# Novel pharmacological targets for the treatment of Parkinson's disease

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Abstract | Dopamine deficiency, caused by the degeneration of nigrostriatal dopaminergic neurons, is the cause of the major clinical motor symptoms of Parkinson's disease. These symptoms can be treated successfully with a range of drugs that include levodopa, inhibitors of the enzymatic breakdown of levodopa and dopamine agonists delivered by oral, subcutaneous, transcutaneous, intravenous or intra-duodenal routes. However, Parkinson's disease involves degeneration of non-dopaminergic neurons and the treatment of the resulting predominantly non-motor features remains a challenge. This review describes the important recent advances that underlie the development of novel dopaminergic and non-dopaminergic drugs for Parkinson's disease, and also for the motor complications that arise from the use of existing therapies.

Bradykinesia
Abnormally slow voluntary movements.

Lewy body
Abnormal aggregates of protein (predominately α-synuclein) that develop inside nerve cells and displace other cell components.

Dyskinesia
Involuntary writhing movements affecting head, trunk and limbs.

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Parkinson's disease (PD) is a multicentric neurodegenerative disease with a prevalence of approximately 1 in 300. Clinical features at presentation include the asymmetric onset of bradykinesia, rigidity and tremor. These are the result of the loss of dopaminergic neurons in the substantia nigra pars compacta, which causes a consequent reduction of dopamine levels in the striatum (FIG. 1). However, additional neuronal fields and neurotransmitter systems are also involved in PD, including the locus coeruleus, dorsal motor nucleus, substantia innominata, the autonomic nervous system and the cerebral cortex (FIG.2). Consequently non-adrenergic, serotinergic and cholinergic neurons are also lost. This loss results in symptoms that include cognitive decline, sleep abnormalities and depression, as well as gastrointestinal and genitourinary disturbances. These 'non-motor' features progress and come to dominate the later stages of PD. Although the clinical consequences of non-dopaminergic neuronal involvement usually become apparent some years after diagnosis, there is debate about the sequence in which PD pathology develops. The distribution of Lewy body formation might include non-dopaminergic areas at an early stage[1]; however, it remains to be shown that cell death occurs in these areas before the substantia nigra.

The three main strategic developments that have led to progress in the medical management of PD have focussed on improvements in dopaminergic therapies, (including those aimed at managing or preventing the onset of motor complications), the identification of non-dopaminergic drugs for symptomatic improvement and the discovery of compounds to modify the course of PD.

## Dopaminergic drugs

Dopamine-replacement therapy has dominated the treatment of motor symptoms of PD since the early 1960s. The effects are predictable (as are the side effects) and none of the more recently introduced synthetic dopamine agonists has surpassed the clinical benefit derived from levodopa (L-DOPA)[2,3] (TABLE 1). Most recently, non-oral delivery has provided more long-lasting anti-Parkinsonian activity through the subcutaneous or intravenous infusion of apomorphine and transdermal patch technology with rotigotine or lisuride[4,5]. However, despite the many dopaminergic agents currently available, the search for novel approaches based on dopamine-replacement therapy continues. The multiplicity of dopamine receptors in the brain offers a range of potential targets, but so far exploitation of drugs acting on specific receptor subtypes has been disappointing. Most currently used drugs only activate $D_2$ and $D_3$ dopamine receptors[6] and no major advance has been made in producing $D_1$ dopamine agonists, a known target for anti-Parkinsonian agents. Partial $D_2$ dopamine agonists are being developed as they might treat the motor symptoms of Parkinson's disease while suppressing both psychosis and dyskinesia[7].

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Although L-DOPA is the most effective drug for the control of motor symptoms, it also causes a high level of motor complications, particularly dyskinesias[8]. By contrast, dopamine agonists produce a lower incidence of involuntary movements, which seems to reflect their longer duration of action and supports the concept of continuous dopaminergic stimulation[9,10]. This has been exploited by the introduction of a range of long-acting dopamine agonists, by the use of L-DOPA in combination with catechol-*O*-methyl transferase inhibitors[11] and more recently by development of once-daily controlled-released formulations of dopamine agonist drugs and the introduction of transdermal dopamine agonist delivery[7]. Whether continuous dopaminergic stimulation explains all of the differences between L-DOPA and dopamine agonists is a matter of contention. There might instead be fundamental differences between the actions of L-DOPA and those of dopamine agonists. Unlike the dopamine agonist drugs, L-DOPA acts on both $D_1$ and $D_2$ receptor families, affects multiple pharmacological targets (including nonadrenaline and 5-hydroxytryptamine (5-HT; serotonin) receptors) and might act as a neuromodulator in its own right[12]. Alternatively, dopamine agonists also have additional properties other than actions at dopamine receptors, which could explain their lower risk for the development of motor complications.

## Cholinergic drugs

Both the cortico–striato–thalamic loop and the nigro–striatal system are largely innervated by cholinergic afferents coming from the tegmentum, the septum and by cholinergic interneurons. Most cholinergic systems are affected in PD, such as muscarinic receptors[13,14], nicotinic receptors[13,15] and choline transporters[16].

