

Parkinson's disease: will therapy move beyond dopaminergic medication?

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Parkinson's disease is a chronic, progressive neurodegenerative disorder that affects more than 1% of individuals older than 60 years. The motor symptoms of Parkinson's disease are accompanied by a multitude of nonmotor symptoms, which usually predominate in the later stages of the disease and influence patients' quality of life. Complex, interconnected neuronal systems involving dopamine and other neurotransmitters participate in the development of the disease and are responsible for the motor and nonmotor symptoms. Effective symptomatic therapies are available, but long-term management and neuroprotection still remain controversial issues. Levodopa is the 'gold standard' of symptomatic therapy, but treatment of the nondopaminergic and nonmotor symptoms of Parkinson's disease necessitates the targeting of transmitter systems beyond dopamine. Among these, 5-HT agonists, glutamate antagonists, adenosine A2 antagonists and the α -adrenergic-receptor antagonists are detailed. Among glutamate antagonists, the neuroactive kynurenes may exert a neuroprotective effect.

Keywords: adenosine • dopamine agonists • glutamate • kynurenes • levodopa
• nondopaminergic medication • Parkinson's disease • serotonin

Parkinson's disease (PD), the second most common chronic, progressive neurodegenerative disorder after Alzheimer's disease (AD), is estimated to affect more than 1% of individuals older than 60 years, with incidence and prevalence increasing with age. It affects over 4 million people worldwide [1,2], a number considered by some to be an appreciable underestimate [3]. The continuing emergence of the disease is a result of a combination of genetic and environmental factors. Certain gene mutations that cause familial PD have been identified; for example, mutations in the *PARK1*, *PARK2*, *PINK1* or *LRRK2* genes, some of which have also been proved in sporadic cases [201]. Among environmental factors, exposure to pesticides and rural residence are believed to play a role in the development of the disease [4,202].

No definitive diagnostic test is available for PD. The disease is classically defined by the presence of two of the first three cardinal motor symptoms: bradykinesia, rigidity, resting tremor and postural instability. The asymmetric or unilateral occurrence of the symptoms and a good therapeutic response to dopaminergic medication are further aids in the diagnosis. The motor symptoms are accompanied by a multitude of nonmotor symptoms, which usually predominate in the later stages of the disease, but may occur before the onset of the motor symptoms. The nonmotor symptoms may be debilitating and influence the quality of life of the patients. Nonmotor symptoms include fatigue, neuropsychiatric features such as depression or anxiety, cognitive impairment, dementia, hallucinations, attention deficit, impulse control disorder, autonomic dysfunction (bladder disturbances, sweating, orthostatic hypotension or erectile dysfunction), gastrointestinal symptoms (nausea, dysphagia, sialorrhea or constipation), sensory complaints such as pain or olfactory disturbance

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and sleep problems for example, rapid eye movement sleep behavioral disorder [5,6].

The cause of the motor dysfunction is the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) and the appearance of Lewy bodies within the pigmented neurons of the substantia nigra (SN). Other neurotransmitter systems, such as the cholinergic, serotonergic and adrenergic systems are also involved in neurodegeneration in PD and are presumed to be responsible for the nonmotor features of the disease. A structurally complex neuronal circuitry with a manifold interconnectivity utilizing different neurotransmitters is required for the smooth operation of the motor and nonmotor functions. A better understanding of the development of the motor and nonmotor symptoms became possible through advances in knowledge concerning the function of the inter-related neuronal circuitry involved in PD, knowledge that is also essential for the development of new dopaminergic and nondopaminergic medication.

The basal ganglia are a group of functionally related nuclei that, besides mediating motor functions, play roles in cognitive function and emotional behavior [7]. Their role in the motor functions is better understood than that played in the nonmotor functions. The nuclei of the basal ganglia are interconnected and are also connected with parts of the cerebral cortex, the thalamus, the red nucleus, the brainstem reticular formation and the spinal cord. There is a convergence and an integration of sensory, motor/behavioral and mnemonic information in the basal ganglia. At the level of the striatum, there is a strong convergence of corticostriatal projections from functionally different cortical areas. The dorsolateral part of the striatum is involved in stimulus–response associations, such as habit learning [8–10]. The medial and ventral parts of the striatum receive inputs from prefrontal cortical areas, the amygdala and the hippocampus, and are involved in stimulus–reward associations [11–13]. The mechanism through which an appropriate response to a particular stimulus is selected is not fully understood. It has been shown that basal ganglia are involved in the modulation of appetitive behavior such as drug addiction [14], and in cognitive information processing for nonmotor tasks [15] such as learning [8] or attention [16].

The motor symptoms are caused by an imbalance between dopamine and acetylcholine due to the degeneration of the dopaminergic nigrostriatal system. The background of the nonmotor symptoms is an imbalance of other functionally connected neurotransmitter systems and their interactions with the dopaminergic system. The nondopaminergic pathways and their receptors have also been implicated in the mechanisms responsible for the occurrence of motor fluctuations and dyskinesias on sustained levodopa treatment [17,18] and are potential new therapeutic targets for the treatment of PD.

Several nondopaminergic drugs are already in use for the treatment of PD and many of those now under development exhibit a complex mechanism of action. For a better understanding of the nondopaminergic mediator systems and their interactions and the nondopaminergic medication currently under development for PD, a short overview of dopaminergic and nondopaminergic pathways is presented in [Figure 1](#).

Dopaminergic & nondopaminergic pathways

■ Dopaminergic neurotransmission

The dopaminergic nigrostriatal pathway terminates in the striatum. The projections are excitatory to striatal neurons bearing dopamine D1 receptors and inhibitory to striatal neurons bearing D2 receptors. The striatal output can be divided into two pathways. The direct pathway originates from striatal neurons bearing D1 receptors and sends an inhibitory GABA/substance P projection to the globus pallidus internus (GPi)/substantia nigra pars reticulata (SNr). This in turn sends an inhibitory GABAergic projection to the thalamus (ventroanterior and ventrolateral nuclei). These thalamic nuclei project to the cortex through excitatory glutamatergic connections. The indirect pathway originates from striatal neurons expressing D2 receptors. It sends inhibitory GABA/enkephalinergic projections to the globus pallidus externus (GPe). The GPe has a reciprocal inhibitory/excitatory GABA/glutamatergic connection with the subthalamic nucleus (STN). The STN has an excitatory glutamatergic projection to the GPi/SNr. In PD, dopaminergic neurons in the SNc degenerate and there is loss of dopaminergic input to the striatum. As a result, there is an increased activity of the indirect pathway and a decreased activity of the direct pathway. The inhibitory activity from the GPi/SNr to the aforementioned thalamic nuclei increases, and subsequently there is a decrease in the excitatory activity from the thalamus to the cortex [1,19].

