



Dopamine agonists in the treatment of Parkinson's disease

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SUMMARY The dopamine agonists bromocriptine and pergolide are useful adjuvants to levodopa in treating Parkinson's disease. Used this way, they can produce clinical improvement and can often permit lowering of the levodopa dosage.

KEY POINTS Bromocriptine or pergolide can be used as initial monotherapy in Parkinson's disease. ■ When used as an adjuvant to levodopa therapy, these drugs can result in clinical improvement and a decreased levodopa requirement. ■ To avoid side effects, the starting dosage should be low (1.25 mg per day of bromocriptine or 0.05 mg of pergolide) and should be increased slowly. The standard daily dose of bromocriptine ranges from 7.5 to 60 mg, and of pergolide, from 0.75 to 4 mg. ■ Combination therapy with low dosages of levodopa and a dopamine agonist may also decrease the incidence of side effects of both agents.

■ INDEX TERMS: PARKINSON'S DISEASE; DOPAMINERGIC AGENTS
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AS PARKINSON'S DISEASE progresses, dopamine replacement therapy with levodopa becomes less and less effective, owing to a decreasing threshold for dose-limiting side effects. Drugs with a different mechanism of action might offer a way to avoid this problem, or might work synergistically with levodopa and at least delay the latter's side effects. This paper reviews recent work with the dopamine agonists bromocriptine and pergolide.

WHY DOPAMINE AGONISTS ARE NEEDED

Levodopa is the most effective drug currently available for Parkinson's disease,¹ but it is not ideal: dyskinesia, dystonia, "wearing-off" phenomena, "end-of-dose deterioration," and, occasionally, abrupt ("random on-off") motor fluctuations² are complications of long-term treatment. The exact mechanism for the development of motor fluctuations is unknown. One possible explanation is that, as Parkinson's disease progresses, the number of dopaminergic cells projecting to the striatum de-

creases, as does dopa-decarboxylase activity,³ resulting in a reduced ability to synthesize dopamine from levodopa, store it, and release it. Hence, each dose of levodopa has a shorter clinical response, resulting in motor fluctuations. Another reason may be a change in the sensitivity or number of postsynaptic dopamine receptors.⁴ Similarly, dyskinesia and dystonia may result from the actions of dopamine on supersensitive postsynaptic striatal receptors.⁵

Alternative drugs that do not require intraneuronal activation within the impaired nigrostriatal dopamine pathway might avoid these problems. Dopamine agonists activate the dopamine receptors directly and have proven beneficial in Parkinson's disease. Multiple dopamine receptor subclasses have been identified; however, dopamine agonists mainly affect the D1 and D2 subtypes.⁶ Stimulation of D1 receptors activates adenylate cyclase, leading to the accumulation of cyclic adenosine monophosphate (cAMP). Stimulation of D2 receptors, on the other hand, inhibits cAMP formation.⁷ Although D2 receptors appear to be more important than D1 receptors in mediating parkinsonian symptoms, combined D1 and D2 agonists have an enhanced antiparkinsonian effect.⁸

Most dopamine agonists are natural or synthetic derivatives of ergot alkaloids. Many have been tested, but only bromocriptine and pergolide are currently available in United States (Table 1). In patients with newly diagnosed Parkinson's disease, monotherapy with bromocriptine or pergolide may initially provide symptomatic benefit comparable to that of levodopa.^{9,10} However, over time, levodopa is usually required for an adequate antiparkinsonian effect.¹¹ Most clinicians believe the role of dopamine agonists is as an adjuvant to levodopa rather than as monotherapy.

