Role of dopamine agonists in Parkinson's disease: an update

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At present, dopamine agonists play an important role in antiparkinsonian therapy since they were proved effective in the management of both advanced- and early-stage Parkinson's disease. In the latter, they are often regarded as first-choice medication to delay the introduction of levodopa therapy. Despite sharing the capacity to directly stimulate dopamine receptors, dopamine agonists show different pharmacological properties as they act on different subsets of dopamine receptors. This, in theory, provides the advantage of obtaining a different antiparkinsonian activity or safety profile with each agent. However, there is very little evidence that any of the marketed dopamine agonists should be consistently preferred in the management of patients with Parkinson's disease. Pergolide and cabergoline are now considered a second-line choice after the proven association with valvular fibrosis. Transdermal administration (rotigotine) and subcutaneous infusion (apomorphine) of dopamine receptor agonists are now available alternatives to oral administration and provide continuous dopaminergic stimulation. Continuous subcutaneous apomorphine infusion during waking hours leads to a large reduction in daily 'off' time, dyskinesias and levodopa daily dose. Almost all currently used dopamine agonists are able to provide neuroprotective effects towards dopaminergic neurons during *in vitro* and *in vivo* experiments. This neuroprotection may be the result of different mechanisms including antioxidation, scavenging of free radicals, suppression of lipid peroxidation and inhibition of apoptosis. However, the disease-modifying effect of these agents in Parkinson's disease remains to be ascertained.

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Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder that clinically manifests as a combination of rest tremor, bradykinesia, rigidity and postural instability. The neurodegenerative process in PD consists of progressive loss of the dopaminergic neurons in the substantia nigra pars compacta. Serotonergic, noradrenergic and cholinergic neurons are also involved, although to a lesser extent. Loss of cells from the substantia nigra in patients with PD results in profound dopamine (DA) depletion in the striatum, particularly in the dorsolateral region of the putamen, with a consequent disruption of the complex basal ganglia circuitry including thalamocortical and brainstem motor systems. The result of such a disruption is an abnormal increment in the inhibitory output activity of basal ganglia toward cortical areas that produces slowness and paucity of movements [1].

Current symptomatic treatments for PD largely aim to improve symptoms of the disease by correcting the neurotransmitter imbalance within the basal ganglia circuitry. DA-replacement therapy has been and remains the mainstay approach for controlling PD symptoms and the DA precursor, levodopa (LD), continues to be the most potent replacement agent. LD is rapidly transformed to DA in nigrostriatal neurons by aromatic decarboxylation and this increases the availability of DA in the striatum [2]. Nonetheless, other dopaminergic drugs, such as DA agonists, have proved to be effective in the management of both advanced- and early-stage PD.

Pharmacological properties of DA agonists

DA agonists are a class of drugs that correct the neurotransmitter imbalance within the basal ganglia circuitry by directly activating

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DA receptors. This capacity is most likely related to the DA-like moiety within their molecular structure [3]. Currently available DA agonists can be classified into:

- Ergot derivates (bromocriptine, pergolide, lisuride, α-dihydroergocriptyne and cabergoline), which are generally referred to as first-generation agonists
- Nonergolines (apomorphine, piribedil, ropinirole, pramipexole and rotigotine).

The latter, except for apomorphine, have a more recent history in the treatment of PD and were developed in the hope that they might provide similar therapeutic effect as the ergoline agents with fewer side effects.

There are undoubtedly pharmacological differences between the various DA agonists as they act on different subsets of DA receptors (TABLE 1). Bromocriptine, lisuride and pergolide bind with high affinity to D2 family receptors but also show affinity of varying degree for the D1 receptors, adrenergic and 5-hydroxytryptamine (5-HT) receptors. Ropinirole and pramipexole are more specific agonists as they bind to D2 and D3 receptors only with high affinity. However, pramipexole, in contrast to ropinirole, is more potent at D3 than at D2 receptors [4]. Rotigotine, the most recently marketed DA agonist, preferentially binds to all DA receptors with a clear preference for the D3 receptors. The affinities to the other DA receptors are approximately eight- to 20-fold less for the D2 and D4 receptors, and approximately 120-fold less for the D1 receptor. The D1 receptor also interacts with α_{2B}, α_{2C}, 5-HT_{1A}, 5-HT_7 and σ-receptors [5].

