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 fluctuations[2] 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]

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

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 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 al[14] found dosages of less than 10 mg per day effective in controlling parkinsonian symptoms. However, Calne et al[15] 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 al[25] 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 al[32] 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. Rinne[41] 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 Alberts[46] reported that a mean pergolide dosage of 2.5 mg per day reduced levodopa requirements by 33%, whereas Jankovic and Orman[47] 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 Muenter[54] 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 months[48–53] and deteriorated slowly thereafter.[48,49,51] Lieberman et al[51] 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. Jankovic[53] 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 al[59] 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 al[60] found bromocriptine and pergolide equivalent in efficacy and adverse effects. In a retrospective study, Lieberman et al[61] 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 al[62] 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.

REFERENCES

1. **LeWitt PA.** The pharmacology of levodopa in treatment of Parkinson's disease: an update. In: Calne DB, editor. Drugs for the treatment of Parkinson's disease. Handbook of experimental pharmacology. Vol 88. Berlin: Springer-Verlag, 1989:325–384.
2. **Lieberman A.** An update on Parkinson's disease. N Y State J Med 1987; **87:**147–153.
3. **Hornykiewicz O.** Brain neurotransmitter changes in Parkinson's disease. In Marsden CD, Fahn S, editors. Movement Disorders. Boston: Butterworth Scientific, 1981:41–53.
4. **Reisine TD, Fields JZ, Yamamura HJ.** Neurotransmitter receptor alterations in Parkinson's disease. Life Sci 1977; **21:**335–344.
5. **Dougan D, Wade D, Mearrick P.** Effect of L-dopa metabolites at a dopamine receptor suggest a basis for "on-off" effect in Parkinson's disease. Nature 1975; **254:**70–72.
6. **Guttman M.** Dopamine receptors in Parkinson's disease. Neurol Clin 1992; **10:**377–386.
7. **Cote TE, Eskay RL, Frey EA, et al.** Biochemical and physiological studies of the beta-receptor and the D-2 dopamine receptor in the intermediate lobe of the rat pituitary gland: a review. Neuroendocrinology 1982; **35:**217–224.
8. **Lieberman AN, Gopinathan G, Neophytides A, et al.** Management of levodopa failures: the use of dopamine agonists. Clin Neuropharmacol 1986; **9(Suppl 2):**S9–S21.
9. **Jankovic J.** Long-term use of dopamine agonists in Parkinson's disease. Clin Neuropharmacol 1985; **8:**131–140.
10. **Riopelle RJ.** Bromocriptine and the clinical spectrum of Parkinson's disease. Can J Neurol Sci 1987; **14:**455–459.
11. **Stern GM, Lees AJ.** Sustained bromocriptine therapy in previously untreated patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1981; **44:**1020–1023.
12. **Goetz CG, Diederich NJ.** Dopaminergic agonists in the treatment of Parkinson's disease. Neurol Clin 1992; **10:**527–540.
13. **Aellig WH, Nuesch E.** Comparative pharmacokinetic investigations with tritium-labeled ergot alkaloids after oral and intravenous administration in man. Int J Clin Pharmacol Biopharm 1977; **15:**106–112.
14. **Teychenne PF, Bergsrud D, Elton R, et al.** Bromocriptine: low-dose therapy in PD. Neurology 1982; **32:**577–583.
15. **Calne DB, Barton K, Beckman J, et al.** Dopamine agonists in PD. Can J Neurol Sci 1984; **11:**221–224.
16. **Lees AJ, Stern GM.** Sustained bromocriptine therapy in previously untreated patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1981; **44:**1020–1023.
17. **Rascol A, Montastruc JL, Guiraud-Chaumeil B, Clanet M.** Bromocriptine as the first treatment of Parkinson's disease. Long-term results. Rev Neurol 1982; **138:**401–408.
18. **Olanow CW.** Single-blind double observer-controlled study of carbidopa/levodopa vs bromocriptine in untreated Parkinson patients [abstract]. Arch Neurol 1988; **45:**206.
19. **UK Bromocriptine Research Group.** Bromocriptine in Parkinson's disease: a double blind study comparing "low-slow" and "high-fast" introductory dosage regimens in de novo patients. J Neurol Neurosurg Psychiatry 1982; **52:**77–82.
20. **Rinne UK.** Combined bromocriptine-levodopa therapy early in Parkinson's disease. Neurology 1985; **35:**1196–1198.
21. **Calne DB, Stoessl J.** Approaches to the use of bromocriptine in Parkinson's disease. In: Fahn S, Marsden CD, Jenner P, Teychenne P, editors. Recent developments in Parkinson's disease. New York: Raven Press, 1986:255–258.
22. **Rinne UK.** Early combination of bromocriptine and levodopa in the treatment of Parkinson's disease: a 5-year follow-up. Neurology 1987; **37:**826–828.
23. **Rinne UK** Early dopamine agonist therapy in Parkinson's disease. Mov Disord 1989; **4:**586–594.
24. **Nakanishi T, Mizurio Y, Goto I, et al.** A nationwide collaborative study on long-term effects of bromocriptine in patients with Parkinson's disease: the fourth interim report. Eur Neurol 1991; **31(Suppl 1):**3–16.
25. **Weiner WJ, Factor SA, Sanchez-Ramos JR, Singer C, et al.** Early combination therapy (bromocriptine and levodopa) does not prevent motor fluctuations in Parkinson's disease. Neurology 1993; **43:**21–27.
26. **Löschmann PA, Klockgether T, Schugens MM.** Combination therapy for PD [letter]. Neurology 1993; **43:**2725.
27. **Horstink MWIM, van't Hof MA, Berger HJC.** Combination therapy for PD [letter]. Neurology 1993; **43:**2725.
28. **Lieberman A.** Combination therapy for PD [letter]. Neurology 1993; **43:**2725–2726.