Anticholinergics were among the first drugs used in PD, and were intended to correct the imbalance between dopamine and acetylcholine levels. Although these drugs do produce some beneficial effects on PD symptoms, they are associated with adverse cognitive effects[17]. Many cholinesterase inhibitors, such as rivastigmine (Exelon; Novartis) and donepezil (Aricept; Eisai/Pfizer), have been tested to counteract PD dementia, and have been found to improve cognition[18–21]. However, they sometimes display mixed effects on motor function[22]. It might be that co-treatment using a combination of anticholinergics and anticholinesterases would correct acetylcholine deficits while counteracting the hypersensitivity of cortical muscarinic receptors.

Nicotinic receptors are not only highly expressed on dopaminergic neurons[23], but also in the cortex and thalamus. Nicotine has been found to protect against degeneration in various PD models[24,25]. In addition, an inverse association between smoking and PD has been consistently demonstrated[26]. However, nicotine itself has no anti-Parkinsonian effect and the mechanism by which smoking might confer protection against PD is not known.

## Serotoninergic drugs

5-HT receptors are crucial to motor control in health and disease[27–33]. In PD, 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_{2A}$ and 5-$HT_{2C}$ deserve special attention, particularly with respect to involvement in L-DOPA -induced dyskinesia (LID).

In monkeys given 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which induces Parkinsonian symptoms, the $5HT_{1A}$ receptor agonists sarizotan (Merck)[34] and 8-hydroxy-2-di-n-propylamino-tetralin (8-OH-DPAT)[35] dramatically reduce LID. In clinical trials, sarizotan and another $5HT_{1A}$ agonist, buspirone, reduced LID[36–38] and extended the duration of L-DOPA action[37]. However, at high doses, sarizotan can exacerbate Parkinsonism[36]. This might reflect an interaction with $D_2$ dopamine receptors. Therefore in developing the next generation of 5-$HT_{1A}$ agonists, it might be beneficial to remove $D_2$ activity. The potential value of developing such compounds is highlighted by recent observations that 5-$HT_{1A}$ agonists might also be neuroprotective (E.B., unpublished observations).

Rodent studies suggest that antagonism of 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors can reduce LID either directly[39] or indirectly by allowing reduction in L-DOPA dosage[40,41]. In MPTP primates, blockade of all 5-$HT_2$ receptor subtypes with methysergide reduces dyskinesia, though with adverse effect on Parkinsonism[42]. The atypical neuroleptics quetiapine (Seroquel; AstraZeneca) and clozapine are 5-$HT_{2A}$ and 5-$HT_{2C}$ antagonists, in addition to being dopamine antagonists[43,44]. In MPTP primates, both quetiapine and clozapine can reduce LID without exacerbating Parkinsonism[45], though at higher doses clozapine does worsen Parkinsonism. In a clinical study, clozapine reduced LID without affecting Parkinsonian disability[46]. However, in another clinical study, quetiapine failed to demonstrate any benefit on dyskinesia, though the doses

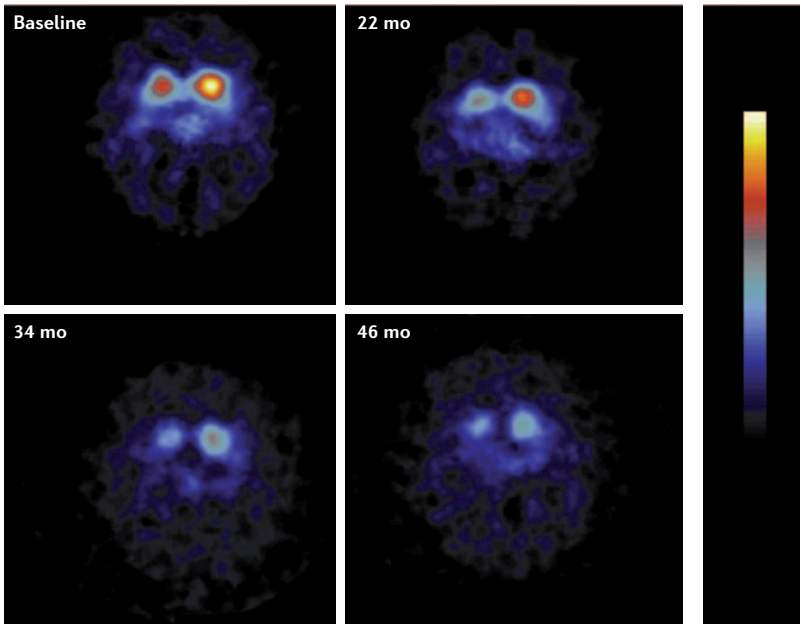



Figure 1 | **A single-photon emission computerized tomographic (SPECT) scan of dopamine transporter density in a Parkinson's disease patient shortly after diagnosis and serially for 46 months.** There is asymmetric loss particularly in the posterior putamen, which progresses bilaterally over time. Levels of SPECT activity are colour-coded from low (black) to high (yellow/white). β-CIT, 2β-carboxymethoxy-3β(4-iodophenyl)tropane. Adapted, with permission, from REF. 95 © (2002) American Medical Association.

used were lower than those found to be effective in monkeys[47]. As with 5-$HT_{1A}$ agonists, it is likely that the therapeutic window of currently available 5-$HT_{2A/C}$ agents will be limited by antidopaminergic actions, though their use could pave the way for more selective compounds in development (for example, ACP-103 (Acadia)).