These different pharmacological properties provide, in theory, the advantage of obtaining a different antiparkinsonian activity or safety profile with each agent. There is, however, very little evidence that any of the marketed DA agonists should be consistently preferred in the management of PD patients. The topic has been covered in detail elsewhere [6].

Table 1. Pharmacological properties of dopamine agonists on different subsets of dopamine receptors.

Drug	Dopamine receptors			
	D1	*D2*	*D3*	*D4*
Bromocriptine	0/±	++	+/++	+
Lisuride	-/±	+++	+++	+++
Pergolide	+	+++	+++	+++
Ropinirole	0	+++	++	0
Pramipexole	0	+++	+++	++
Cabergoline	+	+++	++	++
Rotigotine	++	++	+++	++

Ki(nM)= 0 > 1000; + 100–1000; ++ 10–100; +++ 0–10; ± partial agonist; - antagonist.
Modified from [47].

Briefly, ropinirole, pramipexole and cabergoline showed similar efficacy to bromocriptine in several randomized, double-blind studies. Pergolide showed equivalent or superior efficacy to bromocriptine in improving clinical measures, particularly in activities of daily living and motor examination scores. More recently, several direct comparisons between ergot and nonergot DA agonists have shown that the efficacies of the investigated agents are largely similar [7–9].

Symptomatic effects of DA agonists in Parkinson's disease

In clinical practice, DA agonists have been shown to be efficacious in both early and advanced PD. In advanced PD, these drugs improve both motor disability and motor fluctuations when added to LD reducing 'off' time duration by approximately 20% [10–17]. Several open-label studies have shown that very high doses of DA agonists might decrease LD-related motor complications, particularly dyskinesia, owing to the large reduction of LD daily dose [18–20].

In patients with early PD, controlled studies have demonstrated that cabergoline [21], pergolide [22], bromocriptine [23], pramipexole [24] and ropinirole [25] are superior to placebo or have comparable effects to LD, with less frequent and severe dyskinesia [26–30]. However, the number of patients remaining on agonist monotherapy decreases to less than 50% after 2–3 years of treatment, and owing to the loss of efficacy of DA agonists over time with progressing disease, after a few years of treatment the majority of patients will be co-administered LD.

These agents have a longer half-life than both standard- and controlled-release preparations of LD, thereby inducing a sustained rather than pulsatile stimulation of striatal DA receptors, and this may help explain the lower incidence of motor complications, particularly dyskinesias, in patients taking DA agonists compared with those on LD [23,26–29,31]. However, a recent study has shown that an end of dose deterioration – 'wearing-off' phenomenon – was also present in 30% of PD patients treated with ropinirole (n = 27) or pramipexole (n = 25) monotherapy for less than 2 years [32].

Treatment strategies

Switching one agonist to another

Switching between DA agonists is a current practice in case of waning efficacy, or intolerable side effects such as excessive daytime sleepiness (EDS), sleep attacks (SA), dizziness or hypotension. Additionally, the recent mounting evidence of fibrotic reactions (see side effect section) to ergot DA agonists is increasing the practice of substituting ergot with nonergot DA agonists. Many guidelines for PD treatment propose equivalent charts or conversion factors between dosages of DA agonists with 1:6 for pergolide to ropinirole, 10:6 for bromocriptine to ropinirole, 10:1 for bromocriptine to pergolide and 10:1–1.5 for bromocriptine to pramipexole [33]. TABLE 2 summarizes approximate dose equivalents for DA agonists. Several studies demonstrate that switching from one agonist to another can be carried out rapidly, usually overnight, without any major complications [7,9,34].

Table 2. Approximate dose equivalents for dopamine agonist.

Bromocriptine	Cabergoline	Pergolide	Pramipexole	Ropinirole
10 mg t.i.d	4 mg/day	1 mg t.i.d	1 mg t.i.d	6 mg t.i.d

t.i.d.: Three-times daily.

