Comparison Between Lergotrile and Bromocriptine in Parkinsonism

P. F. Teychenne, MD, R. F. Pfeiffer, MD, S. M. Bern, PharmD,
D. McInturff, and D. B. Calne, DM

The therapeutic and adverse effects of two ergot derivatives, bromocriptine and lergotrile, were compared in idiopathic parkinsonism. At both low (50 mg daily) and high (150 mg daily) dosage there was a similar but not identical profile of response. Initially, lergotrile tended to induce more severe but always transient hypotension. At higher doses, bromocriptine caused more dyskinesia.

Neurological deficits improved with increasing doses up to an average daily level of 80 to 150 mg of ergot derivatives combined with levodopa, 450 to 1,150 mg, and carbidopa, 45 to 115 mg. However, efficacy often declined at the highest doses of antiparkinsonian agents.

Adverse effects caused by ergot derivatives are more common with dosages greater than 100 mg per day. In general, the best overall therapeutic results with bromocriptine and lergotrile were obtained in the dose range of 50 to 100 mg daily for each.

It is concluded that bromocriptine and lergotrile are similar in their therapeutic properties and that both are comparable in efficacy to levodopa plus carbidopa (though optimal results are commonly obtained by combining submaximal doses of levodopa with ergot derivatives). The role for each drug in the treatment of parkinsonism is likely to be determined by factors such as cost (bromocriptine) and hepatotoxicity (lergotrile).

Teychenne PF, Pfeiffer RF, Bern SM, et al: Comparison between lergotrile and bromocriptine in parkinsonism. Ann Neurol 3:319–324, 1978

Bromocriptine (2-bromo-α-ergocryptine methane sulfonate) and lergotrile mesylate (2-chloro-6-methylergoline-8β-acetonitrile methane sulfonate) are ergot derivatives which stimulate dopaminergic receptors [5, 6]. The antiparkinsonian activity of bromocriptine at mean daily dose levels of less than 100 mg has been evaluated by several investigators [3, 4, 9–11, 14, 16, 17, 19, 21, 23, 25], but its quantitative efficacy is controversial. At low dosage (up to 25 mg daily), lergotrile has been reported to have modest antiparkinsonian activity [15].

We compared the effects of bromocriptine and lergotrile in idiopathic parkinsonism. Our aim was to contrast their therapeutic activity and toxicity at relatively low (50 mg daily) and at high dose levels (150 mg daily). In addition, we examined the effect of alterations in concomitant levodopa/carbidopa therapy.

Patients and Methods

Twenty patients suffering from idiopathic parkinsonism were selected. Subjects with cardiovascular, respiratory, hematological, renal, or liver disease were not accepted. All participants were inpatients throughout the period of observation. Three were excluded because of intolerable adverse effects during treatment with lergotrile: supine and postural hypotension in 2, confusion and hallucinations in the third. The results from 3 patients who failed to complete the protocol were not analyzed.

The investigation was performed in three stages. These were separate although there was considerable overlap of patients: 3 out of 7 in study 2 were also involved in study 1, and 14 out of 15 in study 3 had previously been investigated in studies 1 or 2. Study 1 compared ergot derivatives at low dose, study 2 compared them at high dose, and study 3 compared high doses of ergot derivatives combined with maximum tolerated supplements of levodopa/carbidopa.

Study 1: Low-Dose Ergot Derivatives

Nine patients, 7 men and 2 women with a mean age of 58.9 years (range, 38 to 74 years), were studied. Five patients were not receiving any drugs; 4 were taking levodopa/carbidopa, 1,255/125 mg per day (range, 1,000/100 to 1,750/175). The intake of levodopa and carbidopa was not altered during this phase of the study.

After initial assessments the patients were given lergotrile, the dose being increased from a starting level of 0.5 to 2.0 mg daily up to 50 mg. The subjects were then transferred to placebo. Following this, they were given bromocriptine, the dose being built from a starting level of 2.5 to 5 mg daily up to 50 mg daily.