29. **Fisher PA, Przuntek H, Majer M, Welzel D.** Combination treatment of early stages of Parkinson's syndrome with bromocriptine and levodopa: a multi-center evaluation. Dtsch Med Wochenschr 1984; **109:**1279–1283.
30. **Rinne UK, Rinne JO.** Treatment of early Parkinson's disease with controlled-release levodopa preparations. Neurology 1988; **39(Suppl 2):**78–81.
31. **Rinne UK.** Controlled-release levodopa superior to standard levodopa in the treatment of early Parkinson's disease [abstract]. Mov Disord 1990; **5(Suppl 1):**54.
32. **Lieberman A, Kupersmith M, Gopinathan G.** Bromocriptine in Parkinson's disease: further studies. Neurology 1979; **29:**363–369.
33. **Lieberman A, Kupersmith M, Neophytides A.** Long-term efficacy of bromocriptine in Parkinson's disease. Neurology 1980; **30:**518–523.
34. **Caraceni T, Giovanni P, Parati E, et al.** Bromocriptine and lisuride in Parkinson's disease. Adv Neurol 1984; **40:**531–535.
35. **Goetz CG, Tanner CM, Glantz RH, Klawans HL.** Chronic agonist therapy for Parkinson's disease: a five-year study of bromocriptine and pergolide. Neurology 1985; **35:**749–751.
36. **Hoehn MMM, Elton RL.** Low dosages of bromocriptine added to levodopa in Parkinson's disease. Neurology 1985; **35:**199–206.
37. **Lieberman AN, Kupersmith M, Casson I, et al.** Bromocriptine and lergotrile: comparative efficacy in Parkinson's disease. Adv Neurol 1979; **24:**461–473.
38. **Nutt JG, Hammerstad JP, Gancher ST.** Therapy: dopamine agonists. In: Parkinson's disease, 100 maxims. Mosby Year Book: St Louis, 1992:93–101.
39. **Rubin A, Lemberger L, Dhahir P.** Physiologic disposition of pergolide. Clin Pharm Ther 1981; **30:**258–265.
40. **Goldstein M, Lieberman A, Lew JY, et al.** Interaction of pergolide with central dopaminergic receptors. Proceedings of the National Academy of Sciences 1980; **77:**3725–3728.
41. **Rinne UK.** Dopamine agonists as primary treatment in Parkinson's disease. Adv Neurol 1986; **45:**519–523.
42. **Lieberman AN, Leibowitz M, Neophytides A, et al.** Pergolide and lisuride for Parkinson's disease. Lancet 1979; **2:**1129–1130.
43. **Klawans HL, Tanner CM, Goetz CG et al.** Pergolide mesylate therapy in Parkinson's disease: report of a 3-month trial in 20 patients [abstract]. Neurology 1981; **31(Suppl 2):**133.
44. **Lang AE, Quinn N, Brincat S, Marsden CD, Parkes JD.** Pergolide in late-stage Parkinson's disease. Annals of Neurology 1982; **12:**243–247.
45. **Tanner CM, Goetz CG, Glantz RH, Glatt SL, Klawans HL.** Pergolide mesylate and idiopathic Parkinson's disease. Neurology 1982; **32:**1175–1179.
46. **Olanow CW, Alberts MJ.** Double-blind controlled study of pergolide mesylate in the treatment of Parkinson's disease. Clin Neuropharm 1987; **10:**178–185.
47. **Jankovic J, Orman J.** Parallel double-blind study of pergolide in Parkinson's disease. In: Yahr, Bergmann, editors. Adv Neurol 1986; **45:**551–554.
48. **Lieberman AN, Goldstein M, Neophytides A, et al.** The use of pergolide, a potent dopamine agonist in Parkinson's disease. Clin Pharmacol Ther 1982; **32:**70–75.
49. **Shoulson I, Miller C, Kurlan R, Levy R, Macik B.** Parkinsonism and on-off fluctuations: long-term effects of pergolide therapy [abstract]. Ann Neurol 1982; **12:**97.
50. **Goetz CG, Tanner CM, Glantz R, Klawans HL.** Pergolide in Parkinson's disease. Arch Neurol 1983; **40:**785–787.
51. **Lieberman AN, Goldstein M, Leibowitz M, Gopinathan G, Neophytides A.** Long-term treatment with pergolide: decreased efficacy with time. Neurology 1984; **34:**223–226.