■ Cholinergic neurotransmission

The cholinergic system is believed to play a role in the development of cognitive dysfunction in PD [20]. Cognitive decline in PD correlates with a reduction in cholinergic activity in the cortex and a loss of cholinergic neurons in the nucleus basalis of Meynert, an area rich in choline acetyltransferase under normal circumstances [21–23]. The decrease in choline acetyltransferase activity in PD dementia is even higher than that observed in AD [24]. In patients with PD there is a subclinical cholinergic deficit and anticholinergic therapy worsens memory impairment [25]. There are two types of cholinergic receptors: neurons projecting to the SNc, STN, GP and striatum bear muscarinic receptors, whilst neurons projecting to the SNr express muscarinic and nicotinic receptors. It is presumed that an alteration in

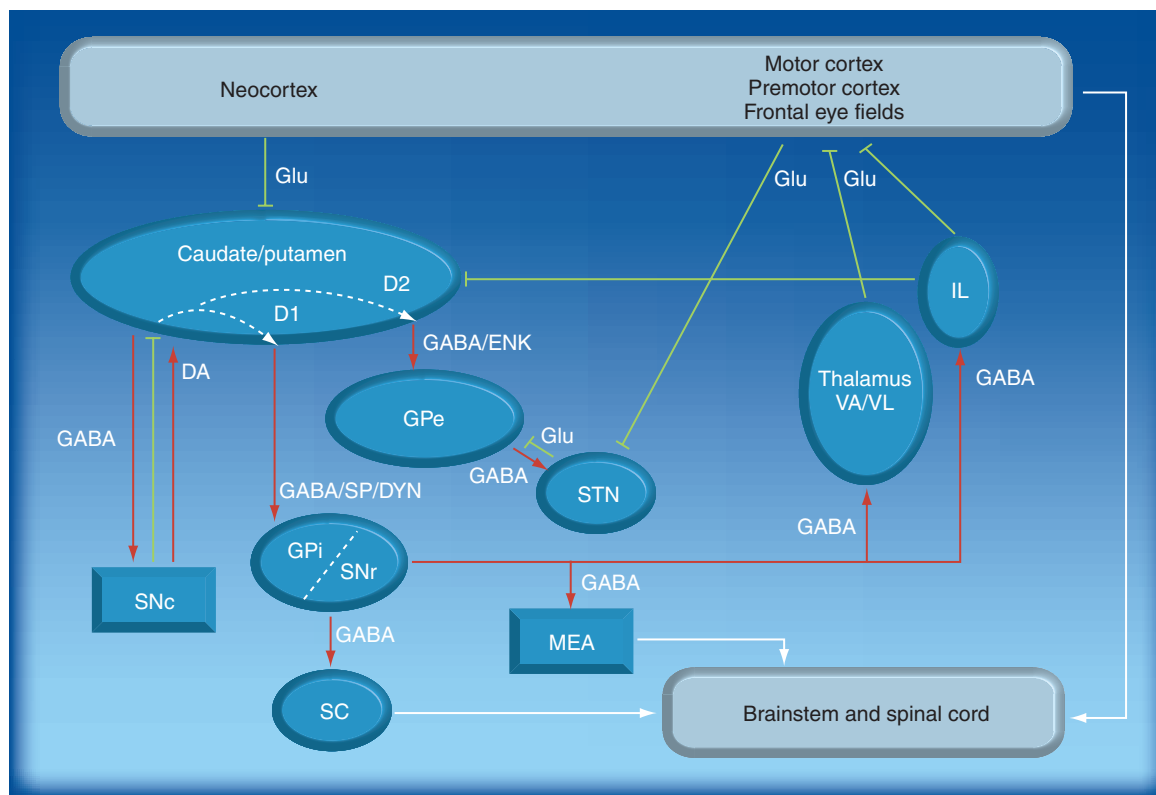


Figure 1. Basal ganglia circuitry. Excitatory connections are indicated with red arrows and inhibitory connections with green arrows. The dopamine-mediated connection from the SNc is both excitatory and inhibitory, depending on the postsynaptic receptor.

DA: Dopamine; D1: Dopamine-1 receptor; D2: Dopamine-2 receptor; DYN: Dynorphin; ENK: Enkephalin; GABA: γ -aminobutyric acid; Glu: Glutamate; GPe: Globus pallidus pars externa; GPi: Globus pallidus pars interna; IL: Intralaminar thalamic nuclei; MEA: Midbrain extrapyramidal area; SL: Superior colliculus; SNc: Substantia nigra pars compacta; SNr: Substantia nigra pars reticulata; SP: Substance P; STN: Subthalamic nucleus; VA/VL: Ventral anterior and ventral lateral nuclei of the thalamus.

nicotinic transmission may play a role in the development of PD symptoms [26]. Cholinergic dysfunction might also be responsible for autonomic dysfunction in PD [27].

■ Serotonergic neurotransmission

Serotonergic neurotransmission plays a role in many aspects of the basal ganglia function, modulating dopaminergic and GABAergic neurotransmission and glutamate release. A dense serotonin-mediated innervation originating from the brainstem raphe nuclei projects to the GP and SN. Serotonin increases the firing rate of neurons in the GP. In PD, there is a decreased serotonin concentration in the basal ganglia nuclei, which contributes to a reduced activity in the GP. There are several types of serotonin receptors. The 5-HT_{1A} receptors are located mainly in the dorsal raphe nucleus and the striatum. The $5\text{-HT}_{1B}/1D$ receptors are located on striatopallidal pathways, and the $5\text{-HT}_{2A/2C}$ receptors within the SNr and the GPi [28]. Stimulation of the

5-HT_{1A} and 5-HT_{1B} receptor subtypes facilitates dopamine release, whilst it is inhibited by stimulation of the 5-HT_{2C} receptors. In PD, there is a loss of serotonin input from the dorsal raphe nucleus to the striatum. In the remaining serotonergic neurons, levodopa may be converted to dopamine and the excessive, nonphysiologic release of dopamine by these neurons leads to dyskinesia [29]. It has been shown that striatal dopamine release can be modulated and dyskinesias reduced by the stimulation of presynaptic 5-HT_{1A} receptors [30]. By suppressing serotonin inputs to the striatum, presynaptic 5-HT_{1A} agonists may reduce dyskinesia, as already proved in preclinical studies [31], although clinical studies with 5-HT_1 agonists did not establish a clinically meaningful antidyskinetic effect [32]. 5-HT_{1A} -receptor agonists lead to hyperpolarization of the cell membrane and inhibition of glutamate release, which may suggest their potential neuroprotective effect [33]. Serotonergic pathways have been implicated in the development of some of the nonmotor symptoms of PD. They play a

role in modulating gastrointestinal motility and pain. Low serotonin levels are associated with alterations in mood, such as depression, and with disorders of sleep. Stimulation of the serotonergic system in PD results in decreases in anxiety, constipation, depression and possibly pain. By contrast, inhibition of serotonergic pathways causes deficits in cognition, executive function and fatigue.

■ Adrenergic neurotransmission

Reduced levels of noradrenaline have been observed in PD patients [34]. The loss of noradrenaline may worsen disease progression [35] and may facilitate the onset of dyskinesia during dopaminergic therapy [36]. The basal ganglia α -2-adrenergic receptors modulate the sensitivity of dopaminergic receptors and are believed to be implicated in the overactivity of the direct pathway, which is responsible for dyskinesias in PD. The noradrenergic system also plays a role in depression in PD patients [1] and the inhibition of adrenergic neurotransmission causes a worsening of anxiety and depression. The effects of adrenergic stimulation depend on the receptor subtypes: the stimulation of α -2 receptors improves attention and executive functions, whilst the stimulation of α -1 receptors has adverse effects [1]. Noradrenaline is also a key neurotransmitter of the endogenous pain system; lower noradrenaline levels are associated with increased symptoms of pain.

