertaken specifically in PD, but rather have involved mixed populations of patients including multiple system atrophy, in which the pathophysiology of orthostatic hypotension is different. Thus, the true efficacy of treatments for orthostatic hypotension in PD remains unclear.

Urinary symptoms

Urinary symptoms can be troublesome in advanced PD. Patients experience various problems due to autonomic dysfunction, including increased frequency, urgency, urge incontinence, and nocturia. Current treatments are drugs used in other neurological diseases complicated by neurogenic bladder dysfunction with overactive bladder symptoms, such as the muscarinic antagonists oxybutynin and tolterodine. However, such drugs are typically poorly tolerated in patients with advanced PD due to central anticholinergic side-effects, hallucinations, and confusion in particular, whereas peripheral anticholinergic effects can exacerbate constipation and cause a bothersome dry mouth. Another muscarinic antagonist, trospium chloride, has potentially fewer central side-effects due to poor penetration of the blood–brain barrier, and is effective for treating overactive bladder symptoms.[69] As is the case for orthostatic hypotension, no RCTs have been done specifically in patients with PD, and there is little active research into new therapeutic options. Solifenacin succinate is another muscarinic antagonist, with a similar pharmacological profile to oxybutynin and tolterodine, that might be more effective than tolterodine in elderly patients with neurogenic bladder problems.[70] Its side-effect profile is similar to that of tolterodine, including dry mouth and constipation.[71] Phase IV studies are planned in PD patients with urge incontinence to assess efficacy and quality of life (table 1).

Constipation

Constipation is a very common complaint in PD, and is due to reduced gastrointestinal motility.[72] 5-HT_4 receptors are located in the gastrointestinal tract and trigger acetylcholine release, thus enhancing gastric and colonic motility.[73] An open-label study of mosapride, a 5-HT_4 agonist, showed increased colonic motility and improved constipation in seven patients with PD.[74] Another 5-HT_4 agonist, tegaserod, has also shown mild benefit in an RCT involving 15 patients with PD.[75] Neither drug had

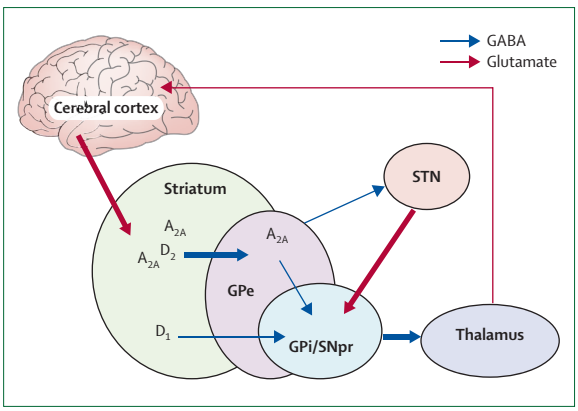

Figure 1: **Neural mechanisms underlying motor symptoms in PD**
Components and connections of the basal ganglia–thalamocortical motor circuitry in PD are shown. Although simplified and not representing all neural mechanisms underlying the pathophysiology, this model has been the basis for development of many non-dopaminergic drugs. PD motor symptoms result from an altered balance of activity in the putamen/caudate (striatal) GABAergic projection pathways, with the net effect being overactivity of the output regions of the basal ganglia, the internal globus pallidus (GPi) and substantia nigra pars reticulata (SNpr), which are represented as a single functional region. Thus, loss of dopaminergic innervation and increased corticostriatal glutamatergic function leads to increased activity of the indirect GABAergic pathway that projects from the striatum to the external globus pallidus (GPe), due to loss of dopamine D_2-receptor-mediated inhibition. Overactivity of the subthalamic nucleus (STN) glutamatergic pathway increases output from the basal ganglia. There is also underactivity of the direct GABAergic pathway from the striatum to the GPi, due to loss of striatal dopamine D_1 stimulation. Adenosine A_{2A} receptors modulate and contribute to overactivity of the D_2-mediated indirect pathway. Overactive pathways are indicated by thick lines, and underactive pathways by thin lines.