BROMOCRIPTINE

Bromocriptine is an ergot alkaloid with potent D2 agonist properties and a mild D1 receptor antagonistic effect. It is rapidly absorbed from the gastrointestinal tract, 94% undergoes first-pass hepatic metabolism, and only 6% of the original dose

TABLE 1
DOPAMINE AGONISTS CURRENTLY AVAILABLE IN THE UNITED STATES

Agonist	Receptor profile	Plasma half-life (hours)	Dose (mg/day)	Preparations
Bromocriptine	D1 antagonist D2 agonist	3–7	7.5–60	2.5-mg tablets 5.0-mg capsules
Pergolide*	D1 agonist D2 agonist	12–24	0.75–4	0.05-mg tablets 0.25-mg tablets 1.0-mg tablets

*Pergolide is approximately 10 times as potent as bromocriptine

reaches the systemic circulation. Its major route of elimination is biliary, and 98% is excreted in the feces. Its plasma half-life is 6 hours.^{12,13}

In patients with mild to moderate Parkinson's disease, bromocriptine in low dosages (less than 30 mg per day) may be used as adjuvant to levodopa. Bromocriptine should be introduced at 1.25 mg per day and the daily dose increased by 2.5 to 5.0 mg each week, as tolerated. A decrease in the dosage of levodopa may be necessary. The daily dose of bromocriptine is 7.5 to 60 mg per day.

Bromocriptine as monotherapy

There are conflicting reports regarding bromocriptine monotherapy in Parkinson's disease. Teychenne et al¹⁴ found dosages of less than 10 mg per day effective in controlling parkinsonian symptoms. However, Calne et al¹⁵ did not find a consistent response in any patient with a low dosage. The incidence of adverse effects with bromocriptine monotherapy in previously untreated Parkinson's disease is low.^{16,17} Although bromocriptine monotherapy may initially be as effective as levodopa, after 6 months levodopa is more effective.¹⁸ However, bromocriptine monotherapy is less likely to cause motor fluctuations and dyskinesia than is levodopa monotherapy.^{15–19}

Bromocriptine plus levodopa in early Parkinson's disease

Mindful of these results, some clinicians recommend early combination therapy with levodopa and bromocriptine to improve efficacy and to delay long-term motor complications.^{12,20–23} In a study reported by Rinne,²⁰ patients found to have Parkinson's disease began taking levodopa; if they subsequently had residual disability, bromocriptine was added while the levodopa dosage was kept the same. This combination was as effective as levodopa

TABLE 2
COMMON ADVERSE EFFECTS OF DOPAMINE AGONISTS

Nervous system complaints	Dyskinesia Hallucinations Somnolence Insomnia Confusion
Digestive complaints	Nausea Constipation Diarrhea Dyspepsia
Respiratory complaints	Rhinitis
Other complaints	Dizziness Orthostatic hypotension

alone, but produced less dyskinesia and motor fluctuation. These benefits persisted for 5 years.²² However, this study was open-label and nonrandomized, and used historically matched controls. In the 5-year follow-up,²² Rinne included only patients whose condition was stable enough to allow them to remain in the study.

Other studies support these findings^{12,20,23,24}; however, Weiner et al²⁵ have raised several issues regarding the conclusions. In a 4-year, double-blind, randomized, parallel-group trial comparing bromocriptine and levodopa alone and in combination, early combination therapy did not prevent or delay the onset of motor fluctuation or dyskinesia in Parkinson's disease. Unfortunately, there were some limitations to this study.^{26–28} Another study (open-label) also did not find any significant differences between the two treatments.²⁹

If dopamine agonists do decrease motor fluctuation and dyskinesia, it is because they provide steady dopaminergic stimulation at the postsynaptic receptors. Controlled-release levodopa preparations also provide steady stimulation and produce fewer long-term complications than do standard levodopa preparations.^{30,31} Therefore, it is our practice to use controlled-release levodopa for initiating levodopa treatment. At present, early combination therapy appears to have no advantage over controlled-release carbidopa-levodopa, and it is more expensive. Further studies are required, however.