■ Glutamatergic neurotransmission

Glutamate is the main excitatory amino acid in the brain. The enhanced release of glutamate and the consecutive prolonged stimulation of its receptors causes damage to the postsynaptic neurons [37]. The process of glutamate-induced excitotoxicity [38] is linked with a mitochondrial dysfunction. An energy impairment can lead to partial membrane depolarization. This results in relief of the magnesium block of the NMDA channel. Thus, glutamate can cause a self-propagating cascade of events, such as a Ca^{2+} overload and free radical generation [39]. The GPi provides excitatory glutamatergic input to the STN. The excitatory glutamatergic corticostriatal projections arise from all areas of the cortex, but particularly from the frontal cortex to the caudate and putamen. The somatosensory, motor and premotor cortices project to the putamen, while the prefrontal areas project to the caudate. Aside from the mentioned nuclei, the cortex also sends projections to the STN. The thalamus, on the other hand, sends projections to both the striatum and the STN. By reducing the abnormally enhanced corticostriatal glutamatergic input in the direct pathway neurons, glutamate antagonists can theoretically reduce dyskinesias. Amantadine is presumed to act through this mechanism.

■ GABAergic neurotransmission

The major inhibitory neurotransmitter in the CNS is GABA. GABAergic pathways regulate signal processing between the striatum and the GP (GPi and GPe) and from the GPi and the SNr to the thalamus [1]. GABA is the main neurotransmitter in the striatal neurons of the direct and indirect pathways. The co-transmitters are neuropeptides derived from preproenkephalin-B for the direct pathway and enkephalins derived from preproenkephalin-A for the indirect pathway [40]. In PD, the loss of the dopamine input from the SNc into the striatum inhibits the function of the striatal neurons of the direct and indirect pathways. A decrease in dopamine levels may lead to an increase in GABA concentration within the striatum [41] and to an increase in the signal output from this region of the brain [41]. The administration of L-dopa is thought to suppress GABA synthesis [42] and reverse this effect. However, in PD an overall decrease in GABAergic activity of the striatal neurons can be observed due to the combined effects of the degeneration of the nigrostriatal pathway and of the long-term levodopa therapy [43]. GABAergic neurotransmission is also involved in the development of several nonmotor symptoms, such as pain, sleep disorders and depression [1].

■ Adenosine-mediated neurotransmission

Adenosine A2a receptors are located on the GABAergic cell bodies and terminals of the indirect striatopallidal pathway and are functionally linked to dopamine D2 receptors.

In the GPe, adenosine induces enhanced GABA release via the A2a receptors and is thought to contribute to the overactivity of the indirect pathway in PD [44]. On the other hand, overactive corticostriatal glutamatergic activity leads to adenosine release and stimulation of the A2a receptors [45]. Enhanced GABA release in the GPe via the activation of adenosine A2a receptors contributes to overactivity in the indirect pathway. Adenosine A2a antagonists can modulate the output of the striatum, which is believed to be critical for the occurrence of the motor complications of PD. These observations indicate that adenosine A2a antagonists are potential antiparkinsonian agents.

In summary, a cholinergic deficit may be responsible for memory loss and cognitive impairment, a serotonergic deficit underlies mood disturbance and depression, and attention deficit may be explained by an adrenergic loss. Glutamatergic systems play a role in the modulation of PD symptoms related to motor function and cognitive impairment. GABAergic- and adenosine-mediated neurotransmission modulate dopaminergic systems. The interactions between neurotransmitter systems are responsible for the nonmotor symptoms of PD [1].

Treatment options for PD

■ Dopaminergic medication

The treatments available for PD either stimulate the brain dopamine receptors or supply the dopamine precursor levodopa, which can cross the blood–brain barrier and enhance dopamine synthesis. The ‘gold standard’ of the symptomatic treatment of PD is the levodopa–peripheral decarboxylase inhibitor combination. Levodopa is decarboxylated to dopamine in the brain and in the periphery, the latter being responsible for side effects such as nausea and vomiting. Levodopa was introduced more than four decades ago. It soon became evident that motor complications, such as motor fluctuations and dyskinesias, emerge after some years of levodopa treatment as a consequence of the noncontinuous receptor stimulation and consecutive receptor hypersensitivity. It was thought that levodopa might accelerate neuronal degeneration owing to the free radicals formed through oxidative metabolism, but levodopa toxicity could not be proved in clinical trials [46,47]. In healthy individuals, the dopamine receptors in the striatum are exposed to relatively constant levels of dopamine. Oral dopamine medication with a short plasma half-life causes a discontinuous or pulsatile stimulation of the dopamine receptors. With disease progression, fewer dopaminergic neurons are available for the storage of dopamine and the regulation of dopamine release. A short-acting dopaminergic agent exposes the dopamine receptors to alternately too-high and too-low levels of dopamine, which cannot be buffered and are believed to lead to motor fluctuations. The continuous dopaminergic stimulation hypothesis holds that continuous, smooth dopamine-receptor stimulation causes less dyskinesia than does pulsatile stimulation. Extensive research is ongoing to develop dopaminergic medication that provides continuous stimulation of the dopamine receptors. The addition of a catechol-*O*-methyltransferase inhibitor to levodopa increases its half-life and provides a more constant plasmatic level.

In this respect, a prospective multicenter, double-blind study (Stalevo Reduction In Dyskinesia Evaluation [STRIDE-PD]) was performed to evaluate the risk of motor complications in patients with PD randomized to levodopa/carbidopa/entacapone (Stalevo) versus levodopa/carbidopa alone [203]. More than 700 early-stage PD patients requiring the initiation of levodopa substitution therapy were enrolled. The time to dyskinesia was significantly shorter and the incidence of dyskinesia during the study period higher in the levodopa/carbidopa/entacapone-treated group. The benefit of entacapone in delaying dyskinesia could not be proven in this study. Levodopa/carbidopa/entacapone provided slightly better PD symptom control in comparison with the levodopa/carbidopa regimen. Therefore, levodopa/carbidopa/entacapone is currently indicated for the

treatment of PD patients with end-of-dose motor fluctuations improperly controlled by the levodopa/cabidopa treatment [48,49].

Continuous levodopa delivery can be ensured by means of intra-intestinal infusion, which is available for clinical use. This approach reduces dyskinesia in the advanced disease stages [50–56]. It requires surgery and is difficult to maintain. Other disadvantages are the potential development of tolerance and the occurrence of psychiatric side effects with 24-h continuous use [57]. Dopamine agonists are also available in continuous-release formulations. A longer-acting dopamine agonist or its continuous delivery may prevent or reverse motor complications [58], as demonstrated in animal models [45] and clinical trials [59,60]. The use of transdermal patches and infusion pumps maintains plasma levels of the drug within the therapeutic range for a prolonged period. Pramipexole, ropinirole and rotigotine are available in 24-h extended-release formulations. Lisuride is an ergot-derived dopamine agonist that can be administered as a continuous infusion [61]. Programmable portable apomorphine infusion pumps are a recent development in this field, and even better control would be provided by the use of autoprogrammable pumps adjusted by the patient [62]. Monoamine oxidase B (MAO-B) inhibitors (e.g., selegiline or rasagiline) can be used in all stages of PD, as a monotherapy and as an adjunct to levodopa. Beside improving parkinsonian symptoms, MAO-B inhibitors have been suggested to exhibit a neuroprotective effect. Oxidative stress and mitochondrial dysfunction play key roles in the development of PD. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD, MPTP is metabolized to 1-methyl-4-phenylpyridinium ion (MPP⁺) interfering with mitochondrial function and leading to the formation (generation) of free radicals. Selegiline prevents MPTP-induced neuronal damage in experimental models. This suggests its antioxidant and putative neuroprotective effects. The presumed neuroprotective effect of MAO-B inhibitors appears to be independent of their enzyme-blocking effects [63,64] and to be related to properties such as the inhibition of apoptosis [65,66] and the modulation of the expression of neurotrophic factors [67–69]. Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP), a multicenter, randomized, placebo-controlled trial evaluated selegiline versus placebo for early PD patients, concluded that selegiline significantly delayed the need for levodopa therapy [204]. This effect was not maintained in a follow-up after the withdrawal of selegiline, suggesting that selegiline had a symptomatic rather than a neuroprotective effect. In the Sinemet-Deprenyl-Parlodel (SINDEPAR) study, patients on selegiline or placebo were treated for 12 months with levodopa/carbidopa or bromocriptine. The selegiline-treated patients' Unified Parkinson's