In MPTP primates, 5-$HT_{1B}$ receptor stimulation reduced LID[35,48]. 5-$HT_{1B}$ agonists and partial agonists are widely available for other indications and are generally unencumbered by direct dopaminergic effects. A 5-$HT_{1B}$ agonist/partial agonist capable of crossing the blood–brain barrier and with pharmacokinetics similar to L-DOPA might be an excellent candidate for a novel antidyskinetic agent.

The diversity of 5-HT receptors involved in PD raises the issue of whether the most effective 5-HT-modulating drugs for PD might be molecules that target a range of receptors rather than highly selective ones. However, a non-selective increase in 5-HT transmission, such as achieved with a selective serotonin-reuptake inhibitor (SSRI), does not reduce LID in either monkeys[48] or humans[49]. However, it would be desirable to discover a molecule combining two or more of the specific agonist and antagonist properties discussed above. The feasibility of this approach is highlighted by findings that mirtazapine (Remeron; Organon), a molecule combining 5-$HT_{1A}$ agonist and $5HT_{2A}$ antagonist properties, can reduce LID in patients[50], while in MPTP monkeys the non-selective serotonergic agent 3,4 methylenedioxymethamphetamine (MDMA, or 'ecstasy') can reduce dyskinesia by stimulating both 5-$HT_{1A}$ or 5-$HT_{1B}$ receptors[48]. Although itself untenable as a therapeutic agent, the MDMA molecule might represent a starting point for novel medicinal chemistry to develop new drugs that combine a propitious mix of 5-HT actions of benefit to PD.

Depotentiation
The reversal of long-term potentiation back to baseline levels.

## Glutamate and GABA drugs

Since the vast majority of pathways in the basal ganglia utilize glutamate and GABA (γ-amino butyric acid) as their respective excitatory and inhibitory neurotransmitters, these systems are obvious drug candidates. Indeed, there is already some evidence that *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as remacemide, amantadine and dextromethorphan, might reduce motor complications associated with L-DOPA therapy.

Targeting these amino-acid receptor systems, although potentially very attractive, is fraught with complications. Firstly, there is the problem of regional selectivity given the ubiquitous nature of these receptor systems in the brain. The second problem is the potential for affecting normal basal ganglia function. For example, antagonizing NMDA receptors could offer neuroprotection and limit pathological plasticity but will interfere with the normal function of these receptors as mediators of high-frequency synaptic transmission and synaptic plasticity (for example, long-term potentiation, long-term depression and depotentiation).

A detailed understanding of the sites and mechanisms of action of the compounds can, however, be used to optimize efficacy and minimize potential side effects. Memantine (Axura; Merz) is an example of how an NMDA receptor antagonist with specific properties can provide therapeutic potential[51]. Because it is a low-affinity and highly voltage-dependent NMDA receptor antagonist it can limit spurious NMDA receptor activation without preventing the intense transient activation that results from the coordinated synaptic release of glutamate. In addition to the mechanism of block, subtype-selective NMDA receptor antagonists provide another potential therapeutic angle. In this context, selective antagonists of NDMA receptor 2B (NR2B) might offer anti-Parkinsonian effects[52,53]. Interestingly, the high expression of NR2D receptors on substantia nigra pars compacta neurons, but relatively low expression of this receptor on many other neuronal types, makes these receptors an interesting target[54]. Lead compounds for developing NR2D-selective antagonists are now available[55].

Targeting metabotropic glutamate (mGlu) receptors (mGluRs) is another interesting possibility. The eight receptor subtypes (mGlu1–8) have a varied distribution in the brain. Recent evidence suggests that profound alterations in depotentiation, a process that probably utilizes mGlu receptors, could underlie dyskinesia[56]. Interesting candidates for development are allosteric potentiators of group III mGluRs. For example, it has been shown that *N*-phenyl-7-(hydroxylimino)cyclopropa[*b*]chromen-1a-carboxamide selectively activates mGlu4 receptors and markedly reverses reserpine-induced akinesia[57]. Another prime target is the AMPA (α-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid) receptor, which mediates most

fast excitatory synaptic transmission in the brain. AMPA receptor antagonists, such as E-2007, GYKI-47261 and the non-competitive inhibitor talampanel, have entered into clinical trials as potential neuroprotectants in PD. Conversely, several strategies have been used to potentiate AMPA receptor function, with a view to providing cognitive enhancement and neurotrophic effects[58]. The other major excitatory amino-acid receptor, the kainate receptor, is widely expressed in the basal ganglia and is a potentially promising drug target. Of the five subunits that can form various heteromeric kainate receptor assemblies, highly selective antagonists are now available for mGlu5 receptors[59]. Finally, considering the possible involvement of pallidal GABA receptors in