Preliminary data for switching from an oral DA agonist to transdermal rotigotine are also available. The results from a Phase IIIb, open-label trial were presented at the First World Parkinson Disease Congress in Washington in 2006. This study has shown that an overnight switch from ropinirole, pramipexole and cabergoline to rotigotine can be achieved safely and is well tolerated. The maximum doses at entry were ropinirole 9 mg, pramipexole 2 mg salt and cabergoline 3 mg, which corresponded to rotigotine 8 mg/day (40 cm^2, 18 mg total drug content). A total of 80% of the patients required no dose adjustments after switching to rotigotine, 9.5% had one adjustment and 10.3% withdrew early (4.4% owing to side effects) [35].

Dual DA agonist treatment

Combining two different DA agonists has been suggested as an alternative strategy for prolonging DA agonist monotherapy in early PD and avoiding LD increases in more advanced patients. Since DA agonists have different receptor-binding properties and different pharmacokinetic characteristics, it has been postulated that two DA agonists induce a more complete activation of DA receptors than a single agonist and consequently a better clinical effect. Unfortunately, no controlled studies addressing this issue are available. In a recent open study, 37 PD patients with and 12 without motor fluctuations received cabergoline as an adjunct to their therapy with pramipexole or ropinirole at the maximal permitted dose. In the fluctuating group, cabergoline decreased the time spent in 'off' by 65.6%, and reduced the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores by 19.24% during the 'off' condition and by 7.1% during the 'on' condition. Nocturnal akinesia also improved. In the 12 patients without motor fluctuation, UPDRS scores improved by 34.4% when cabergoline was added to the current treatment [36].

Transdermal administration of DA agonists

Rotigotine, a lipid-soluble nonergoline D3/D2/D1 receptor agonist, is the first DA agonist developed as a transdermal formulation and is currently licensed as monotherapy for early-stage PD. The silicone-based transdermal patch, which is applied to the skin once daily, delivers rotigotine at a constant rate over 24 h producing a continuous dopaminergic stimulation of striatal DA receptors. Three Phase III, multicenter studies of rotigotine in untreated patients with early PD have been performed [37–39]. In the first study, conducted by the Parkinson Study Group, four different doses of rotigotine patch (4.5, 9.0, 13.5 or 18.0 mg corresponding to 2, 4, 6 and 8 mg/24 h, respectively) or placebo were administered to 242 early PD patients for 11 weeks in a parallel-group paradigm. In the second randomized controlled trial [38], 277 patients were given placebo or increasing doses of rotigotine (from 2 mg to a maximum of 6 mg/24 h), and then maintained for 6 months. In both studies, the UPDRS (part II and III) score significantly improved with the higher doses (6 and 8 mg/24 h) relative to placebo. Interestingly, in the second study, the proportion of responders at the end of treatment (patients showing a decrease in UPDRS part II and III score from baseline by 20% or greater) was significantly higher in the rotigotine group than in the placebo group (48 vs 19%; $p < 0.0001$). A 3-year, open-label extension of this trial is currently ongoing to monitor the longevity of rotigotine treatment effects as well as clinical safety. Similar results for responders to the treatment were obtained in the third 6-month controlled study [39] where maintenance dose of rotigotine was 6 mg/day. In these studies, application site reactions were common in rotigotine-treated patients (approximately 50% of patients receiving the higher doses), but required discontinuation of treatment only in 5% of patients [37–39].

A recently published study [40] demonstrated that rotigotine 8 or 12 mg/day compared with placebo was able to reduce the duration of 'off' periods by 2.7 and 2.1 h, respectively, in a large group of PD patients not optimally controlled with LD and with off periods lasting more than 2.5 h.

Another study investigated the efficacy and safety of rotigotine as an adjunctive treatment to LD in patients with advanced inadequately controlled PD compared with placebo or pramipexole [41]. Patients received either placebo (n = 101), rotigotine up to maximum dose of 16 mg/day (n = 204) or pramipexole up to maximum dose of 4.5 mg/day (n = 201) for 16 weeks. Rotigotine showed clinically relevant and statistically significant reduction in 'off' time compared with placebo and a similar effect compared with pramipexole.