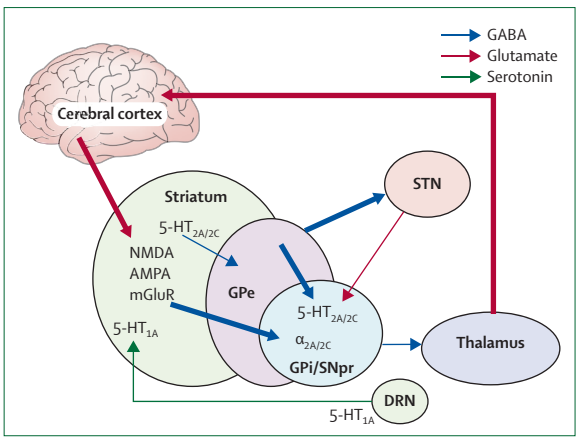

Figure 2: **Neural mechanisms underlying levodopa-induced dyskinesia**
After long-term levodopa therapy, corticostriatal glutamatergic activity is increased and activity of the striatopallidal GABAergic pathways is altered. In particular, increased dopamine D_1-mediated activity of the direct pathway leads to increased inhibition of the output regions of the basal ganglia, the internal globus pallidus (GPi) and substantia nigra pars reticulata (SNpr), resulting in loss of normal thalamocortical inhibition and the development of dyskinesia. Glutamatergic receptors (NMDA, AMPA, and metabotropic glutamate receptors [mGluR] subtypes) are thought to increase activity of the GABAergic direct pathway, whereas noradrenergic α_{2C} receptors increase GABA release in the basal ganglia output regions. 5-HT_{1A} receptors reduce serotonin and dopamine release from serotonergic terminals, as well as striatal (and possibly pallidal) glutamate, whereas $5\text{-HT}_{2A/2C}$ receptors might modulate GABA and glutamate in the striatum or GPi or SNpr. Overactive pathways are indicated by thick lines, and underactive pathways by thin lines. DRN=dorsal raphe nucleus. STN=subthalamic nucleus.

any significant adverse effects. To date, no further development of these drugs has been reported.

Non-dopaminergic therapies for motor symptoms

The basal ganglia circuitry that controls movement uses various non-dopaminergic neurotransmitters and neuromodulators that have been implicated in the neural mechanisms that underlie the motor symptoms of PD, as well as the development of motor fluctuations and dyskinesia after long-term levodopa therapy (figures 1 and 2).[76,77] Several drugs targeting these non-dopaminergic systems are in development for PD. There are clear potential advantages to such an approach: non-dopaminergic drugs with antiparkinsonian action can provide additional relief of PD disability by supplementing dopaminergic drugs, and long-term reduction of the dose of dopaminergic drugs will reduce further motor fluctuations (that develop as a consequence of chronic levodopa therapy). In addition, use of non-dopaminergic drugs to treat motor fluctuations directly allows continued use of optimum doses of levodopa, the most effective antiparkinsonian agent.

Symptomatic treatments

A wide range of non-dopaminergic drugs directed at improving motor symptoms of PD or reducing so-called "wearing-off" or end-of-dose deterioration are in development (table 2).

Adenosine A_{2A} antagonists

Adenosine A_{2A} receptors are selectively located on the GABAergic cell bodies and terminals of the indirect striatopallidal pathway (figure 1). Adenosine, via the A_{2A} receptors, is functionally linked to dopamine D_2 receptors and enhances GABA release in the external globus pallidus, a mechanism that is thought to contribute to the overactivity of the indirect pathway in PD.[104] In addition, overactive corticostriatal glutamatergic activity via NMDA receptor stimulation that occurs in PD also leads to adenosine release and stimulation of A_{2A} receptors.[105] Adenosine A_{2A} antagonists have thus been proposed as potential antiparkinsonian agents and several such drugs are in development.