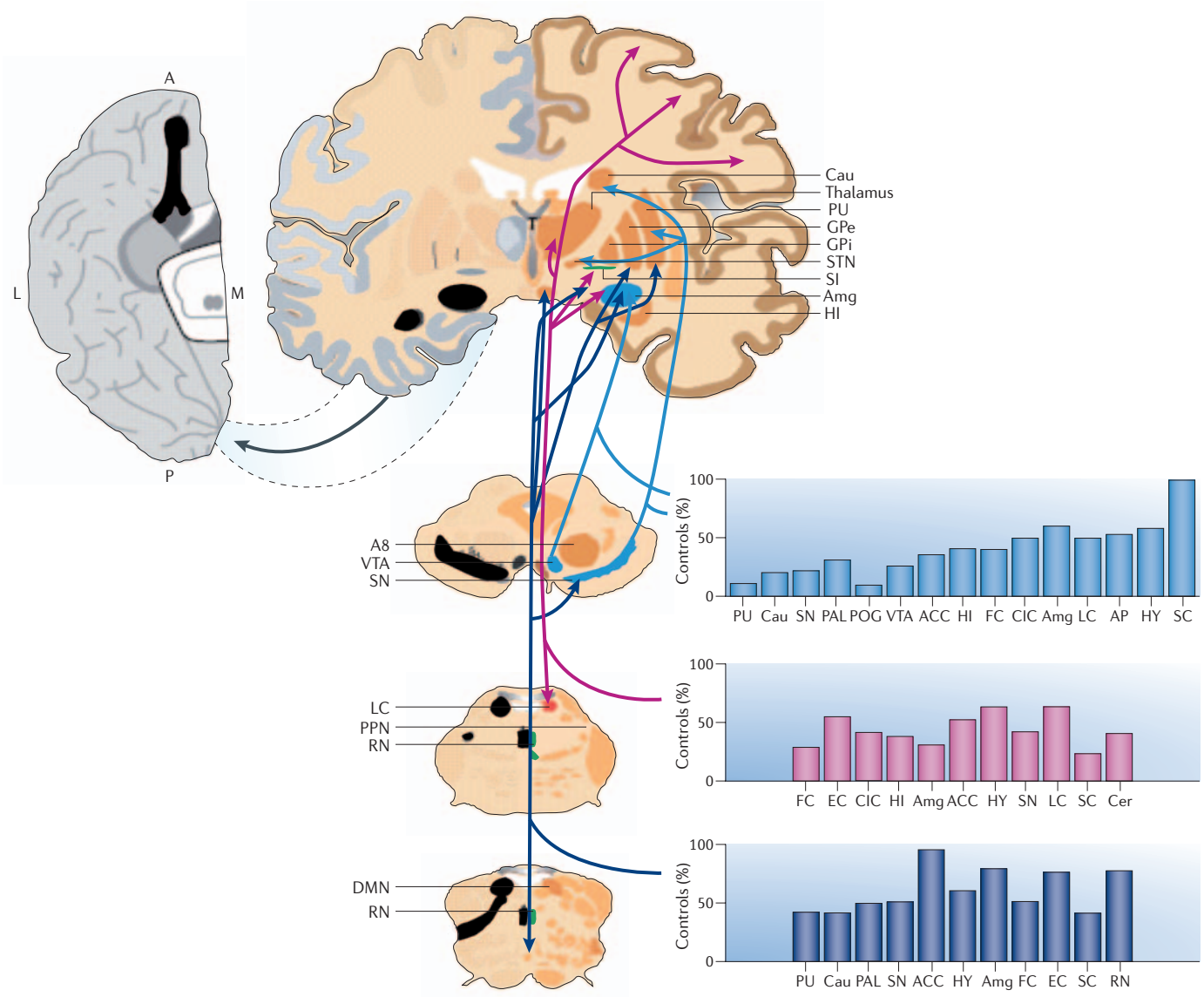



Figure 2 | **Schematic representation of the neurodegenerative changes in the central nervous system in Parkinson's disease.** The figure on the left shows the basal view of the right cerebral hemisphere, including the olfactory bulb (in the grey brain on the far left, A = anterior; P = posterior; L = lateral; M = medial). On the left of the coronal section and on the left of the brainstem sections (from top to bottom: midbrain, pons and medulla), the areas affected by pathological lesions are marked in black or shades of grey (black indicating severe pathological lesions in early and middle stages; grey indicates later or milder involvement). On the right, projection pathways of the affected monoamine neurotransmitters are marked (turquiose = dopamine; pink = noradrenaline; blue = serotonin). Acetylcholine pathways, which are also severely affected in Parkinson's disease, have been omitted for the sake of clarity. The graphs show the extent of dopamine (turquiose), noradrenaline (pink) and serotonin (blue) loss (% of normal controls) in various projection regions. A8, A8 dopamine area; Amg, amygdala; ACC, nucleus accumbens; AP, area postrema; Cer, cerebellum; CIC, cingular cortex; DMN, dorsal motor nucleus of the vagus nerve; EC, entorhinal cortex; FC, frontal cortex; GPe, external segment of globus pallidus; GPi, internal segment of globus pallidus; HI, hippocampus; HY, hypothalamus; LC, locus coeruleus; PU, putamen; Cau, caudate; SN, substantia nigra; PAL, pallidum; POG, parolfactory gyrus; PPN, pedunculopontine nucleus; RN, raphe nuclei; SI, substantia innominata; SC, spinal cord; STN, subthalamic nucleus; VTA, ventral tegmental area. Adapted, with permission, from REF 119 © (2004) Elsevier Science.