From the Experimental Therapeutics Branch, National Institute of Neurological and Communicative Disorders and Stroke, and the Department of Pharmacy, National Institutes of Health, Department of Health, Education, and Welfare, Bethesda, MD.

Accepted for publication Oct 10, 1977.

Address reprint requests to Dr Calne, Experimental Therapeutics Branch, NINCDS, Bldg 10, Room 6D20, National Institutes of Health, Bethesda, MD 20014.

Study 2: High-Dose Ergot Derivatives

In this study, 7 patients were investigated; 3 of them had been in study 1. The remaining 4 subjects included 3 men and 1 woman with a mean age of 60.8 years (range, 56 to 66). The mean dose of levodopa/carbidopa was 575/57.5 mg per day (range, 200/20 to 1,750/175).

Lergotrile or bromocriptine was built up to a daily dose of 150 mg. The dose of levodopa/carbidopa was not altered. Since cross-tolerance between the two ergot derivatives has been found [26], the patients were transferred at random from 150 mg per day of lergotrile to 150 mg per day of bromocriptine, or vice versa. These rapid changes from one ergot to the other were accomplished without any adverse effect. Placebo for the ergot derivatives was introduced at random but for no longer than 24 hours because of severe deterioration in neurological status.

Study 3: High-Dose Ergot Derivatives with Maximum Tolerated Levodopa/Carbidopa

Fifteen patients were investigated; 7 had been included in study 2, 7 in study 1, and 1 subject, a man of 56 years, had not been previously evaluated. Based on current experience it was considered advisable to limit the dose of ergot derivatives to 150 mg daily. Thirteen of the subjects were maintained on 150 mg per day of lergotrile or bromocriptine. Levodopa/carbidopa was either added or, for those patients already on it, increased to a maximum tolerated level: mean 873/87.3 mg per day (range, 200/20 to 1,750/175) with lergotrile and mean 672/67.2 mg per day (range, 200/20 to 1,750/175) with bromocriptine.

Two patients unable to tolerate 150 mg daily of either ergot derivative were built up to their maximum tolerated combination of levodopa/carbidopa: 200/20 mg with 50 mg of bromocriptine and 1,250/125 mg with 100 mg of bromocriptine daily, respectively.

Evaluations

A single physician assessed neurological deficits blind according to an arbitrary scoring protocol in which 0 represented normality and 4 was the maximum deficit for each clinical feature. Four timed tests were also used to assess drug efficacy: writing time, walking time, timed repetitive thumb-to-finger movement, and timed flexion/extension movements of the fingers [23].

Adverse effects were evaluated by both a "blind" physician and a patient self-monitoring method. Scores were assigned from 0 (no adverse reaction) to 4 (drug withdrawal required).

Routine hematological and biochemical tests were performed every week. Increases in the serum activities of the enzymes alanine aminotransaminase (SGPT) and aspartate aminotransaminase (SGOT) were noted in 12 of the 20 patients receiving lergotrile (Teychenne PF, Jones EA, Ishak KG, et al: Hepatocellular injury associated with lergotrile therapy. In preparation.)

Results

Study 1: Low-Dose Ergot Derivatives

The mean scores from three evaluations made on every patient during initial baseline, lergotrile, bromocriptine, and placebo periods were compared.