Disease Rating Scale (UPDRS) score deteriorated less compared with that of the placebo groups [70]. The 2-month washout period to the final follow up was later considered to be of insufficient length to state a disease-modifying effect of selegiline [70,71]. Two double-blind, delayed-start trials, Rasagiline (TVP-1012) in Early Monotherapy for Parkinson's disease Outpatients (TEMPO) and Attenuation of Disease progression with Azilect® Once-daily (ADAGIO) investigated the potential neuroprotective effects of rasagiline [72,73]. In these studies, during the initial period the active group was on rasagiline, while the delayed-start group was on placebo. In the second part of the trials, both groups were on active medication. Subjects in the active treatment groups had a smaller increase in UPDRS score compared with the delayed-start group. This may indicate a disease-modifying effect of rasagiline.

■ **Nondopaminergic medications under development for the treatment of PD**

Among the compounds now being studied for the treatment of PD, some are well known and already used in other diseases, and some are newly developed (Table 1).

Adenosine A2a antagonists

Among the adenosine A2a antagonists, istradefylline (KW-6002) has been extensively studied in preclinical studies and as adjunct to levodopa in Phase II and III trials. A randomized, placebo-controlled study compared istradefylline with placebo in 363 patients on levodopa with motor fluctuations. It concluded that 20 and 40 mg istradefylline doses are effective in improving the motor symptoms during the 'on' period and in reducing the length of the 'off' period, without severe side effects [74]. Other A2a antagonists are undergoing development.

SYN 115 is an orally bioavailable and potent selective inhibitor of the adenosine A2a receptors. SYN 115 crosses the blood-brain barrier and modulates the production of dopamine, glutamine and serotonin in specific regions of the brain. It inhibits the over-activated indirect pathway and inhibits cortical activity in a manner that improves alertness and attention [75]. Phase IIa and IIb efficacy trials with SYN 115 were initiated in 2009 [76]. The Phase II trial was a randomized, double-blind, placebo-controlled, crossover study in patients with mild-to-moderate disease stages. The effects of different doses

Table 1. Compounds in clinical trials for the treatment of Parkinson's disease.

Mechanism of action	Drug	Targeted symptoms
Adenosine A2a antagonists	Istradefylline	Motor symptoms
	SYN 115	Motor symptoms
	SCH (420814)	Motor symptoms, dyskinesia
	Preladenant	Motor fluctuations
Serotonin modulators	Buspirone	Dyskinesia
	Sarizotan	Dyskinesia
	Piclozotan	L-dopa induced motor symptoms
	Pardoprunox (SLV308)	Motor symptoms, dyskinesia
	Pimavanserin	Dyskinesia
α 2-adrenergic-receptor antagonists	Fipamezol (JP 1730)	Dyskinesia
	Idazoxan	Dyskinesia
	Piribedil	Impairment of vigilance and cognitive function
Catecholamine-reuptake inhibitor	Methylphenidate	Impairment of gait, awareness and attention
Antiepileptic drugs with complex mechanism of action	Safinamide	Motor symptoms, disease progression
	Zonisamide	Motor symptoms, disease progression
	Levetiracetam	Dyskinesia
Vitamins	Folic acid	Disease progression
	Vitamin D	Motor symptoms
Antioxidants, scavenger of free radicals, compounds acting on mitochondria,	Coenzyme Q10	Disease progression
	Creatine	Disease progression
	Inosine	Disease progression
Nicotine-receptor agonist	Nicotine	Motor symptoms, dyskinesia
L-type Ca ²⁺ -channel blocker	Isradipine	Dyskinesia
Glutamate antagonists	Neu120	Motor symptoms, dyskinesia
	Amantadine	Motor symptoms, dyskinesia
	Kynurenines	Dyskinesia

(60 and 20 mg) of SYN 115 were evaluated in the absence of levodopa and in the presence of a low dose of levodopa on motor symptoms and cognitive function, using the UPDRS rating scale, the tapping speed, cognitive tests and functional magnetic resonance imaging tests. The UPDRS motor score was 20% lower in the SYN 115 group compared with placebo, and the cognitive test improved significantly [205].

SCH 420814, pyrazolo (4,3-e)-1,2,4-triazolo(1,5-c)pyrimidine, is another potent, highly selective competitive antagonist of the human adenosine A_{2a} receptor [206]. The efficacy and safety of another adenosine A_{2a} antagonist, preladenant, is currently being studied in a Phase III, double-blind placebo and active-controlled trials in patients with early PD as well as in patients with moderate-to-severe disease experiencing motor fluctuations. The effects of different doses of preladenant on PD symptoms and levodopa-caused motor fluctuations, respectively, are compared with placebo and rasagiline [207,208].

Serotonin modulators

The effects of a number of 5-HT_{1A} agonists that are already used have been studied on PD symptoms and dyskinesia. In a study on ten PD patients, the partial 5-HT_{1A} agonist buspirone significantly reduced the dyskinesia without worsening the motor symptoms [77]. Sarizotan extended the duration of action of levodopa and significantly reduced the dyskinesia in a cohort of 18 patients [30], but in further investigations the higher doses were associated with increased 'off' times [32,78], and an increase in 'on' time without dyskinesia could not be proven. The explanation of the lack of effectiveness is that sarizotan also exerts D₂ antagonist properties.

Piclozotan, a highly selective 5-HT_{1A} agonist with high selectivity on dopamine D₂ receptors, has no dopaminergic antagonist activity. In a pilot study on patients with levodopa-induced motor complications, piclozotan appeared to be both safe and effective in improving the 'on' time without dyskinesia and in reducing the 'off' time [79].

Pardoprunox (SLV308), developed for the treatment of PD, is a full 5-HT_{1A} agonist and a partial dopamine D₂/D₃ agonist. It appears to be effective on the motor symptoms of early PD, but its action on dyskinesia is currently unknown [80].