Subcutaneous administration of DA agonists

Apomorphine is a DA agonist with a receptor affinity similar to DA, and is prescribed for subcutaneous use as bolus injections or continuous infusion. Intermittent subcutaneous apomorphine therapy is generally used as rescue therapy for severe intractable 'off' periods in patients with fluctuating PD owing to its rapid onset, usually within 10 min, and robust response with a rapid improvement of 'off' periods lasting 90–120 min [42].

Disease progression, however, may necessitate an increase in the number of injections to 10 or more per day. In these cases, apomorphine can be administered by continuous subcutaneous infusion using an automated syringe driver. Several studies, including a recent prospective one, indicate that apomorphine continuous subcutaneous infusion during waking hours leads to a large reduction in daily 'off' time, dyskinesias and LD daily dose [42–44]. The antidyskinetic effect of apomorphine is

comparable to that observed with deep brain stimulation of the subthalamic nucleus, but despite increasing evidence of its efficacy and safety, apomorphine infusion is still underused.

Lisuride is also administered subcutaneously. Its bioavailability, which is between 10 and 20% when given orally owing to a large first-pass metabolism, becomes near to 100% when administered subcutaneously or transdermally. In a recent study, subcutaneous administration of lisuride over a long period of time (4 years) was compared with conventional oral LD treatment in 40 patients [45]. Over 4 years, mean 'off' time in the lisuride treatment group decreased by 2.9 h, whereas it increased by 0.9 h in the LD group ($p < 0.001$). This effect, evidenced since the beginning of the treatment, was maintained over time, indicating that tolerance is not likely to develop. Moreover, there was a 40.9% reduction in dyskinesias in the lisuride group compared with a 59.1% increase in the LD group ($p < 0.001$), as indicated by mean Abnormal Involuntary Movement Scale (AIMS) scores.

Controlled-release formulation of DA agonists

The ongoing development of slow-release formulations for DA agonists opens new ways of continuous DA receptor stimulation.

The results of a large, randomized controlled study of the efficacy and safety of ropinirole 24 h prolonged-release formulation (Efficacy and Safety Evaluation in PD Adjunct) have recently been published [46]. A total of 393 PD patients poorly controlled by LD alone were randomly assigned to ropinirole 24 h (202 patients) or placebo (191 patients) as an adjunct to LD for 24 weeks. Ropinirole was titrated to a starting dose of 2 mg/day and increased in steps of 2 mg/day as necessary, until an optimal therapeutic dose was reached. At week 24, the mean ropinirole dose was 18.6 mg/day with a mean reduction in daily LD of 278 mg. The mean reduction in daily 'off' time (primary study outcome) was 2.1 h in the ropinirole 24 h group, and 0.3 h in the placebo group. The mean difference was 1.7 h ($p < 0.0001$). The authors also found a significant increase in patients' percentage of 'on' time as well as 'on' time without troublesome dyskinesias. Other secondary study outcomes, including quality of life, sleep, depression, emotional wellbeing, stigma and communication, were also significantly improved with ropinirole 24 h compared with placebo. Dyskinesias occurred in 13% of patients receiving ropinirole 24 h compared with 3% of those on placebo. Other side effects occurring in a higher percentage of patients receiving ropinirole 24 h were nausea, dizziness, somnolence, hallucination and orthostatic hypotension. Ropinirole 24 h prolonged release has not yet been approved by the US FDA.

Neuroprotective effects of DA agonists

In addition to their symptomatic effects, DA agonists may exert a neuroprotective action in PD. The topic has been covered in detail in a previous issue of this journal [47] and only a brief summary is reported in this review.