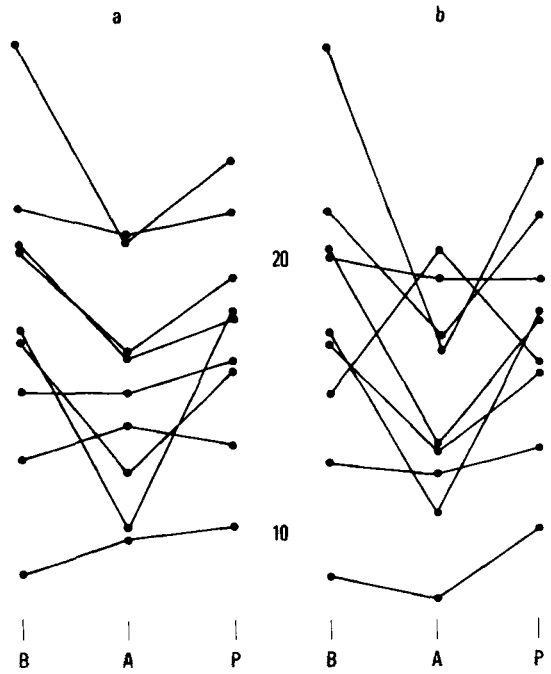


Fig 1. Mean total scores for physical signs and functional disability in each patient during baseline (B), *active drug* (A), *and placebo* (P) *stages.*

During treatment with either lergotrile or bromocriptine, scores improved (reduced) for physical signs and functional disability (Fig 1), and improved (increased) in counts for repetitive thumb-to-finger movement ($p < 0.025$) (Fig 2).

Treatment with bromocriptine resulted in a significant ($p < 0.05$) reduction in the time taken to arise from a chair and walk 20 m from the times recorded during the baseline and placebo periods, while lergotrile therapy significantly ($p < 0.025$) decreased this time compared with baseline but not with the placebo phase.

Improvement in six individual clinical features during treatment with the ergot derivatives is shown in Figure 3A. Tremor was decreased with both drugs, and deficits associated with hypokinesia improved. In contrast, rigidity was unaffected. There was no significant difference between the responses to lergotrile and bromocriptine.

The main adverse effects resulting from the drugs are shown in Figure 3B. Both drugs induced sedation. Lergotrile caused more constipation than did bromocriptine, and it increased nausea compared with baseline and placebo phases. At the start of treatment, lergotrile caused more orthostatic hypotension than did bromocriptine. The latter drug induced more dyskinesia and insomnia than did lergotrile; the incidence of insomnia with lergotrile was less than that recorded during baseline and placebo periods.

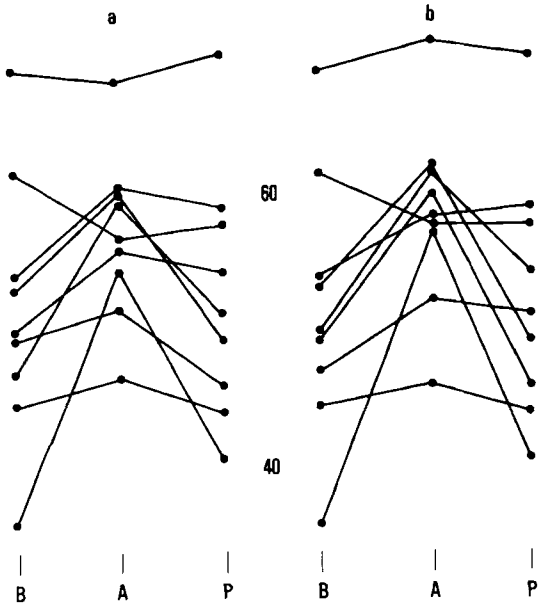


Fig 2. Mean total scores for the number of times the patient could oppose the tip of the thumb to the tip of each finger in turn over 20 seconds during baseline (B), *active drug* (A), *and placebo* (P) *stages.* a *represents lergotrile, 50 mg daily.* b *represents bromocriptine, 50 mg daily.*

Study 2: High-Dose Ergot Derivatives

The mean scores from three evaluations made during treatment with lergotrile or bromocriptine were compared with each other and with the scores obtained on placebo.

Treatment with either ergot derivative induced a significant ($p < 0.05$) improvement in the total scores for physical signs and functional disability (Fig 4). An increase in counts during timed repetitive thumb-to-finger movement and a decrease in writing time ($p < 0.05$) occurred during treatment with lergotrile but not with bromocriptine (Fig 5).