Istradefylline has shown efficacy as monotherapy and adjunctive therapy in preclinical studies, and as adjunctive therapy in phase II studies.[78,106,107] A phase III study in 196 PD patients with motor fluctuations, with 40 mg istradefylline daily as add-on to optimised dopaminergic therapy, showed a significant reduction in off-time from baseline (mean –1·8 h/day *vs* –0·6 h/day with placebo).[79] Two larger phase III studies have been reported in abstract form only: 20 mg daily in 231 patients with advanced PD reduced off-time by –1·58 h/day versus –0·86 h/day with placebo,[80] whereas 10 mg, 20 mg, and

	Mechanism of action	Clinical studies	Comments
All PD motor symptoms or wearing-off			
Istradefylline	Adenosine A_{2A} antagonist	Phase IIb study;[78] phase III study;[79] phase III studies[80,81]	..
BIIB014	Adenosine A_{2A} antagonist	Phase II study underway[82]	Also in development for neuroprotection
SCH 420814	Adenosine A_{2A} antagonist	Phase II study underway[83]	
Safinamide	Glutamate release inhibitor and MAO-B inhibitor	Phase II study;[84] phase III studies;[85,86] further phase III studies underway in PD[28]	Dose range of safinamide that mediates MAO-B inhibition and glutamate release function remains unclear
Zonisamide	Possible Na^+ channel blocker; glutamate release inhibitor; MAO-B inhibitor	Phase III study[87]	Some of the improvement might indicate dopaminergic effects of zonisamide because the dose of levodopa used in the study was low (mean daily dose 350 mg)
FP0011	Glutamate release inhibitor	Phase IIa study[88]	..
Unilateral surgical infusion of *GAD65* and *GAD67* genes by use of adeno-associated virus into the subthalamic nucleus	Switches glutamate to GABA and reduces overactive subthalamic nucleus	Phase I trial; possible dose-related improvement in UPDRS (n=12);[89] phase II study planned[90]	..
Pardoprunox (SLV308)	Full 5-HT_{1A} agonist/partial dopamine D_2/D_3 agonist	Phase III study underway for early and advanced PD[91,92]	..
Piclozotan	Highly selective 5-HT_{1A} agonist	Phase II study underway[93]	..
Gait			
Methylphenidate	Enhances noradrenaline and dopamine	Phase III (high-dose) study;[94] phase IV (low-dose) study underway[95]	Methylphenidate has also been suggested to improve fatigue in PD[96]
Peak-dose levodopa-induced dyskinesia			
Fipamezole	α_{2C} Adrenoceptor antagonist	Phase IIb study underway[97]	Fipamezole might also extend on-time
Perampanel	AMPA receptor antagonist	Phase III study (terminated)[98]	Development has now stopped
Talampanel	AMPA receptor antagonist	Phase II study completed (no results available)[99]	..
CP 101,606	NR2B-selective NMDA receptor antagonist	Phase II study[100]	..
Eliprodil	NR2B-selective NMDA receptor antagonist	Phase II study completed (no results published)[101]	..
AFQ056	$mGluR_5$ antagonist	Phase II study underway[102]	..
Pimavanserin (ACP-103)	5-HT_{2A} receptor partial agonist	Phase II study underway[103]	..

All clinical studies are randomised controlled trials (RCTs), unless otherwise stated. Further information is available at ClinicalTrials.gov (http://www.clinicaltrials.gov/). AMPA=amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid. MAO-B=monoamine oxidase B. $mGluR_5$=metabotropic glutamate receptor.

***Table 2*: Non-dopaminergic treatments for motor symptoms in PD**

40 mg in 610 patients with PD resulted in no significant change in off-time from baseline versus placebo (–1·11 h, –1·14 h, –1·45 h *vs* –1·42 h, respectively[81]), but produced a significant improvement in on-period unified PD rating scale (UPDRS) III scores in the 40 mg group.[108] However, istradefylline did not receive US Food and Drug Administration approval for PD.[109] Other A_{2A} antagonists are in earlier stages of development (eg, BIIB014, SCH 420814; table 2). However, no preclinical data have been published to assess the potential efficacy of these agents.

Glutamate release inhibitors

Enhanced glutamate transmission is a key component of the neural mechanisms underlying the symptoms of PD (figure 1).[77,110] Several agents are in development for PD that are able to reduce glutamate release and thus might affect overactive glutamatergic pathways (table 2). Safinamide and zonisamide were both originally developed as antiepileptic agents; both have multiple modes of action, including MAO-B inhibition (ie, potentially a mechanism of action in treating wearing-off) and glutamate release inhibition.