The LD sparing effect was the initial basis for considering DA agonists as neuroprotective agents in PD. These drugs, in contrast to LD, do not undergo oxidative metabolism and do not generate toxic free radicals or induce oxidative stress. Moreover, DA agonists may also decrease free radical production and the risk of oxidative damage by inhibiting DA synthesis, release and metabolism via activation of presynaptic receptors [48]. Many agonists share a hydroxylated benzyl ring structure and so may function as free radical scavengers. Antioxidant activity has been demonstrated for several DA agonists in different *in vitro* systems and *in vivo* models, including the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned macaque model and 6-hydroxydopamine toxicity models (TABLE 3). In several experimental studies, DA agonists have demonstrated anti-apoptotic activity by interfering with several steps of apoptotic cascades through mechanisms independent of their antioxidant actions [49–51]. The issue of whether or not this anti-apoptotic effect is dependent on the activation of DA receptors remains uncertain. Another proposed mechanism to explain neuroprotection induced by DA agonist is the inhibition of excitotoxicity mediated by overactivity of the subthalamic nucleus. Excess glutamate release might, in fact, induce excitotoxic damages in targets of the subthalamic nucleus [52]. Finally, DA agonists may promote neuronal survival by stimulating the synthesis of neurotrophic factors, which have been shown to have neuroprotective/neurorestorative properties in dopaminergic nigral neurons [53], and by inducing proliferation of neural precursor cells in the adult brain.

Several recent clinical trials have been performed to directly compare the effects of DA agonists (ropinirole, pramipexole, pergolide and cabergoline) and LD on the natural course of PD in *de novo* patients [26–29]. The result of the drugs on disease progression was evaluated using clinical and/or imaging outcome measures. The clinical end point was generally based on the incidence of dyskinesias or the time to development of any motor complication, whereas the imaging outcome was the rate of change in imaging markers of dopaminergic function between baseline and end-of-study evaluation.

As previously mentioned, the consistent results of these studies are that DA agonists produce less dyskinesias compared with LD over 2–5 years of therapy. However, there is currently no indication that this effect is related to neuroprotective activity of these agents. Functional imaging studies in these trials have provided a valuable adjunct to clinical data, but they eventually failed to demonstrate a clear-cut neuroprotective effect.

The neuroprotective effect of rotigotine has not yet been investigated in PD patients. However, a recent paper has evaluated the protective property of this agent in a progressive MPTP-lesioned macaque model. After 38 days of treatment followed by 2 weeks of washout, rotigotine-treated animals were significantly less parkinsonian than the nontreated ones. A significant preservation of dopaminergic terminals, as detected by *ex vivo* ^{125}I-nortropane DA transporter (DAT) labeling, was also seen in the rotigotine group compared with the nontreated group. However, the magnitude of preservation was modest and could not be detected *in vivo* using the single photon emission computed tomography (SPECT) DAT tracer ^{99m}Tc-TRODAT-1 [54].

Table 3. Antioxidant effects of dopamine agonists.

Dopamine agonists	(OH)	(O_2^-)	(NO)	SOD activity	Catalase activity	GSH content	Lipid peroxidation
Bromocriptine	↓	↓	↓	ND	ND	ND	↓
Pergolide	↓	↓	↓	↑	ND	ND	↓
Pramipexole	↓	↓	↓	ND	ND	ND	ND
Ropinirole	↓	NE	↓	↑	↑	↑	↓
Cabergoline	↓	NE	↓	ND	ND	↑	↓

GSH: Glutathione; ND: No data; NE: No effect; NO: Nitric oxide radicals; OH: Hydroxyl radicals; O_2^- : Superoxide radicals; SOD: Superoxide dismutase.
Reproduced with permission from [47].

Side effects & limitations of DA agonists: an update

Nausea, vomiting, postural hypotension and dizziness, which are primarily due to stimulation of DA receptors at a peripheral level outside the BBB, are the most common side effects of DA agonists. These symptoms tend to occur with the initiation of treatment and often subside as tolerance develops over time. In order to minimize side effects, DA agonists are commonly initiated at subtherapeutic doses and titrated gradually to achieve the required clinical response. Starter packs to assist with dose titration are now available for several marketed DA agonists (e.g., pergolide, ropinirole and rotigotine). Some clinicians, however, prefer a more rapid titration to therapeutic doses. In these cases, cotreatment with the peripheral D2 receptor antagonist domperidone 20 mg three-times weekly is commonly employed to reduce unwanted side effects and increase tolerability. Domperidone, however, does not seem to be effective in reducing postural hypotension.

Peripheral edema is another common peripheral side effect associated with DA agonist treatment. Edema is usually limited to ankles but in more severe cases involves calves and knees. It has been reported with all of the DA agonists and seems to be dose related but its mechanism is unknown.