5-HT_{2A/2C} receptor antagonists may also reduce levodopa-induced dyskinesia. Clozapine exhibits affinity for many nondopaminergic receptors, including 5-HT_{2A/2C} receptors, and alters dopamine D₂-receptor binding [81]. In a randomized clinical trial, it significantly reduced levodopa-induced dyskinesia at rest, without influencing dyskinesia with activity and without worsening the PD symptoms [82]. Its clinical use is limited by

side-effects such as agranulocytosis. Quetiapine did not prove more effective than placebo on PD dyskinesia [83]. Pimavanserin (ACP-103) is an inverse 5-HT_{2A} agonist under development for the treatment of dyskinesia. Monoamine-reuptake inhibitors have also been tried in the treatment of PD. A serotonin–noradrenaline–dopamine reuptake inhibitor, tenofensine, was dropped from development for use in PD after early trials failed to prove its efficacy [84–86].

α₂-adrenergic receptor antagonists

In this group of medication, fipamezol (JP 1730) has been shown to attenuate levodopa-induced dyskinesia in MPTP primate models. A double-blind, randomized, placebo-controlled, dose-escalation design, Phase IIb clinical trial (Fipamezole from Juvantia for treatment of Dyskinesia [FJORD]) demonstrated that fipamezole (Zydis® formulation) reduces dyskinesia in PD. The study results also suggested that this drug has the potential to reduce the 'off' time and improve cognitive function. Furthermore, the reduction in dyskinesia was found to be strongly correlated with the investigator's clinical global impression of improvement in the overall condition [209]. Fipamezol is currently under clinical development [87]. The selective α₂ antagonist idazoxan has been shown to reduce dyskinesias in preclinical and Phase II clinical trials [88], but the results between studies were inconsistent [89]. Piribedil is a nonergot dopamine D₂/D₃ agonist with α₂-noradrenergic antagonistic properties. An ongoing prospective, randomized study is now exploring the influence of piribedil on vigilance and cognitive function in patients with PD, compared with other nonergot dopamine agonists [210].

■ Treatment of nonmotor symptoms

As detailed above, the nonmotor symptoms predominate in the later stages of the disease and may be debilitating. Effective disease management also requires the recognition and treatment of nonmotor symptoms. Only a few randomized controlled trials were conducted for their treatment. Rivastigmine was approved for the treatment of PD dementia based on the proof-of-efficacy in a double-blind, placebo-controlled trial [90]. Other agents used for PD dementia are memantine and donepezil [91,92]. Exposure to dopaminergic medication is the major cause of psychosis, which develops later in the course of PD: hallucinations occur in the presence of dementia. Among antipsychotics, quetiapine, clozapine, olanzapine, risperidone and pimavanserin, and a 5-HT_{2A}-receptor inverse agonist were investigated for PD patients [17,93]. For the treatment of depression in PD patients, serotonergic and noradrenergic agents can be used and there are few data regarding the role of dopaminergic therapy in the control of depression in PD [94]. Acamprostate, a GABA and

taurine analog that reduces glutamate-mediated neurotransmission, is being investigated in PD for compulsive behavior and cravings [93]. BF 2649, a selective histamine H3 inverse agonist that increases histaminergic transmission in the brain, increases wakefulness and is, therefore, being studied for the treatment of excessive daytime sleepiness in PD patients [95]. Methylphenidate is a psychostimulant that inhibits catecholamine reuptake and increases dopamine levels in the brain, thereby stimulating the nervous system. Methylphenidate improves attention in attention-deficit and hyperactivity disorder, but the effects on the motor function are controversial. Small pilot studies have indicated that low doses may improve gait, and especially freezing in patients with advanced PD, without the need for exogenous levodopa [96–98], although these results have not been confirmed in other trials [99]. A 6-week treatment period with methylphenidate in a pilot study lowered the fatigue scores in patients with PD [100]. A randomized, placebo-controlled, double-blind clinical trial to assess the efficacy of methylphenidate against gait impairment in PD was conducted in 2007. Commencing in 2009, the Study of Methylphenidate to Treat Gait Disorders And Attention Deficit In Parkinson's Disease (PARKGAIT-II) is a clinical trial designed to evaluate the effects on gait disturbance and attention [211].

Safinamide & zonisamide

Safinamide and zonisamide, originally developed as antiepileptic agents, both have multiple modes of action, including MAO-B inhibition and glutamate-release inhibition. They may affect overactive glutamate transmission, a key mechanism underlying the symptoms of PD. The mechanism of action of safinamide combines the blockade of voltage-dependent Na^+ and Ca^{2+} channels with the potent, selective and reversible inhibition of MAO-B and the inhibition of glutamate release. The mechanism of action is dose dependent. At low doses, safinamide acts only as a MAO-B inhibitor, whereas at high doses its glutamate-inhibitory function is observed. In experimental models, it has also been demonstrated to have neuroprotective and neurorescuing effects. Safinamide has excellent bioavailability, with linear kinetics and can be administered once daily. In early PD, safinamide may be used in combination with dopamine agonists to improve motor function [101], later with levodopa to reduce the levodopa dosage [102], and in advanced PD to decrease motor fluctuations [103].

In a clinical trial involving 172 patients with early PD, safinamide resulted in a significant improvement in motor scores, particularly when combined with dopamine agonists [101]. At the most effective dose (1 mg/kg, daily dose 40–90 mg), both MAO-B inhibition and glutamate-release inhibition occurred, whereas the lower dose induced only MAO-B inhibition. In another study

of 269 patients with early PD treated with dopamine agonists, the safinamide 50–100 mg dose led to a significant decrease in the UPDRS III score from baseline versus placebo at 6 months, whereas the 150–200 mg dose did not [104]. An extension of the study to 12 months suggested that safinamide might extend the time required between dopaminergic medications [105]. Safinamide was also subjected to trials for patients with advanced PD, and in a small open-label study it was demonstrated to decrease motor fluctuations [101]. In a small pilot study involving 13 PD patients receiving a high dose of safinamide, a symptomatic motor benefit was detected [103]. Several clinical trials are ongoing to assess the effect of safinamide in early PD as an add-on to dopamine agonists, to explore its action in levodopa-induced dyskinesia (Safinamide in Levodopa-Induced Dyskinesia in Parkinson's Disease Subjects [Safinamide-LID]), and to explore its potential benefit on the cognitive impairment associated with PD, or on the motor fluctuations as an add-on to levodopa (Safinamide in Idiopathic Parkinson's Disease [IPD]) With Motor Fluctuations, as add-on to Levodopa [SETTLE]).

Zonisamide acts on Na^+ and Ca^{2+} channels and influences the dopamine, serotonin and acetylcholine metabolisms. It may exert neuroprotective action, independently of its antiepileptic activity. In a small clinical study, eight patients received zonisamide for a mean period of 7.5 years (5.5–9 years). The wearing-off and the tremor improved and the benefit proved to be maintained for at least 3 years with no disabling dyskinesia or adverse event occurring [106].

Levetiracetam

Levetiracetam is an antiepileptic drug with a complex mechanism of action. It has an indirect effect on the GABAergic system, modulates ionic currents, influences the expression of several genes and binds to the synaptic vesicle protein 2a. On the basis of the manifold mechanism of action, levetiracetam has been tried as therapy for levodopa-induced dyskinesia. In nine patients with moderate-to-severe dyskinesia, high doses of levetiracetam titrated up to 3000 mg/day were not well tolerated because of the worsening PD symptoms and dyskinesia on the one hand, and the side-effects such as somnolence on the other [107]. Lower mean doses of 625 ± 277 mg/day proved effective in improving the 'on' time without dyskinesia or with nontroublesome dyskinesia in PD patients with peak-dose dyskinesia [108]. A multicenter, randomized, double-blind, placebo-controlled trial (Efficacy and Safety of Levetiracetam Versus Placebo on Levodopa-induced Dyskinesias in Advanced Parkinson's Disease [LeLe-Dys]) to determine the efficacy and safety of levetiracetam in advanced PD patients with levodopa dyskinesia is ongoing.