Significant improvement in six individual clinical features occurred during treatment with the ergot derivatives (Fig 6A). At this high dose, bromocriptine was more effective than lergotrile in suppressing tremor. As with the lower doses, neither drug improved rigidity.

Lergotrile and bromocriptine produced similar adverse effects (Fig 6B) much like those seen at lower dose levels. Both drugs induced constipation and dyskinesia, but involuntary movements were more prominent with bromocriptine. Bromocriptine induced less insomnia at the higher dosage than at the 50 mg daily dose or in the baseline period.

Study 3: High-Dose Ergot Derivatives with Maximum Tolerated Levodopa/Carbidopa

Seven patients achieved an optimum response, receiving levodopa/carbidopa at a mean daily dose of 729/72.9 mg combined with 150 mg of lergotrile and levodopa/carbidopa in an average daily dose of 614/61.4 mg with 150 mg of bromocriptine. Once the optimal response was achieved, there was no significant difference in the mean scores from three assessments obtained either on the lergotrile-levodopa-carbidopa or the bromocriptine-levodopa-carbidopa combination. The remaining patients showed no improvement over study 1 or 2; in some cases a deterioration occurred in their performance.

Five patients on lergotrile at a mean dose of 80 mg daily plus levodopa/carbidopa at an average dose of 1,153/115.3 mg daily achieved an optimum response; but when lergotrile was increased to a mean of 150 mg

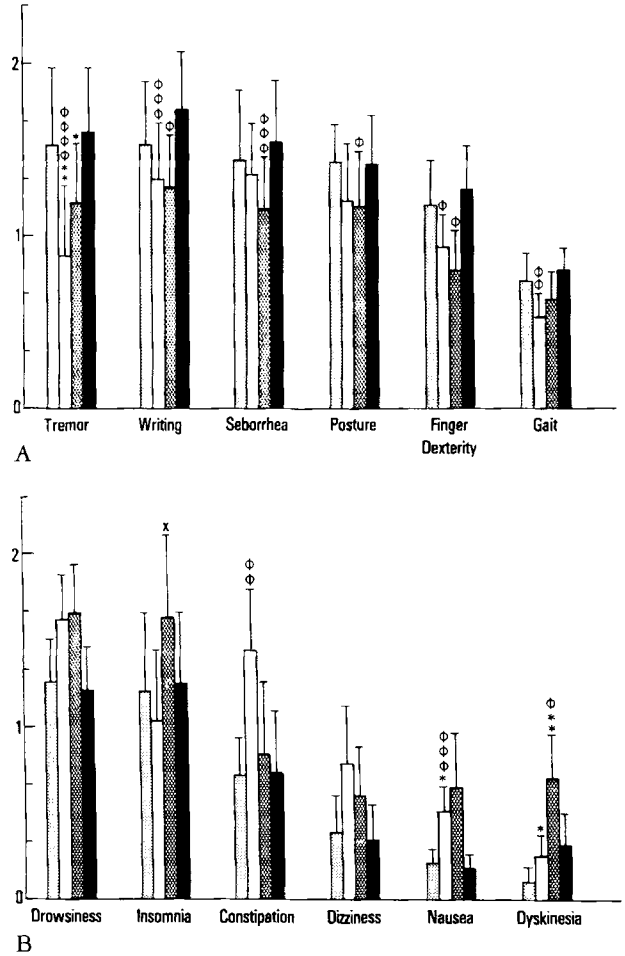


Fig 3. Mean scores plus SEM from all patients for (A) individual physical signs which showed most change and (B) adverse effects. From left to right, baseline (dotted bars), *lergotrile* (open bars), *bromocriptine* (cross-hatched bars) *and placebo* (black bars) *stages. All statistical analyses were done by one-tailed paired* t *tests except for comparison of placebo against baseline or bromocriptine against lergotrile, for which two-tailed paired* t *tests were used. (* represents ergot derivatives compared with baseline; * = $p < 0.05$; ** = $< p < 0.025$; Φ represents ergot derivatives compared with placebo; Φ = $p < 0.05$; ΦΦ = $p < 0.025$; ΦΦΦ = $p < 0.01$; ΦΦΦΦ = $p < 0.005$; X represents bromocriptine compared with lergotrile:* X = $p < 0.05$.)