52. **Kurlan R, Miller C, Levy R, et al.** Long-term experience with pergolide therapy of advanced parkinsonism. Neurology 1985; **35:**738–742.
53. **Jankovic J.** Long-term study of pergolide in Parkinson's disease. Neurology 1985; **35:**296–299.
54. **Ahlskog JE, Muenter MD.** Pergolide: long-term use in Parkinson's disease. Mayo Clin Proc 1988; **63:**979–987.
55. **Langtry HD, Clissold SP.** Pergolide: a review of its pharmacological properties and therapeutic potential in Parkinson's disease. Drugs 1990; **39:**491–506.
56. **Lieberman AN, Goldstein M, Leibowitz M, et al.** Treatment of advanced Parkinson's disease with pergolide. Neurology 1981; **31:**675–682.
57. **Leibowitz M, Lieberman A, Goldstein M, et al.** Cardiac effects of pergolide. Clin Pharmacol Ther 1981; **30:**718–723.
58. **Ahlskog JE, Muenter MD.** Treatment of Parkinson's disease with pergolide: a double-blind study. Mayo Clin Proc 1988; **63:**969–978.
59. **Tanner CM, Chhablani R, Goetz CG, et al.** Pergolide mesylate: lack of cardiac toxicity in patients with cardiac disease. Neurology 1985; **35:**918–921.
60. **LeWitt PA, Ward CD, Larsen TA, et al.** Comparison of pergolide and bromocriptine therapy in parkinsonism. Neurology 1983; **33:**1009–1014.
61. **Lieberman AN, Neophytides A, Leibowitz M, et al.** Comparative efficacy of pergolide and bromocriptine in patients with advanced Parkinson's disease. Adv Neurol 1983; **37:**95–108.
62. **Goetz CG, Tanner CM, Glantz RH, Klawans HL.** Chronic agonist therapy for Parkinson's disease: a five year study of bromocriptine and pergolide. Neurology 1985; **35:**749–751.
63. **Goetz CG, Shannon KM, Tanner CM, et al.** Agonist substitution in advanced Parkinson's disease. Neurology 1989; **39:**1121–1122.
64. **Duby SE, Cotzias GC, Papavasiliou PS, et al.** Injected apomorphine and orally administered levodopa in parkinsonism. Arch Neurol 1972; **27:**474–480.
65. **Obeso JA, Luqin MR, Martinez-Lage JM.** Lisuride infusion pump: a device for the treatment of motor fluctuations. Lancet 1986; **1:**467–470.
66. **Frankel JP, Lees AJ, Kempster PA, Stern GM.** Subcutaneous apomorphine in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry 1990; **53:**96–101.
67. **Lees AJ, Montastruc JL, Turjanski N, et al.** Sublingual apomorphine and Parkinson's disease [letter]. J Neurol Neurosurg Psychiatry 1990; **521440.**
68. **Kapoor R, Turjanski N, Frankel J, et al.** Intranasal apomorphine: a new treatment in Parkinson's disease [letter]. J Neurol Neurosurg Psychiatry 1990; **53:**1015.
69. **Hughes AJ, Bishop S, Lees AJ, Stern GM, Webster R, Bovingdon M** Rectal apomorphine in Parkinson's disease [letter]. Lancet 1991; **337:**118.
70. **Di Salle E, Ornati G, Briatico G.** FCE 21336, a new ergoline derivative with a potent and long-acting lowering effect on prolactin secretion in rats [abstract]. J Endocrinol Invest 1982; **5(Suppl 1):**45.
71. **Lieberman A, Imke S, Muenter M, et al.** Multicenter study of cabergoline, a long-acting dopamine agonist, in Parkinson's disease patients with fluctuating responses to levodopa/carbidopa. Neurology 1993; **43:**1981–1984.
72. **Mierau J, Schingnitz G.** Biochemical and pharmacological studies on pramipexole, a potent and selective dopamine D2 receptor agonist. Eur J Pharmacol 1992; **215:**161–170.
73. **Eden RJ, Costall B, Domeney AM, et al.** Preclinical pharmacology of ropinirole (SK&F 101468-A) a novel dopamine D2 agonist. Pharmacol Biochem Behav 1991; **38:**147–154.