Table 1 | **Current drugs for Parkinson's disease**

| Drug | Advantages | Disadvantages |
|---|---|---|
| Levodopa (L-dopa) + dopa decarboxylase inhibitor | • Probably the most potent dopaminergic drug for symptom relief<br>• Generally well tolerated | • Motor complications (cumulative risk 10% per annum) |
| Catechol-*O*-methyl transferase inhibitors, for example, entacapone, tolcapone | • Increase levodopa half-life<br>• Reduce 'off' time | • Tolcapone can cause liver damage.<br>• Diarrhoea |
| Ergot dopamine agonists (for example, bromocriptine, pergolide, cabergoline<br>Non-ergot dopamine agonists for example, pramipexole, ropinirole, rotigitine | • Good efficacy<br>• Delay onset of motor complications<br>• Generally well tolerated<br>• Once-a-day preparations available with some<br>• Transdermal patch for rotigitine<br>• Theoretical neuroprotective action<br>• Some antidepressant action with pramipexole | • Increased risk of somnolence, confusion, hallucinations, peripheral oedema and behavioural changes<br>• Cardiac valve fibrosis with ergot drugs |
| Monoamine oxidase B inhibitor; selegiline; rasagiline | • Improve motor features in early and late disease<br>• Easy to use, once-a-day<br>• Well tolerated<br>• Theoretical neuroprotective effect | • Relatively mild efficacy<br>• Selegiline metabolized to amphetamines — potential cognitive effects |
| Amantadine | • Mild anti-Parkinsonian effect<br>• Improves dyskinesias | • Cognitive disturbances<br>• Peripheral oedema<br>• Livedo reticularis |
| Anticholinergics | • Mild anti-Parkinsonian effect | • Limited by side effects such as confusion |

LID[60,61], targeting GABA systems could provide a complementary strategy, although again subtype-selective compounds would seem to be the way forward.

### Adenosine $A_{2A}$ receptor antagonists

Several distinctive features of the adenosine $A_{2A}$ receptor ($A_{2A}R$) have made its antagonism a leading candidate strategy for the improved treatment of PD[62,63]. First, and perhaps uniquely among currently pursued non-dopaminergic targets in PD research, $A_{2A}$Rs in the central nervous system are relatively selectively expressed in the striatum, which is innervated by the dopaminergic nigrostriatal neurons lost in PD. Moreover, within the striatum $A_{2A}$Rs are largely restricted to the subset of medium spiny output neurons that project to the globus pallidus and co-express dopamine $D_2$ receptors[64]. This discreet anatomical localization reduces the liability of $A_{2A}$ antagonists for adverse CNS effects such as those that limit the usefulness of current non-dopaminergic (anticholinergic and antiglutamatergic) agents in PD.

Second, $A_{2A}$ antagonists consistently reverse Parkinsonian motor deficits in all preclinical models of PD, and do so without inducing or exacerbating dyskinesias in non-human primate models[63,65]. This symptomatic effect can be explained by blockade of the $A_{2A}R$ on the $D_2$R-coexpressing striatopallidal neurons, which inhibits their release of GABA in the globus pallidus, ultimately leading to enhanced motor function through the so-called indirect motor pathway of the basal ganglia[66]. Initial human studies with an $A_{2A}$ antagonist have indeed demonstrated modest symptomatic improvements, apparently without increasing troublesome dyskinesias in moderately advanced patients already experiencing motor fluctuations[62,63,67,68] (TABLE 2).

Third, the $A_{2A}R$ might have an important role in the underlying neurodegenerative process, suggesting that $A_{2A}$ antagonists possess neuroprotective properties. Epidemiological data linking the consumption of caffeine (a non-specific adenosine antagonist) with a reduced risk of developing PD have converged with laboratory studies showing that caffeine and more specific $A_{2A}$ antagonists protect against dopaminergic neuron toxicity *in vivo*[69,70]. Another potential disease-modifying benefit of $A_{2A}$ antagonism — preventing the development of LID in PD — has been proposed based on rodent and monkey studies[71,72]. These findings have further encouraged clinical trials that will investigate $A_{2A}$ antagonists in early PD[62].

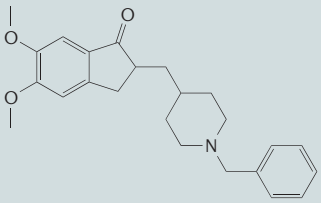
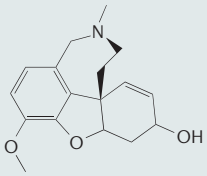
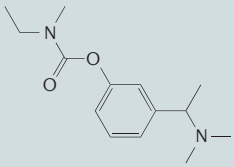
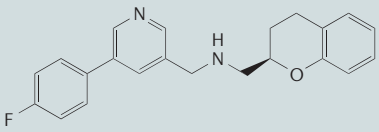
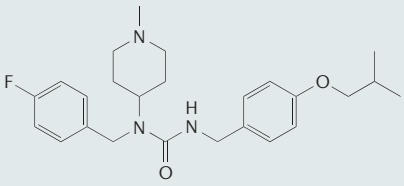
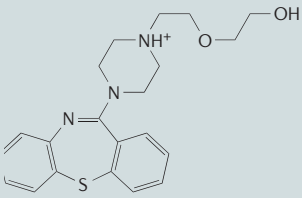
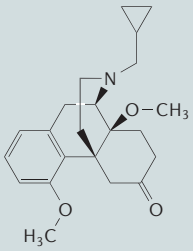
Lastly, the recent discovery that the $A_{2A}R$ can form functional heteromeric receptor complexes with other G-protein-coupled receptors such as $D_2R$ and the mGlu5 receptor has suggested new opportunities for leveraging the multiple potential anti-Parkinsonian benefits of $A_{2A}$ antagonists[73]. For example, combining $A_{2A}$ and mGlu5 blockade synergistically reverses Parkinsonian deficits in rodents[74,75]. On the other hand, enthusiasm for these agents in PD is tempered by the possibility that they might produce untoward CNS or systemic effects. On balance, $A_{2A}$ antagonism represents one of the most realistic and promising therapeutic candidates for PD.