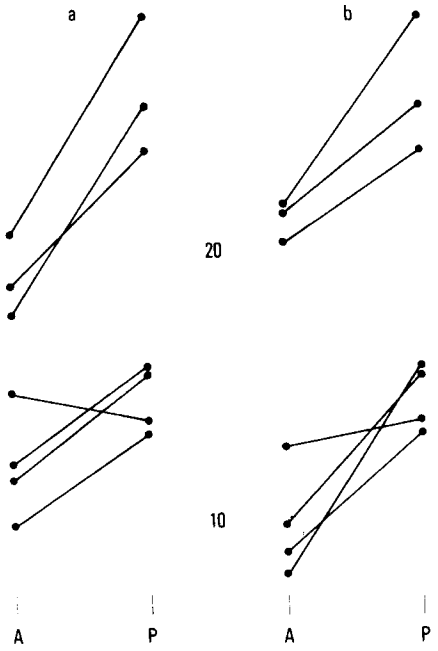


Fig 4. Mean total scores for physical signs and functional disability in each patient during active drug (A) *and placebo* (P) *stages.*

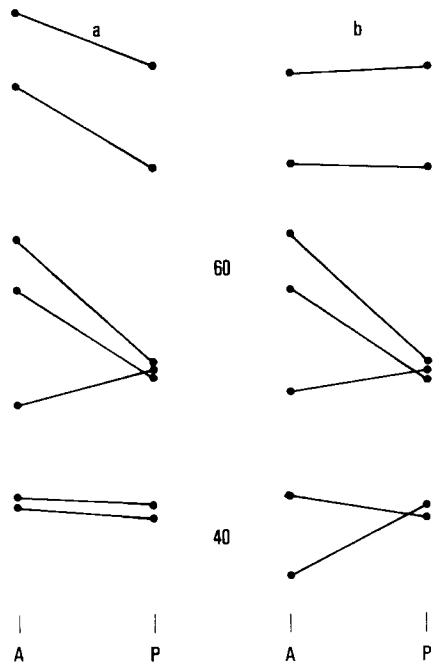


Fig 5. Mean scores for the number of times the patient could oppose the tip of the thumb to the tip of each finger in turn over 20 seconds during active drug (A) *and placebo* (P) *stages.* a *represents lergotrile, 150 mg daily.* b *represents bromocriptine, 150 mg daily.*