Safinamide showed significant improvement in motor scores in 172 patients with early PD, particularly when combined with dopamine agonists (37·5% responded *vs* 21·4% on placebo; responders had ≥30% improvement in baseline UPDRS motor scores).[84] It was suggested that at the most effective dose (1·0 mg/kg, daily dose 40–90 mg), both MAO-B inhibition and inhibition of glutamate release occurred, whereas the lower, ineffective dose (0·5 mg/kg) only resulted in MAO-B inhibition. A preliminary report from a phase III study that used two higher doses of safinamide (50–100 mg and 150–200 mg) in 269 patients with early PD on dopamine agonists indicated that only 50–100 mg resulted in a significant decrease in UPDRS-III score from baseline versus placebo at 6 months (–6·0±7·2 and –3·6±7·1, respectively).[85] A 12-month extension suggested that safinamide might delay time to require further dopaminergic medications.[86] In a small open-label study in 11 patients with advanced PD, safinamide (100 mg, 150 mg, and 200 mg) decreased motor fluctuations.[111] Further phase III trials are planned to assess adjuvant safinamide therapy with dopamine agonists or levodopa in PD (table 2).

Zonisamide has shown efficacy in small studies in advanced PD patients with motor fluctuations.[112] A recent large phase III RCT in patients with PD who were taking relatively low doses of levodopa reported a significant reduction in off-time from baseline (–1·3 h on 50 mg, –1·63 h on 100 mg *vs* –0·2 h on placebo).[87] There was also a significant improvement in on-period motor UPDRS scores, but no significant effect on dyskinesia. Further studies are required to fully assess the mechanism of action and effects in PD patients with motor fluctuations who take higher doses of levodopa.

FP0011 is a glutamate release inhibitor that is in development for motor symptoms of PD (table 2). To date, only abstracts have been published, but these suggest that it might provide improvement in motor symptoms in preclinical studies and a phase IIa "n-of-1" clinical trial in eight patients with PD.[88,113]

Enhancers of GABA in the subthalamic nucleus

Overactivity of the subthalamic nucleus is an integral part of the abnormal basal ganglia circuitry that results in PD symptoms (figure 1). To date, the most successful non-pharmacological treatment for advanced PD is bilateral subthalamic nucleus deep brain stimulation surgery.[114] Surgical infusion of the glutamic acid decarboxylase (*GAD*) gene via adeno-associated virus into the subthalamic nucleus has been proposed to directly inhibit subthalamic nucleus neurons via increased GABA, and possibly to alter subthalamic nucleus output from excitatory (glutamatergic) to inhibitory (GABAergic).[115] A phase I trial reported a possible dose-related improvement in contralateral on and off motor UPDRS scores over 12 months after surgery in 12 patients with advanced PD,[89] and a phase II study is planned (table 2).

Noradrenaline modulators

Phasic discharge of the locus coeruleus is implicated in the righting reflex, suggesting a role of noradrenaline in gait and balance.[116] Small open-label studies using the adrenergic agent L-threo-DOPS have suggested a potential benefit on gait disturbance in PD, particularly freezing.[117] Methylphenidate is a mixed dopamine and noradrenergic reuptake inhibitor that alters locus coeruleus noradrenergic neurotransmission,[118] while also enhancing extracellular dopamine.[119] These pharmacological effects of methylphenidate depend on the dose and duration of treatment, which are not known for PD brains. However, acute methylphenidate (1·2 mg/kg) failed to augment the antiparkinsonian action of levodopa in PD,[120] suggesting that any effects it might have in PD are noradrenergic. An RCT that used a higher dose of methylphenidate (3 mg/kg) in 17 patients with advanced PD with subthalamic nucleus deep brain stimulation showed benefit on gait and freezing scores, even when patients were off medication; an enhancement of the effects of levodopa on gait was also reported.[94] An RCT using a lower dose of methylphenidate (1 mg/kg) in patients with less advanced PD with gait impairment is underway (table 2).