Ergot-derived DA agonists have been associated with pleuropulmonary fibrosis and retroperitoneal fibrosis; the higher incidence of fibrotic reactions during either bromocriptine or pergolide chronic therapy is biased by their more extended availability from the point of view of number of patients exposed and time after the commercial launch [55]. However, for bromocriptine a prevalence of fibrotic reactions of 2–5% over a 5-year period has been reported [56], suggesting that before starting treatment with these agonists, it is appropriate to obtain a chest x-ray and blood tests including the erythrocyte sedimentation rate, C-reactive protein and serum creatinine. During treatment, patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure and abdominal pain, and annual screening with chest x-rays and blood tests is warranted.

Over the recent years, ergot-derived DA agonists, particularly pergolide and cabergoline, have also been associated with an increased risk of valvular heart disease [57–61]. Both restrictive and regurgitative valvular heart disease has been reported in PD patients on pergolide, but also on bromocriptine and cabergoline. Histological findings appear to resemble those of valvulopathies associated to the carcinoid syndrome and the use of antimigraine ergot alkaloid agents or fenfluramine [62–64]. The mechanism of fibrotic reaction by ergot-derived DA agonists has not yet been completely clarified yet. Suggested mechanisms include immune-mediated reaction and/or modulation at peripheral serotonin subtype receptors, mainly the receptor subtype 5-HT_{2B}, which is expressed in heart valves and is known to mediate mitogenesis [65,66]. Interestingly, the ergolinic lisuride, which acts as a pure antagonist to the 5-HT_{2B} receptor [67], has never been reported to cause cardiac valvular fibrosis. Similarly, ropinirole and pramipexole, which have low affinity to the human 5-HT_{2B} receptor, seem to have a lower risk of inducing cardiac valve disease [59,60].

In summary, the number of cases reported so far seems to be low with respect to the total population of drug consumers worldwide. Additionally, there is little information regarding the total dose at risk, the duration of exposure and comorbidities that could be facilitating factors for valvular degeneration (i.e., aging, diabetes, arterial hypertension, hypercholesterolemia and smoking). Crucial information will come from longitudinal studies in which individual patients are followed before and after starting ergot-derived DA agonists and from further investigations on the relationship between drug exposure and individual predisposing factors. In the mean time, it should always be recalled when prescribing a DA agonist that any increase in the risk of a certain complication must be counterbalanced with an increased benefit. Pergolide and cabergoline should be reserved for second-line treatment. Additionally, an ECG should be performed at least twice a year when these agonists are used.

Central adverse effects similar to those seen with LD can also occur and are mainly psychiatric, including vivid dreams, delusions, mood changes, paranoid psychoses and hallucinations. The previously mentioned comparative studies between DA agonists and LD, however, showed that neuropsychiatric symptoms, particularly hallucinations, are more common with DA agonists (7–17%) than LD (0–5%) and are more frequent in elderly or cognitively impaired patients.

Several lines of evidence suggest that DA agonist play a role in the origin of EDS and sudden onset of sleep or SA, controversially defined as an 'event of overwhelming sleepiness that

occurs without warning' [68]. The most compelling evidence of DA agonists as a cause of EDS is the well-established observation of acute drowsiness related to single doses of the drugs. This is not surprising as all of the DA agonists have a sedating, probably dose-related, effect [69], although agonists that activate the D2/D3 receptors (such as ropinirole and pramipexole) may be more likely to induce irresistible somnolence than those that stimulate the D1/D2 receptors [68].

A large-scale questionnaire survey reported a 42.9% prevalence of SA in PD patients and a higher risk of SA with nonergoline DA agonists in younger patients (<70 years) [70]. Another recent survey has shown the occurrence of episodes of uncontrollable somnolence in 22% of 929 PD patients, but a similar risk was seen for the three agents pramipexole, ropinirole and pergolide [71]. The precise relationship of the DA agonists to EDS and SA, however, remains to be determined as both age and disease-related disturbances of the sleep–wake regulation appear to contribute to hypersomnia in PD [72]. As a general rule, concomitant sedative medication should be avoided; a reduction of the dose of a DA agonist or the substitution with another DA agonist could alleviate EDS and/or SA. The effect of modafinil in patients with EDS is controversial [73–74].