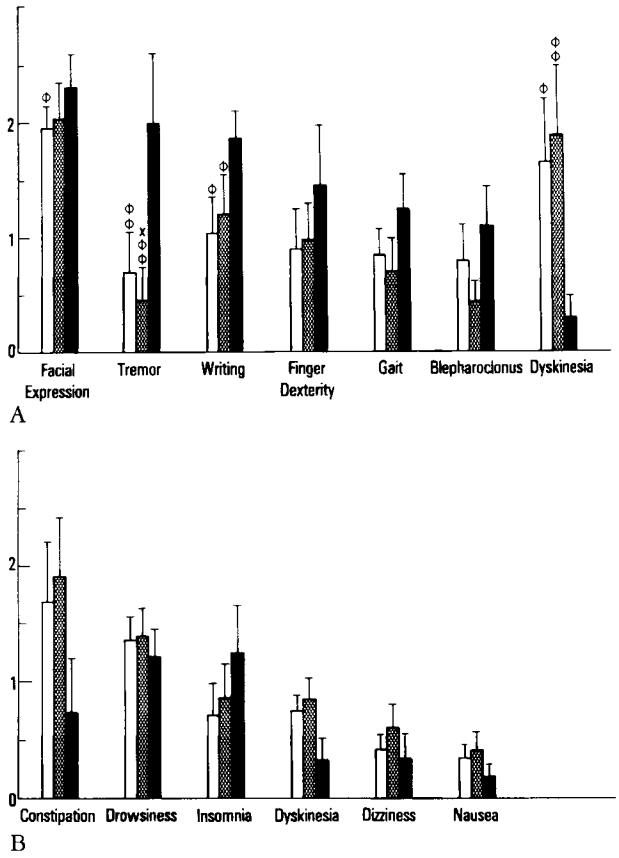


Fig 6. Mean scores plus SEM from all patients for (A) individual physical signs which showed most change and (B) adverse effects. From left to right, lergotrile (open bars), *bromocriptine* (cross-hatched bars), *and placebo* (black bars) *stages. All statistical analyses were done by one-tailed paired* t *tests except for comparison of bromocriptine against lergotrile, for which two-tailed paired* t *tests were used. Dyskinesia was assessed by the blind observer in A and by the patient in B.* (Φ *represents ergot derivatives compared with placebo;* Φ = $p < 0.05$; ΦΦ = $p < 0.025$; X *represents bromocriptine compared with lergotrile;* X = $p < 0.05$.)

per day and levodopa/carbidopa to an average of 1,655/165.5 daily, a mean 9% decrement in clinical response occurred. Similarly, 4 patients reached optimum clinical response on a mean daily dose of 104 mg of bromocriptine and 441/44.1 mg of levodopa/carbidopa; yet while they were taking an average dose of 112.5 mg of bromocriptine and 644/64.4 mg of levodopa/carbidopa, an 11% decrease in clinical response was noted. One patient experienced a deterioration at maximum tolerated dosage on both bromocriptine and lergotrile.

Toxicity

Elevated transaminase levels in 12 of the patients receiving lergotrile cleared when the drug was stopped. Three patients had liver biopsies while the enzymes were increased. Light microscopy revealed

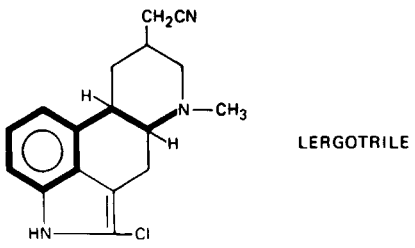
features of mild hepatocellular injury, and electron microscopy showed mitochondrial damage and proliferation of the smooth endoplasmic reticulum. The presence of a cyanide moiety in the lergotrile molecule may have relevance to the high incidence of hepatocellular injury induced by this drug (Teychenne PF, Jones EA, Ishak KG, et al: Hepatocellular injury associated with lergotrile therapy. In preparation.)

Discussion

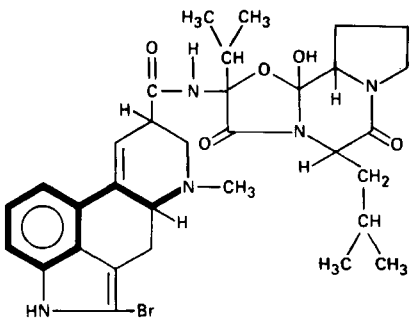
Previous studies on the treatment of parkinsonism with ergot derivatives resulted in equivocal results for low doses of bromocriptine [9]. In contrast, high doses of bromocriptine have been found to have therapeutic efficacy comparable to that of levodopa [10, 11, 14, 23]. It has also been reported that an optimal response can be obtained by combining an ergot derivative with levodopa [11]. Our findings establish the therapeutic similarity between the two major ergot derivatives to have been studied in parkinsonism—bromocriptine and lergotrile (Fig 7).