Treatment of levodopa-induced dyskinesia

Alpha$_{2C}$ adrenoceptor antagonists

Noradrenergic receptors are located within the striatum, subthalamic nucleus, and substantia nigra,[121] and might modulate dopaminergic and GABAergic function. In particular, α_{2C} adrenoceptors located on striatal GABAergic medium spiny neurons might modulate GABA release and contribute to the overactivity of the direct striatopallidal pathway, resulting in dyskinesia (figure 2).[71,122] Preclinical studies have assessed non-selective adrenergic antagonists (ie, clonidine) and selective $\alpha_{2A/2C}$ adrenoceptor antagonists (ie, idazoxan, rauwolscine, and fipamezole), and shown a potential ability to reduce dyskinesia and to extend the duration of action of levodopa.[123,124]

In phase IIa studies, idazoxan had variable effects, with one positive and one negative study.[125,126] Idazoxan was not developed further for PD partly because of peripheral α_{2A} side-effects on vasculature, including flushing and headache. Fipamezole, which is more selective for α_{2C} adrenoceptors than idazoxan, and thus potentially better tolerated, is in development for PD. A phase IIa study in 21 PD patients with motor fluctuations showed a significant reduction in dyskinesia.[127] Nausea and diaphoresis were the most common side-effects. A multicentre phase IIb trial of fipamezole for dyskinesia is underway (table 2).

Glutamate antagonists

One key abnormality underlying peak-dose dyskinesia is abnormally enhanced glutamatergic activity within the striatum, involving ionotropic glutamate receptors (NMDA and AMPA subtypes) and metabotropic glutamate receptors (mGluR; figure 2).[77,128] This enhanced glutamatergic transmission might drive increased activity in the D_1-mediated direct striatopallidal pathway, with resultant inhibition of the basal ganglia outputs and generation of dyskinesia.[129] The current standard treatment for dyskinesia is the non-selective NMDA receptor antagonist amantadine.[130] This drug might induce side-effects (confusion, leg oedema, livedo reticularis), and can have waning benefit over time. However, other non-selective glutamate antagonists (ie, memantine,[131] riluzole,[132] and remacemide[133]) lacked efficacy in reducing dyskinesia. In addition, the poor tolerability of non-selective glutamate antagonists relates to non-specific binding to glutamate receptors in multiple brain regions. Thus, more selective targeting of glutamate receptor subtypes is probably preferable.

Several subtype-selective NMDA and AMPA receptor antagonists have been investigated in preclinical studies, but with conflicting results. Thus, in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primate model of PD, NR2B-subtype-selective receptor antagonists have both decreased and increased dyskinesia, or increased dystonia.[134–136] AMPA receptor antagonists can also reduce

dyskinesia in MPTP-lesioned monkeys.[137,138] However, there are few clinically available agents in these categories. The NMDA receptor antagonist ifenprodil had no effect on dyskinesia or PD disability in an open-label study involving 20 patients.[139] Other phase II clinical studies undertaken in PD patients with dyskinesia have not been reported (eg, NR2B antagonist eliprodil, and AMPA antagonist talampanel; table 2). Development of the selective non-competitive AMPA receptor antagonist perampanel for PD has been halted due to lack of efficacy.[140]

Antagonism of excessive striatal glutamate activity via the metabotropic subtype of glutamate receptor has been suggested as a better option for PD due to a wider therapeutic index.[141] Antagonists of the $mGluR_5$ receptor subtype have shown efficacy in preclinical studies.[142] AFQ056 is an $mGluR_5$ receptor antagonist that is in development for dyskinesia (table 2).

Serotonin modulators

Serotonergic neurotransmission is involved in many aspects of basal ganglia function. 5-HT_{1A} receptors in the dorsal raphe nucleus and striatum, 5-$HT_{1B/1D}$ receptors on striatopallidal pathways, and 5-$HT_{2A/2C}$ receptors within the substantia nigra pars reticulata and internal segment of the globus pallidus are thought to modulate dopamine, GABA, and glutamate release within the basal ganglia to improve motor symptoms of PD and reduce dyskinesia (figure 2).[143]