Kinase inhibitors

Genetic investigations to unravel the molecular basis of PD suggest that the kinase-signaling pathway may play a role in programmed cell death and may be central to its pathogenesis. A recently completed, large, double-blind clinical trial (Parkinson Research Examination of CEP-1347 Trial [PRECEPT]) of a mixed-lineage kinase inhibitor (CEP1347) did not prove its efficacy in slowing the disease progression [109].

Coenzyme Q10

Mitochondrial dysfunction, cellular energy depletion and oxidative stress all play roles in the development of PD. Coenzyme Q10 (CoQ10) is a scavenger of free radicals. It is an electron acceptor bridging mitochondrial complexes I and II/III and a potent antioxidant. CoQ10 1200 mg versus placebo led to a slower decline in the UPDRS score and an average 44% lower decline in mental function, movement and the ability to perform activities of daily living. A Phase II clinical trial proved that doses of 300–600 and 1200 mg/day were safe and well tolerated in patients with early, untreated PD. The data indicated that CoQ10 may slow the progression of PD as measured by UPDRS [110,111]. A randomized, placebo-controlled Phase III trial of 1200 and 2400 mg/day CoQ10 was initiated, in which the independent function, cognition and quality of life were evaluated [110].

Creatine

Creatine is a nutritional supplement studied for the treatment of PD in view of its antioxidant property, which improves mitochondrial function. In a mouse model of PD, creatine prevented the loss of dopaminergic cells. The administration of creatine increases the brain concentrations of creatine and phosphocreatine. It interacts with the mitochondrial isoform of creatine kinase to inhibit the mitochondrial transient pore. A randomized, double-blind, Phase II trial in early PD failed to prove its efficacy [112]. A Phase III, 5-year follow-up, multicenter, double-blind, placebo-controlled study of creatine for the treatment of PD is ongoing (Neuroprotective Exploratory Trials in Parkinson's Disease, Large Study 1 [NET-PD LS1]). The main objective of the study is to determine whether creatine can slow the clinical decline in PD patients, as defined by a combination of cognitive, physical and quality-of-life measures. Efficacy, safety and tolerability of creatine will also be investigated [212].

Inosine

Inosine is a urate precursor capable of penetrating the blood–brain barrier. Urate is a natural antioxidant. It has been shown that blood and cerebrospinal fluid (CSF) urate levels are predictors of the risk of PD in healthy individuals, and predictors of the disease progression in

PD patients. In this respect, higher levels of urate in the blood and CSF of PD patients are associated with the slower progression of the disease. A retrospective analysis of patients in the DATATOP [113] and PRECEPT [114] trials revealed that patients with a higher baseline serum urate level displayed a 40% slower clinical progression. A lower rate of loss of striatal dopamine transporter was proved by DAT SPECT in these patients, an observation verified on 804 patients with early PD in the PRECEPT trial. Inosine administered orally crosses the blood–brain barrier and elevates the serum urate level. The safety and tolerability of inosine and its ability to elevate the serum and CSF urate levels are under study in early PD patients in a randomized, double-blind, placebo-controlled, dose-ranging, Phase II clinical trial (Safety of Urate Elevation in Parkinson's Disease [SURE-PD]) [213]. Further trials could be designed to evaluate the potential of inosine to slow the disease progression.

Vitamin D

It is presumed that an inadequate intake of vitamin D in the elderly may be a significant factor in the pathogenesis of PD. A vitamin D deficiency occurs in 55% of patients with PD, as demonstrated by a retrospective systematic analysis on a clinical research database. Accordingly, low vitamin D levels have been associated with poorer memory, thinking, depression and slower walking speed [115]. An ongoing, Phase IV, randomized, double-blind, active-controlled efficacy study was designed to evaluate the effects of high-dose vitamin D supplementation (54,200 IU/week) on the clinical symptoms of PD (Clinical Effects of Vitamin D Repletion in Patients With Parkinson's Disease [VIDIP PILOT]).

Folic acid

Folic acid is an essential vitamin, but some concerns have been raised regarding the administration of folate due to the association with a greater risk of cardiovascular disease and some forms of cancer [116]. Hyperhomocysteinemia, related to folate deficiency, is characteristic of PD. In some patients, folate cannot properly enter the brain as a consequence of antibody production, which results in worsening of some PD symptoms and in cognitive function [117]. A study is under way to assess the impact of folate on the progression of PD [116].

Nicotine

It has been proven in experimental studies that nicotine exerts a protective effect against neurotoxic insults [118]. Along with hydroquinone, it inhibits α -synuclein aggregation and affords protection against nigrostriatal damage [119]. Nicotine can attenuate levodopa-induced dyskinesias in animal models [120]. It has been demonstrated in epidemiologic studies that smoking can delay the onset of

PD symptoms [121]. In clinical studies, nicotine exhibited variable and moderate symptomatic benefit as reported from an open-label pilot study [122], but this effect was not confirmed by larger trials in 1999 and 2001 [123,124]. Nicotine and nicotinic-receptor ligands may be beneficial to patients with PD by slowing the disease progression, improving the motor symptoms and reducing dyskinesias [125]. A Phase II, controlled, single-blinded, randomized study (Efficacy of Transdermal Nicotine on Motor Symptoms in Advanced Parkinson's Disease [NICOPARK2]) in two parallel groups (one receiving transdermal nicotine therapy and the other without additional therapy) to assess the efficacy of transdermal nicotine administration is ongoing. The primary objective is to verify the correlation between UPDRS motor score and the administered nicotine dose. This study will also allow the evaluation of nicotine neuroprotective effect [214].

Isradipine

Elevated levels of intracellular Ca^{2+} play a role in neurodegeneration by causing oxidative stress, mitochondrial dysfunction, energy deficit and excitotoxicity. Isradipine blocks L-type Ca^{2+} channels. It has been revealed to have a neuroprotective effect in preclinical models of parkinsonism [126]. A multicenter, randomized, double-blind, placebo-controlled study was initiated to assess the safety and tolerability of isradipine CR (Dynacirc® CR) in individuals with early PD. Pilot data will be obtained with regard to the potential ability of isradipine to slow disease progression [215]. Isradipine may also be a treatment option for the prevention of levodopa-induced dyskinesia in PD; its safety and tolerability are currently being assessed in a Phase II clinical trial initiated in 2008.

Glutamate antagonists

Interactions between dopamine and glutamate in the striatal neurons play a role in the pathogenesis of PD, and glutamate antagonists may improve PD symptoms and exert a neuroprotective effect. Several drugs used for PD treatment, such as amantadine, some anticholinergic drugs and various recently studied agents, also exhibit antiglutamatergic activity, which contributes to their efficacy.

NMDA antagonists

The antiparkinsonian effect of NMDA antagonists has been reported in animal models, but could not be proven in clinical trials. Dextrometorphan and the α -methyl derivative of amantadine, rimantadine, are NMDA-receptor antagonists that have provided a slight motor benefit in PD [127,128]. An open study involving 11 parkinsonian patients treated with dextrometorphan suggested that high doses can improve tremor and rigidity [129].