### Opioid drugs

Recognition of the enhanced opioid peptide transmission in the striatum of animal models and PD patients with LID motor complications has raised the possibility of controlling these by targeting opioid transmission in the basal ganglia[76]. Interestingly,

Indirect motor pathway
Globus pallidus-mediated control of motor activity.

Table 2a | **Selected drugs in Phase II–IV study for PD or novel indications in PD**

| Structure | Drug | Status |
|---|---|---|
| *Cholinergic drugs* | | |
|  | Donepezil | Launched for Alzheimer's disease |
|  | Galantamine | Launched for Alzheimer's disease |
|  | Rivastigmine | Launched for Alzheimer's disease |
| *Serotoninergic drugs* | | |
|  | Sarizotan | |
|  | ACP-103 | Phase II |
|  | Quetiapine | Launched for psychoses |
| *Opioid drugs* | | |
|  | Cyprodine | Discovery/research tool |

studies in the brain of monkeys and human patients have shown that non-dyskinesiogenic dopamino-mimetic treatments are associated with a correction of increased preproenkephalin-A expression back to control levels[10,77]. So far, however, the use of non-selective opioid receptor antagonists such as naloxone and naltrexone has provided contradictory or species-dependent results in non-human primates[78,79] and inconclusive results in PD patients[80,81].

The use of selective μ- and δ-receptor antagonists, but not of κ-receptor, however, looks more promising[78]. Almost none of the previous studies have considered opioid transmission at the peak of dyskinesia, but have instead measured precursor levels a few hours or days after the actual presence of involuntary movements. The correlation between opioid expression and dyskinesias reported might therefore not be associated with dyskinesia *per se*, but rather with the supersensitive state of striatal dopamine receptors. If this hypothesis is correct, detection of preproenkephalin-A mRNA overexpression through imaging technology might help predict the susceptibility of patients to dyskinesia. In addition, although opioid precursor levels have been extensively characterized, both the actual identity of their end products, the opioid peptides, and the levels of opioid receptors are poorly known. Indeed, opioid precursors are potentially processed into a number of opioid peptides[82], which then bind with various affinities to the three classes of opioid peptide receptors[83,84]. Considering the discrepancy between a wide range of binding peptides and only three different receptors, and the complex anatomical distribution of these receptors in the basal ganglia[85], calls for developing innovative approaches, possibly based on local delivery of small interfering RNA specific for the opioid precursors instead of classic pharmacological approaches.

## Disease modification

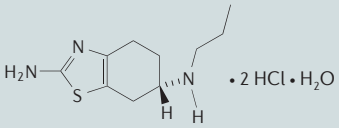
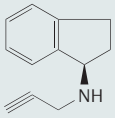
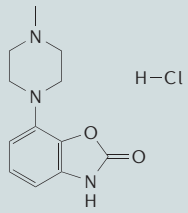
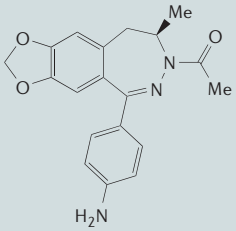
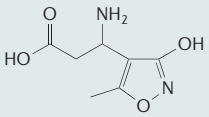
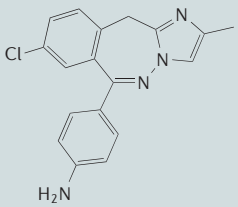
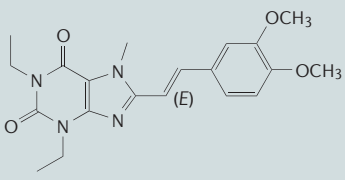
The development of drugs to slow or prevent the progression of PD might logically be thought to evolve from an improved understanding of the aetiology and pathogenesis of PD. There have certainly been major advances in these areas over the past few years and the prospects for the introduction of 'neuroprotective' therapies is much improved. Mutations in six different genes have been demonstrated in familial PD: *α-synuclein*, *parkin*, *UCHL1* (ubiquitin carboxyl-terminal esterase L1), *DJ1*, *PINK1* (PTEN induced putative kinase 1) and *LRRK2* (leucine-rich repeat kinase 2). Other gene mutations such as in *NURR1* (Nur-related factor 1) and *HTRA2* might also be associated with PD. Although these are still considered uncommon causes of PD, understanding the biochemical consequences of their expression will provide important insights into the pathogenesis of the idiopathic disease[86].