The neurodegenerative processes underlying PD result in loss of serotonin input from the dorsal raphe nucleus to the striatum, but to a lesser extent than loss of dopamine input. Levodopa might be converted to dopamine in the remaining serotonergic neurons, and the non-physiological release of dopamine by these neurons might lead to abnormal dopamine receptor stimulation in the striatopallidal pathways, resulting in the generation of dyskinesia.[144] Suppressing the activity of these serotonin inputs to the striatum, via presynaptic 5-HT_{1A} agonists, has been proposed to reduce dyskinesia. Preclinical studies have suggested that some potential 5-HT_{1A} agonists can reduce dyskinesia.[144,145] The anti-depressant buspirone is a partial 5-HT_{1A} agonist and significantly reduced dyskinesia without worsening parkinsonian disability in ten patients with PD.[146] A phase II study in 18 patients with advanced PD showed that the 5-HT_{1A} agonist sarizotan significantly reduced dyskinesia, in addition to extending the duration of action of levodopa.[147] However, further clinical studies failed to show increase in on-time without dyskinesia compared with placebo, and higher doses were associated with increased off-times,[148,149] possibly due to the additional dopamine D_2 antagonist properties of sarizotan.

Piclozotan is a highly selective 5-HT_{1A} agonist with very high (1000 times) selectivity over dopamine D_2 receptors.[150] No published preclinical studies are available to predict potential efficacy or side-effects in PD. A multicentre phase II trial is underway to assess the effects of piclozotan in PD patients with dyskinesia (table 2). Another drug in development for PD with full 5-HT_{1A} agonist properties is the partial dopamine D_2/D_3 agonist pardoprunox (SLV308; table 2). Preliminary reports suggest efficacy on motor symptoms of PD in early disease,[151] but its effects on dyskinesia are unknown.

5-$HT_{2A/2C}$ receptor antagonism might also reduce levodopa-induced dyskinesia. In one RCT, clozapine (mean daily dose 39 mg) significantly reduced levodopa-induced dyskinesia without worsening PD; however, this effect was only evident on dyskinesia at rest and not with activity.[152] This effect might be due to altered dopamine D_2 receptor binding, and the drug's affinity for various non-dopaminergic receptors, including 5-$HT_{2A/2C}$.[39] However, use of clozapine for dyskinesia is rare in practice, because mandatory blood monitoring is needed to prevent agranulocytosis. The other atypical antipsychotic quetiapine, which has 5-$HT_{2A/2C}$ antagonist properties, was effective in preclinical studies,[153] but failed to show antidyskinetic effects compared with placebo, although a very low dose (25 mg) was used.[154] The inverse 5-HT_{2A} agonist ACP-103 is in development for dyskinesia (table 2) as well as for visual hallucinations.

Conclusions

Optimisation of symptomatic treatments for many of the motor and non-motor problems of PD requires the targeting of non-dopaminergic neurotransmitter systems. Many such agents are now in development. However, future strategies need to focus on more selective targeting of subtypes of neurotransmitter receptors to reduce side-effects and optimise benefit. Clinical studies need to be done in appropriate study populations, and the translation of preclinical findings into phase II and III trials in PD must be improved.[155] Finally, the development of neuroprotective agents in PD has to date focused on preventing dopamine cell loss. However, to be optimally effective, such therapies will also need to target non-dopamine cells involved in the multisystem disease process.[156]

Search strategy and selection criteria

References for this Review were obtained from websites for active clinical trials (currently recruiting), including PDPipeline.org (http://www.pdpipeline.org/) and ClinicalTrials.gov (http://www.clinicaltrials.gov/), with additional references from PubMed searches between 1990 and July, 2008, by use of the search terms "Parkinson's disease" and "clinical trial" in combination with "serotonin", "5-HT", "acetylcholine", "noradrenaline", "norepinephrine", "adenosine", "glutamate", "histamine", "dyskinesia", "motor fluctuations", and various symptoms including, but not limited to, "sleep", "autonomic", "mood", and "cognition". Other sources include conference proceedings. Only articles or abstracts in English were reviewed.

Contributors

SHF drafted the Review, and AEL and JMB critically reviewed and edited the Review.

Conflicts of interest

SHF has consulted for Novartis, Teva, Prestwick, UCB Kyowa, and Eisai. JMB has received consultancy fees from, and holds an equity position in, Atuka Ltd. Atuka has provided consultancy services to assess preclinical efficacy of treatments for Juvantia and Faust. AEL has consulted for Neuromolecules, Ceregene, Eisai, Medtronic, GlaxoSmithKline, Schering-Plough, Serono, Solvay, Taro, Teva, Novartis, and UCB.

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