Another study could not prove these effects. The lower doses were ineffective, whilst the higher doses induced intolerable side effects [130]. The dextrometorphan metabolite 3-hydroxymorphinan is potent in neuroprotection against the neurotoxicity induced by lipopolysaccharides and MPTP, as shown in *in vitro* and *in vivo* studies [131–133].

Neu 120 is a potent and selective noncompetitive NMDA-receptor modulator developed as an adjunct to levodopa in patients with motor fluctuations and in those who do not tolerate optimal levodopa doses, in order to improve the motor symptoms and to reduce levodopa-induced dyskinesias. It has a complex mechanism of action; *in vitro*, it inhibits MAO-B and glycogen synthase kinase 3 β . It does not interact with other receptors, transporters or enzymes. Neu 120 is currently undergoing evaluation in a randomized, double-blind, placebo-controlled Phase IIa trial [216].

Amantadine is an antiviral agent with NMDA-antagonist and dopamine-agonist properties that can be used in all stages of PD. Amantadine ameliorates motor symptoms and improves the motor fluctuations and levodopa-induced dyskinesias. A large meta-analysis compared the effects of amantadine and other NMDA-receptor antagonists (e.g., dextrometorphan) on levodopa-induced dyskinesias with placebo and concluded that the NMDA-receptor antagonists significantly reduce the severity of dyskinesias, but no significant effect on the motor function was detected [134]. A retrospective report relating to 19 PD patients treated with amantadine demonstrated sustained effects on levodopa-induced dyskinesia and motor impairment [135].

α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor antagonists

In this class of glutamate antagonists, talampanel and perampanel were recently studied for their antiparkinsonian effects. Perampanel was tested in clinical trials as an adjunct to levodopa in PD patients, but did not improve the 'off' time or dyskinesia as compared with the placebo [93]. Riluzole, which blocks activated Na^+ channels and inhibits glutamate release, failed in clinical trials, although there is some evidence of its antidyskinetic effect [136]. The metabotropic glutamate receptor antagonist AFQ056 is under active development [137].

Kynurenines

The kynurenine pathway is the main pathway of tryptophan metabolism [138]; it is responsible for nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate production. The central compound of the nonprotein tryptophan metabolism is L-kynurenine (L-KYN). It can be metabolized in the brain in two distinct ways, to yield kynurenic acid (KYNA) or

3-hydroxy kynurenine (3-OH-L-KYN) and quinolinic acid (QUIN) [139]. These metabolites are referred to as neuroactive kynurenines due to their properties observed in experimental studies.

L-kynurenine is converted to KYNA through an irreversible transamination catalyzed by three subtypes of kynurenine aminotransferases (KATs) [140,141] and mitochondrial aspartate aminotransferase. The main KYNA-producing enzyme in rat and human brains is KAT-II [142]. The neuronal expression of KAT-I seemingly exerts effects on developmental processes, such as programmed cell death [143]. The expression of KAT-I in the SN decreases after MPTP administration [144]. In the rat cerebral cortex, MPP⁺ diminished KAT-II activity, resulting in a depletion of KYNA [145].

Kynurenic acid is an antagonist of excitatory amino acid receptors such as the NMDA and kainate/ α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors [146,147]. In this respect, it can competitively bind the strychnine-insensitive glycine-binding allosteric site of the NMDA receptors and thereby inhibit the overexcitation of these receptors [148,149]. It also exerts antagonist effects on the AMPA and kainite receptors [150]. In micromolar concentrations, KYNA has a neuroinhibitory effect, whereas in nanomolar concentrations it exerts facilitatory action [151]. KYNA noncompetitively blocks the presynaptic α 7-nicotinic acetylcholine receptors [152] and can increase the expression of the non- α 7-nicotinic acetylcholine receptors. The activation of these receptors is involved in the regulation of glutamate release [153].

Quinolinic acid and 3-OH-L-KYN are neurotoxic compounds. QUIN is formed by the action of 3-hydroxyanthranilate 3,4-dioxygenase, and 3-OH-L-KYN by the action of kynurenine 3-hydroxylase [154,155]. QUIN, localized to glia and immune cells, is a weak, but specific competitive agonist of the NMDA receptors containing the NR2A and NR2B subunits [156]. It can activate these receptors directly [157], leading to the release and uptake inhibition of endogenous glutamate [158,159], and induce lipid peroxidation [160] and the production of reactive oxygen species [161]. QUIN has excitotoxic properties, and hence can activate excitatory amino acid receptors and produce axon-sparing neuronal lesions. It causes damage to the striato-pallidal encephalinergic neurons. It has been demonstrated that a QUIN-induced axon-sparing injury to the developing striatum results in a decrease in dopaminergic neurons in the adult SNc [146]. 3-OH-L-KYN exerts its action by means of free radical production and not through glutamate receptors [162,163]. Some of its neurotoxic actions are due to its metabolite, 3-hydroxyanthranilic acid (3-OH-ANA), which undergoes auto-oxidation and leads to O₂⁻ production [164]. In PD, as a consequence of the defect in mitochondrial complex I activity, the dopaminergic neurons are more vulnerable to

excitotoxic injury [165–167]. Endogenous excitotoxins have also been implicated in the degeneration of dopaminergic neurons in the SNc. The red blood cells and plasma of PD patients indicate an altered KYNA metabolism [168]. Elevation of the QUIN concentration and decrease of the KYNA level cause overexcitation of the glutamate receptors, with consecutive cell damage. Changes in the concentrations of KYNA and QUIN may play a role in PD. The kynurenine pathway can be influenced in several ways. Analogs of KYNA cross the blood–brain barrier and are antagonists of the glutamate receptors. An endogenous KYNA level increase can protect the nigrostriatal dopaminergic neurons against QUIN-induced excitotoxic damage, as revealed by experimental studies. 4-chlorokynurenine is the prodrug of 7-chlorokynurenine. It penetrates the blood–brain barrier, is a selective NMDA antagonist at the glycine site and prevents QUIN-induced neurotoxicity. A clinical study of the neuroprotective properties of this compound was designed. The KYNA analog gavestinel (GV150526A) did not prove neuroprotective in a randomized double-blind, placebo-controlled, clinical trial. Neuroprotection could be achieved through the inhibition of enzymes involved in the synthesis of neurotoxic compounds of the kynurenin pathway. The synthesis of QUIN and 3-OH-L-KYN can be blocked by kynurenine-3-hydroxylase inhibitors (nicotinylalanine, meta-nitrobenzoylalanine, PNU 156561 and Ro-61–8048) and kynureninase inhibitors (*S*-aryl-L-cysteine-*S*, *S*-dioxide and ortho-methoxybenzoylalanine). Owing to their ability to bind to excitotoxin receptors, neuroactive kynurenines may have an antidyskinetic effect, as was demonstrated in animal models, where Ro 61–8048 co-administered with levodopa in cynomolgus monkeys led to a moderate, but significant reduction in the severity of dyskinesias, while maintaining the motor benefit [169]. A sustained KYNA level elevation induced by the inhibition of kynurenine 3-hydroxylase resulted in a significant reduction in the levodopa-induced dyskinesias, but did not affect the benefits of chronic levodopa therapy [170]. Experimental studies also showed that kynurenine 3-mono-oxygenase inhibitors enhance brain KYNA synthesis and selectively reduce the extracellular glutamate concentration in the basal ganglia [171].