Finally, several reports have indicated an association between pathological gambling and DA agonist therapy in PD patients [75–80]. It has been suggested that this may relate to disproportionate stimulation of D3 receptors, which are primarily localized to the mesolimbic reward system [75]. A recent prospective study has assessed prevalence of pathological gambling and medication association in 297 PD patients [79]. The authors found a 7.2% prevalence of pathological gambling on any DA agonist. Interestingly, pathological gambling was associated with earlier PD onset but not with agonist subtype or doses. In a recent study, patients with PD who were a younger age at PD onset, higher novelty seeking traits and a personal or family history of alcohol use disorders showed a greater risk for pathological gambling with DA agonists [80].

A comparison of the most frequent dopaminergic adverse events in the previously mentioned comparative studies shows that pramipexole and ropinirole are associated with higher frequencies of somnolence and hallucinations compared with cabergoline and pergolide, but pergolide is associated with a slightly higher frequency of nausea than the other DA agonists. These findings are consistent with those found in other studies and in clinical practice.

Expert commentary

DA agonists have been commonly used as an adjunctive therapy to LD in patients developing motor complications. In early PD and particularly in patients younger than 65 years of age, DA agonists are possibly the first-line treatment as they provide enough benefit without dyskinesias. When DA agonist effects wane and LD is added, those patients on combined dopaminergic therapy still show lesser motor complications compared with patients starting with LD monotherapy.

There is insufficient evidence to conclude that any of the current available DA agonists should be consistently preferred in the management of PD patients. Prescribing decisions are usually made on the basis of personal experience with a particular agent, cost or a wish (by the clinician and/or the patient) to try a new drug. The patient's concomitant diseases (i.e., kidney or liver diseases) may lead one to choose an agonist that is metabolized by the liver (ropinirole) or excreted via the kidney (pramipexole) [81].

In case of waning efficacy of a DA agonist, switching from one agonist to another may be useful to prolong DA agonist monotherapy in early PD and to avoid LD increases in more advanced patients. The introduction of rotigotine patches and the development of controlled-release ropinirole have opened new ways of continuous DA receptors. Hopefully, this will have a positive impact on the time to development of dyskinesias and other motor complications. Apomorphine and lisuride subcutaneous infusion are underused resources for patients with more severe LD motor complications.

Although the fibrotic complications due to ergoline DA agonists are not very frequent, it is important to weigh risks against benefits when deciding which DA agonist to use in a certain patient, in other words ergoline versus nonergoline. Cabergoline and pergolide must be considered second-line therapies.

Five-year view

There are several issues that will direct research on DA agonists in the near future:

- Long-term prospective studies to evaluate the real incidence of motor complications, for example end-of-dose deterioration and dyskinesias, and nonmotor complications, such as sleep attacks and impulse control disorders, in patients taking DA agonists
- Development of new DA agonists more powerful than those already available and/or capable of ensuring a good clinical effect for more than 5 years when used in monotherapy
- Full evaluation of the effects of DA agonist therapy on imaging markers that are currently used for measuring PD progression by means of PET and SPECT

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Key issues

- Dopamine (DA) agonists have proved to be effective in the management of both advanced- and early-stage Parkinson's disease (PD).
- In early PD, monotherapy with DA agonists has been shown to be almost as effective as levodopa, with lower propensity to induce motor complications compared with levodopa.
- Several direct comparisons between ergot and nonergot DA agonists have shown that the efficacies of the investigated agents are largely similar. Safety issues suggest nonergot DA agonists as first-line choice.
- DA agonists share similar side-effect profiles except for fibrotic reactions that are uncommon and are induced by ergolines; sleepiness and sleep attacks are associated with both levodopa and DA agonists, especially the nonergolines.
- An agonist can be switched to another as fast as overnight by using appropriate equivalent doses; the substitution may be made for the waning effectiveness of a certain agent or for the appearance of side effects.
- Rotigotine patches theoretically produce a continuous noninvasive dopaminergic stimulation of striatal DA receptors.
- Apomorphine and lisuride subcutaneous are safe and underused resources for patients with severe motor fluctuations.

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