This understanding has led to the trial of anti-oxidants and pro-mitochondrial drugs in PD, with the latter showing some promise[88]. Activated microglial cells are present in the substantia nigra and it has been reported that these cells express tumour-necrosis factor-α, interferon-γ, interleukin 1-β, the low-affinity immunoglobulin E receptor CD23, inducible nitric

oxide, cyclooxygenase 2, complement 3 receptor and increased ferritin[89]. A microglial reaction has also been observed in animal models of PD induced by several toxic compounds (6-hydroxydopamine (6-OHDA), MPTP, rotenone and annonacine), indicating that the glial reaction is the consequence of dopamine degeneration, whatever the cause. Epidemiological studies have suggested that the use of anti-inflammatory drugs might reduce the risk for PD[90]. The identification of these biochemical abnormalities has helped the development of disease-modifying therapies.

No drug has yet been shown to be neuroprotective in PD, although several have been tested in clinical trials. It is accepted that such a strategy will only be successful if degeneration is ameliorated in multiple neurotransmitter systems, preventing the progression of both motor and non-motor features. The drugs that have received most attention in relation to neuroprotection include the dopamine agonists and monoamine oxidase (MAO) type B inhibitors, although others, including co-enzyme $Q_{10}$, growth factors, anti-apoptotic agents and glutamate inhibitors, have also been the subjects of clinical trials in PD.

Table 2b | **Selected drugs in Phase II–IV study for PD or novel indications in PD**

| Structure | Drug | Status |
|---|---|---|
| *Dopaminergic drugs* | | |
|  | Pramipexole | Launched |
|  | Rasagiline | Launched |
|  | SLV-308 | Phase III |
| *Glutamatergic and GABAergic drugs* | | |
|  | Talampanel | Phase II |
|  | E-2007 | Phase III |
|  | GYKI-47261 | Discovery |
| *Adenosine $A_{2A}$ drugs* | | |
|  | KW-6002 or istradefylline | Phase III |
| Structure unavailable | SCH 420814 | Phase II |
| Structure unavailable | BIIB014/V2006 | Phase I |

***Dopamine agonists.*** Dopamine agonists have demonstrated neuroprotective properties in a wide range of *in vitro* and *in vivo* studies[91]. The $D_2/D_3$ agonist pramipexole (Mirapex; Boehringer Ingelheim) has been shown to protect non-human primates against MPTP toxicity[92]. The basis for this protection is not understood, but it does not seem to depend on the presence of dopamine receptors[93]. Dopamine agonists have been studied in clinical trials to assess potential disease modification with neuroimaging markers as endpoints[94,95] (FIG. 3). Both pramipexole and ropinirole showed slowed progression of their respective imaging endpoints compared with L-DOPA. These results could be interpreted as demonstrating neuroprotection. However, this interpretation is potentially confounded by a theoretical effect of the drugs on imaging endpoints and could not discriminate between agonist protection and L-DOPA toxicity given the absence of a placebo group[96]. Further trials are underway to address these issues.

## MAO-B inhibitors

The MAO-B inhibitor selegiline (deprenyl) has demonstrated neuroprotective properties in a number of model systems relevant to PD[97–103]. The DATATOP (Deprenyl And Tocopherol Antioxidant Therapy of Parkinson's disease) trial demonstrated that selegiline could delay the introduction of L-DOPA in early PD by 9–12 months[104]. The interpretation of this result was confounded by selegiline's symptomatic effect. Rasagiline (Azilect; Teva) is a new potent MAO-B inhibitor and has also shown neuroprotective effects in *in vitro* and *in vivo* models of PD[105–108]. These effects are independent of its MAO-B inhibition. The potential for rasagiline to delay progression in PD was evaluated in the 12-month extension study TEMPO (TVP-1012 Early Monotherapy for Parkinson's disease Outpatients; FIG. 4)[109]. At 12 months, those who started rasagiline 6 months before the delayed- start group maintained better clinical scores. The results cannot be explained by a symptomatic effect alone and at face value represent

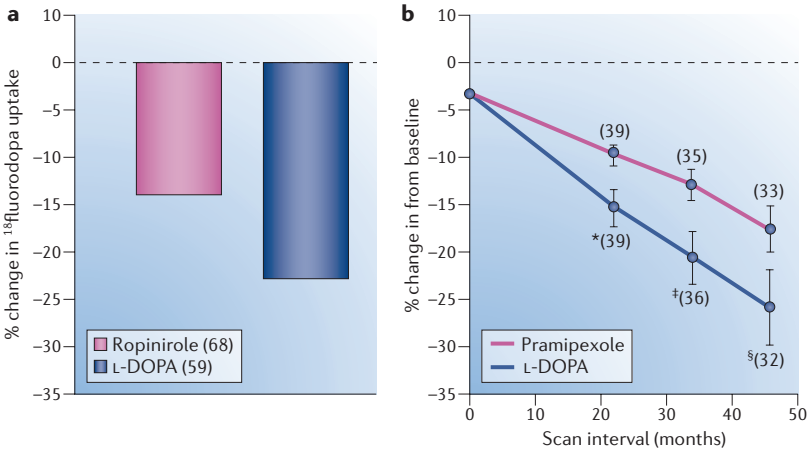



Figure 3 | **Data from imaging studies in dopamine agonist neuroprotection trials showing a slowing of progression in Parkinson's patients in comparison to L-DOPA. a** | Shows the percentage change in putamen F-DOPA emission $p < 0.001$. **b** | Shows the percentage change in putamen 2β-carboxymethoxy-3β (4-iodophenyl)tropane binding (*$p = 0.005$; ‡$p = 0.001$; §$p = 0.03$). Numbers in parentheses refer to patient numbers. Data adapted, with permission, from REF. 95 © (2002) American Medical Association.