Bromocriptine in late Parkinson's disease

Bromocriptine as an adjuvant to levodopa has undergone both open-label and double-blind studies

in Parkinson's disease patients who have motor fluctuations and dyskinesia. Lieberman et al³² gave bromocriptine to 66 patients who had advanced Parkinson's disease and who were taking optimal levodopa dosages. In 45 patients, rigidity, tremor, bradykinesia, postural stability, and gait improved significantly. The mean bromocriptine dosage was 47 mg per day, and the investigators were able to decrease the dosage of levodopa by 10%. However, bromocriptine was discontinued in 29 patients because of adverse effects, including mental changes and increased dyskinesia. Follow-up of 28 of these patients for at least 2 years revealed that bromocriptine at a mean dosage of 56 mg per day resulted in improvement in 75% of them.³³ Sixteen of the patients maintained improvement after 2 years. Other studies have reported similar findings.^{34,35} However, in most of the long-term studies, the beneficial effects of bromocriptine waned over time.¹² Although the exact mechanism is unknown, disease progression or changes in dopamine receptors may be responsible.

Adverse effects of bromocriptine

One of the main drawbacks of dopamine agonists is frequent side effects (Table 2), many of which are caused by dopaminergic stimulation. Starting dopamine agonists at a low dosage and slowly titrating upward minimizes this problem. Orthostatic hypotension and gastrointestinal dysfunction occur early in treatment. Approximately 33% of patients report orthostatic hypotension, light-headedness, or syncope.¹² Nausea and vomiting are reported in 20% to 30% of patients. Adverse effects related to central dopaminergic stimulation include confusion, hallucinations, depression, psychosis, and dyskinesia.³⁶ These side effects are more common in patients with severe disease and in those with dementia. Mental changes occur in 30% of patients,³⁶ dyskinesia in about 40%.³⁷ Dyspnea may occur, caused by dopaminergic drugs or pulmonary fibrosis.³⁸ Erythromelalgia, cardiac arrhythmias, angina, reactivation of peptic ulcer, dry mouth, headache, and nasal stuffiness are other adverse effects reported with bromocriptine.³⁸

PERGOLIDE

Pergolide, a semisynthetic ergoline dopamine agonist, is 10 times more potent than bromocriptine. Its half-life is 12 to 24 hours,³⁹ it reaches

a peak plasma concentration within 1 to 2 hours, and a single dose is completely cleared within 7 days.¹² Fifty-five percent is excreted in the urine, 5% is excreted in expired air, and the remaining 40% to 50% is excreted in the feces.³⁹ Pergolide has an affinity for both D1 and D2 receptors and stimulates striatal adenylate cyclase activity in the presence of guanosine triphosphate (GTP).⁴⁰

The dosage-escalation schedule for pergolide appears more complicated than it really is. The main aim is to increase the dosage slowly to avoid adverse effects. We prefer to start with one 0.05-mg pergolide tablet per day and increase by one tablet every fourth day, until the patient is receiving five 0.05-mg tablets (or one 0.25-mg tablet) three times a day.

Pergolide as monotherapy

Pergolide has not been extensively studied as monotherapy in Parkinson's disease. Rinne⁴¹ found that pergolide at a mean dosage of 2.6 mg per day alleviated parkinsonian symptoms in 10 previously untreated patients; however the degree of improvement was less than with levodopa alone.

Pergolide as an adjuvant to levodopa

In several short-term studies (less than 3 months), adding pergolide (0.1 to 15 mg per day) to levodopa decreased disability, dyskinesia, and "off" time in patients with Parkinson's disease.⁴²⁻⁴⁵ Many patients were able to reduce their levodopa dosage,^{43,45} and a few were able to discontinue it altogether.^{42,44}

Placebo-controlled studies have yielded similar findings. Olanow and Alberts⁴⁶ reported that a mean pergolide dosage of 2.5 mg per day reduced levodopa requirements by 33%, whereas Jankovic and Orman⁴⁷ reported that 4.6 mg per day reduced levodopa requirements by 78%. This also resulted in a decrease in "off" time, disability, and disease severity.