Neuropeptides

Dopaminergic cell loss in the nigrostriatal system leads to a decrease of dopamine content in the SNc and disrupts the balance between neurotransmitters and neuropeptides in the basal ganglia circuitry. Alterations in the transcript and translation of neuropeptides have been described [172]. In parkinsonism, the regulation of opioid peptide synthesis in the basal ganglia is disturbed. It has been shown that the striatal RNA message

for preproenkephalin-A, the precursor of enkephalin, is increased, whereas for preproenkephalin-B, the precursor for dynorphin, it is decreased [173–175]. A study on unilaterally 6-hydroxydopamine-lesioned mice with and without subchronic L-DOPA administration showed that striatal peptides from different precursors, such as secretogranines, somatostatin, preproenkephalin-B and cholecystokinin, were significantly altered [176]. Some therapeutic approaches rely on alterations of neurotransmitters or neuromodulators induced by nigrostriatal denervation [177].

Cannabinoid receptors

CBI cannabinoid receptors and mRNA in the basal ganglia are upregulated in PD patients and in animal models of PD [178] and the increased cannabinoid transmission contributes to PD. The selective CBI antagonist rimonabant reduces PD symptoms in animal models. A

study on a PD rat model confirmed that it can be therapeutic in itself and can enhance the therapeutic effect of a moderate, but not a high dose of levodopa [179]. The endocannabinoid system is a promising target for the treatment of PD and levodopa-associated motor complications. The inhibition of the fatty acid amide hydrolase, the degrading enzyme of anandamide and the degradation of 2-arachidonoyl-glycerol, could be possible therapeutic approaches [180].

Future perspective

The most effective symptomatic treatment for PD remains levodopa-substitution therapy, but in the long term, dyskinesias and motor fluctuations develop due to noncontinuous dopaminergic-receptor stimulation and the hypersensitivity of the dopamine receptors. Dyskinesias are thought to be avoidable by continuous

Executive summary

- Parkinson's disease (PD) is the second most common chronic neurodegenerative disorder after Alzheimer's disease, affecting more than 1% of individuals over 60 years of age.
- Besides the dopaminergic system, the complex interconnected neuronal circuitry regulated by neurotransmitters beyond dopamine, such as adrenaline, GABA, glutamate, adenosine and serotonin, plays a role in the development of the motor and nonmotor symptoms of PD. Therefore, targeting only the dopaminergic system cannot treat all of the symptoms of the disease.
- The 'gold standard' of symptomatic treatment in PD is still levodopa therapy. However, in time motor fluctuations and dyskinesias develop, due to the noncontinuous receptor stimulation and consecutive receptor hypersensitivity. Monoamine oxidase B (MAO-B) inhibitors and dopamine agonists can be used in all stages of the disease. Besides improving the motor symptoms, there is some, controversial, evidence for the disease-modifying effects of MAO-B inhibitors.
- Among nondopaminergic agents, adenosine A2a antagonists, glutamate antagonists, antiepileptic agents such as zonisamide, safinamide or levetiracetam, nicotine, dietary supplements such as creatine or inosine and 5-HT_{1A}-receptor agonists have been tested as antiparkinsonian medication in clinical trials with regard to their safety, tolerability and effectiveness on motor symptoms, dyskinesias and nonmotor symptoms, respectively.
- Among the adenosine A2a antagonists, istradefylline led to symptomatic benefit in a randomized, placebo-controlled study in patients on levodopa with motor fluctuations. Other A2a antagonists, such as SYN115 and preladenant are currently under development.
- Piclozotan and pardoprunox are selective 5-HT_{1A} agonists that appear to be both safe and effective in improving the motor symptoms, and the former in improving dyskinesias too.
- α 2-adrenergic receptor antagonists, in addition to improving motor symptoms and reducing dyskinesias, may improve nonmotor symptoms. Fipamezol has been demonstrated to attenuate dyskinesias and improve cognitive function in a clinical trial on PD patients.
- A challenging aspect is the treatment of nonmotor symptoms. Medication used for the treatment of neuropsychiatric features such as depression, cognitive impairment, dementia, hallucinations and attention deficit, as well as for gait disturbance, is briefly presented.
- Safinamide, zonisamide and levetiracetam are antiepileptic drugs that have promising results in the treatment of motor symptoms in patients with early PD and in improving dyskinesia in more advanced disease stages. Several trials with these agents are still ongoing.
- An interesting approach is the use of dietary supplements such as creatine, coenzyme Q10 or the urate precursor inosine, based on their antioxidant properties. It has been demonstrated that blood and cerebrospinal fluid urate levels are predictors of the risk of PD in healthy individuals, and predictors of the disease progression in PD patients.
- Nicotine or nicotinic-receptor ligands may be beneficial for patients with PD by slowing the disease progression, improving the motor symptoms and reducing the dyskinesias.
- Among glutamate antagonists, kynurenes are presented more extensively. The central compound of the nonprotein tryptophan metabolism is L-kynurenine, which can be converted to kynurenic acid, 3-hydroxykynurenine and quinolinic acid, compounds referred to as neuroactive kynurenes. Increasing the neuroprotective effect of kynurenic acid and decreasing the levels of neurotoxic 3-hydroxykynurenine and quinolinic acid can be therapeutic considerations for PD.
- The endocannabinoid system is a promising target for the treatment of PD and levodopa-associated motor complications.

stimulation of the dopaminergic receptors. In this respect, further development is mandatory in an effort to find dopaminergic medication that meets this goal without significant side effects.

The recognition and treatment of the nonmotor symptoms without worsening the motor symptoms are essential in order to improve the quality of life of PD patients. In this respect, the investigation of newly developed and existing therapeutic agents for these symptoms is of importance. Although typically regarded as nonresponsive to dopaminergic medication, some of the nonmotor symptoms might respond to targeted dopaminergic therapy.

A complex, interconnected neuronal circuitry is involved in the pathomechanism of PD. Besides dopamine, the mediators involved are glutamate, serotonin, adrenaline, adenosine and GABA. Influencing only the dopaminergic system cannot relieve all motor and nonmotor symptoms of the disease.

New therapeutic approaches include the use of nondopaminergic treatment, of compounds targeting mechanisms involved in the pathogenesis of the disease, such as oxidative stress, mitochondrial dysfunction, excitotoxicity, protein aggregation or receptors of different transmitters expressed on striatal neurons. Interesting new approaches are the use of agents influencing the endocannabinoid system or different neuropeptides involved in PD pathomechanism. Further studies are needed to allow the promising preclinical evidence to progress to a real clinical application.

The ultimate goal of PD treatment is a disease-modifying approach aimed at preventing cell loss from the involved areas of the basal ganglia. The most important future therapeutic approach will probably comprise a search for neuroprotective agents in order to prevent dopaminergic and nondopamine cell loss. Neuroactive kynurenes could be further studied in this respect. Increasing the neuroprotective effect of KYNA and decreasing the levels of neurotoxic 3-hydroxykynurenine and QUIN can be therapeutic considerations for PD.

A very important issue is the understanding of and continuous search for markers of the preclinical stages of PD. This could offer the possibility of preventive therapies targeting the population at risk before the clinical onset of the disease. It might be possible that, in these very early stages, the compounds so far found to be ineffective in the more advanced disease stages could prove beneficial.

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