Microglial reaction
Inflammatory-mediated reaction.

an early disease-modifying effect. However, there are potential confounding effects, including the beneficial effect of early start therapy *per se* (see below).

## GDNF

Attempts have also been made to regenerate existing dopaminergic neurons. The use of daily intraventricular or striatal infusions of glial-derived nerve growth factor (GDNF) in MPTP monkeys produced restoration of the nigrostriatal system and improvement in motor function without dyskinesias[110]. There was a >20% increase in the number of tyrosine hydroxylase-positive nigral neurons, increases in neuronal size, in dopamine levels and a five-fold increase in striatal tyrosine hydroxylase-positive fibre density. GDNF delivered by lentivirus transfection one week after MPTP exposure produced similar results[111]. The beneficial effects of GDNF could be a consequence of both protective and restorative properties. An early study of low-dose, monthly intraventricular injections of GDNF into PD patients did not produce any clinical benefit, or any evidence of dopaminergic regeneration in the one patient that underwent autopsy[112,113]. A pilot study reported on direct putaminal infusion of GDNF in five PD patients with advanced disease[114]. In contrast to intraventricular delivery of GDNF, putaminal infusion was well tolerated and produced significant clinical improvement and a reduction in dyskinesias. Furthermore, fluorodopa PET scans showed a significant increase in uptake in the putamen and substantia nigra at 18 months. However, a larger controlled clinical trial of GDNF in PD was negative and terminated prematurely because of side effects[115]. This trial has been criticized for its design and the dosage of GDNF used[116].

Other compounds have been evaluated for disease-modifying effect in PD with varying results (see REF. 96 for a review).

It has recently been suggested that early symptomatic treatment of PD might itself have some neuroprotective effect by modifying the compensatory mechanisms that maintain normal motor function in the pre-symptomatic period during which nigral dopaminergic cell death is progressing[117]. The results of the TEMPO, ELLDOPA (Early versus Late Levodopa) and DATATOP studies would support such an effect. The identification and validation of preclinical markers for PD would be an important development. Certain non-motor features, including olfactory loss, depression and disorders of rapid-eye-movement sleep behaviour, can precede the onset of the motor symptoms and signs of PD, but none are specific for this disease[118]. Nevertheless, it might be possible to enrich an at-risk population for PD with a combination of these features. Various imaging modalities, including PET with $^{18}$fluorodopa and single-photon emission computerized tomography with ligands for the dopamine transporter, have already found applications in neuroprotection trials[94,95], but the interpretation of the results of these trials remains complex. Further study of these modalities as markers of disease progression, even with the potentially confounding factor of drug treatment, is important.

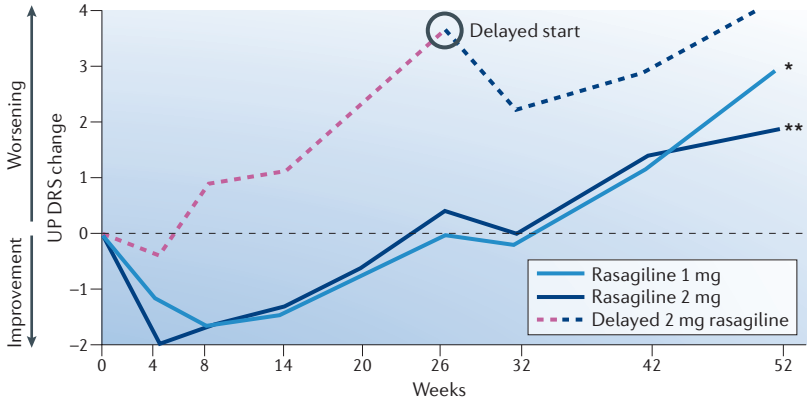



Figure 4 | **Delayed start TVP-1012 Early Monotherapy for Parkinson's disease Outpatients (TEMPO) study with rasagiline, 371 subjects.** Patients randomised to early treatment had better clinical outcome at 12 months compared to those early Parkinson's disease patients on placebo for the first 6 months. UPDRS, Unified Parkinson's Disease Rating Scale *$p = 0.05$ and **$p = 0.01$. Adapted, with permission, from REF. 110 © (2004) American Medical Association.

## Conclusion

PD is a progressive multicentric neurodegenerative disease involving several neurotransmitter systems. Dopamine-replacement therapies have been highly successful in improving the motor features of the disease but the value of these treatments, particularly L-DOPA, is limited by the development of motor complications. There are now several novel therapeutic approaches emerging for PD, as summerized in TABLE 2. These are focussed on the non-dopaminergic systems and are designed to improve motor function without the risk for motor complications associated with L-DOPA, and also to improve dyskinesia itself. Disease modification remains the most important goal in PD. Although no drug has yet been proven to be neuroprotective, several candidates have shown promise.

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**Competing interests statement**
The authors declare competing financial interests: see Web version for details.


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