There have been many long-term, open-label trials of pergolide.⁴⁸⁻⁵⁴ Ahlskog and Muentner⁵⁴ found that patients who initially had a dramatic response to pergolide were likely to show a sustained response. In a number of studies, the response to pergolide peaked at 2 to 12 months⁴⁸⁻⁵³ and deteriorated slowly thereafter.^{48,49,51} Lieberman et al⁵¹ treated 17 patients with pergolide for more than 2 years. At a mean dosage of 2.2 mg per day, there was a 20% reduction in disability and a 40% increase in "on" time compared with baseline; however, none of these changes reached statistical significance. Jankovic⁵³ reported his experience with 18 patients; the

mean disability score was 49 at baseline, 17 at 10 weeks of pergolide therapy, and 31 after 2.4 years. Similarly, the "on" time increased 117% after 10 weeks of therapy, and after 2.4 years it was still 63% greater than at baseline. These long-term studies are similar to those reported with bromocriptine.

Adverse effects of pergolide

The adverse effects of pergolide are similar in frequency and type to those of bromocriptine.¹² In clinical trials involving approximately 1200 patients, 27% discontinued pergolide because of adverse effects.⁵⁵ The most common side effects include dyskinesia, nausea, dizziness, hallucinations, rhinitis, confusion, constipation, somnolence, orthostatic hypotension, and insomnia. Pergolide can also cause electrocardiographic changes, palpitations,^{44,52,56} and asymptomatic arrhythmias.⁵⁷ New-onset, dose-related angina, probably due to vasospasm, has been reported in a few patients.⁵⁸ However, Tanner et al⁵⁹ studied six patients who had Parkinson's disease and stable heart disease and found no worsening of cardiac status during 1 year of therapy. There are no contraindications to the use of pergolide in Parkinson's disease patients with stable heart disease.

WHICH DOPAMINE AGONIST TO USE

Since two drugs are currently available with comparable efficacy and action, which one should be used? Further, when should one be substituted for the other?

In a double-blind crossover study in nine patients with mild Parkinson's disease and 15 patients with advanced disease, LeWitt et al⁶⁰ found bromocriptine and pergolide equivalent in efficacy and adverse effects. In a retrospective study, Lieberman et al⁶¹ found pergolide more useful than bromocriptine because of its efficacy at a more advanced stage of the disease. In a 5-year study, Goetz et al⁶² gave 10 patients bromocriptine until its efficacy waned and then changed their medication to pergolide. Even though bromocriptine was losing its effect, pergolide still produced a response, and remained effective longer than bromocriptine. In a similar study,⁶³ the investigators switched the regimen from pergolide to bromocriptine, and the patients continued to do well clinically.

These studies provide little guidance regarding which drug to use. However, bromocriptine is about twice as expensive as pergolide in an equivalent

dose. For this reason, we use pergolide in preference to bromocriptine in treating Parkinson's disease.

OTHER DOPAMINE AGONISTS

Apomorphine and lisuride, dopamine agonists available in Europe, are lipophilic and soluble in aqueous solution and can be given parenterally.¹² The subcutaneous route is most commonly employed, with subcutaneous infusions given via battery-powered ambulatory pumps.⁶⁴⁻⁶⁶ Apomorphine is also effective when used sublingually,⁶⁷ intranasally,⁶⁸ and rectally.⁶⁹

Cabergoline, pramipexole, and ropinirole are dopamine agonists presently undergoing clinical trials in the United States. Cabergoline, a synthetic dopaminergic agonist specific for the D2 receptor, is more potent and longer-acting than bromocriptine

or pergolide. Its plasma half-life is approximately 65 hours,^{70,71} and it can be given once a day. Pramipexole, a selective dopamine D2 agonist, has therapeutic potential for use in schizophrenia and may decrease the incidence of mental adverse effects seen with dopamine agonists.⁷² Similarly, studies with ropinirole indicate a lower incidence of gastrointestinal side effects and orthostatic hypotension.⁷³

SUMMARY

The role of dopamine agonists in treating Parkinson's disease has not yet been fully worked out, but most clinicians feel they are best used as adjuvants to levodopa therapy. Used in this way, these drugs can produce clinical improvement and can often permit a lowering of the levodopa dosage.

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