Bromocriptine has a higher molecular weight (750.6) than lergotrile (395.9), so in molecular terms bromocriptine is more potent than lergotrile. Potency, however, is not necessarily an important determinant of therapeutic potential. Other factors such as the therapeutic index (ratio of toxic to effective dose) and cost may have greater bearing on the applications of a new drug. In this context it is notable that for the same therapeutic response, lergotrile appears to carry a high risk of toxicity (impairment of liver function tests).

Fig 7. Structure of lergotrile and bromocriptine. Heavy lines indicate the dopamine-like moiety which is the presumed basis for therapeutic activity in parkinsonism.



LERGOTRILE



BROMOCRIPTINE

The mechanism of action of ergot derivatives is not clear. While these agents display the properties of dopaminergic agonists in several in vivo tests, they do not stimulate dopamine-sensitive striatal adenylyl cyclase in vitro; indeed, in certain circumstances these drugs actually antagonize this dopaminergic screening test [12, 20, 27]. They may have presynaptic actions (releasing dopamine from nerve endings and blocking reuptake) that contribute to the therapeutic response [22], particularly when levodopa is administered concomitantly [11]. Ergot derivatives have also been reported to have such diverse actions as alpha-adrenoreceptor agonism and antagonism [8]. Nevertheless, if all the current evidence is taken into consideration, it seems that the major action of bromocriptine and lergotrile, together with any active metabolites which they might form, is dopaminergic agonism.

High doses of dopamine agonists or levodopa can exacerbate parkinsonism [18, 24, 25]. Excess dopaminergic receptor stimulation may induce a change in receptor state from an agonist to an antagonist conformation [7]. The clinical findings are consistent with in vitro studies in which very high tissue concentrations of agonists lead to receptor blockade [13]. Another clinical situation that may have some analogy to our findings in parkinsonism is the induction of a cholinergic crisis when patients with myasthenia gravis are given too much anticholinesterase.

The clinical changes we observed were unusually consistent, which allowed us to establish statistical significance with relatively small numbers of patients. Another point to emerge from the design of our study was the absence of any rebound deterioration when treatment with ergot derivatives was stopped—our initial baseline scores were not significantly different from the placebo values. In this respect, therapy with ergot derivatives is similar to treatment with levodopa [2] and contrasts to that with anticholinergic agents [1].

We are grateful to Ms P. Barnicoat, Ms B. Shryock, and Ms A. Miller for administrative and secretarial assistance. Bromocriptine was kindly supplied by Sandoz, Ltd, and lergotrile by Eli Lilly and Company.

References

1. Calne DB: Parkinsonism, in Calne DB: Therapeutics in Neurology. Oxford, Engl, Blackwell Scientific Publications, 1975, p 202
2. Calne DB, Spiers ASD, Stern GM, et al: L-Dopa in idiopathic parkinsonism. Lancet 2:973–976, 1969a
3. Calne DB, Teychenne PF, Claveria LE, et al: Bromocriptine in parkinsonism. Br Med J 4:442–444, 1974

4. Calne DB, Teychenne PF, Leigh PN, et al: Treatment of parkinsonism with bromocriptine. Lancet 2:1355–1356, 1974
5. Clemens JA, Smalstig EG, Shaar CJ: Inhibition of prolactin secretion by lergotrile mesylate: mechanism of action. Acta Endocrinol 79:230–237, 1975
6. Corrodi H, Fuxe K, Hokfelt T, et al: Effect of ergot drugs on central catecholamine neurones: evidence for a stimulation of central dopamine neurones. J Pharm Pharmacol 25:409–412, 1973
7. Enna SJ, Bennett JP Jr, Burt DR, et al: Stereospecificity of interaction of neuroleptic drugs with neurotransmitters and correlation with clinical potency. Nature 263:338–341, 1976
8. Flückiger E: The pharmacology of bromocriptine, in Bayliss RIS, Turner P, Maclay WP (eds): Pharmacological and Clinical Aspects of Bromocriptine. Tunbridge Wells, Engl, MCS Consultants, 1976, pp 12–26
9. Gerlach J: Effect of CB154 (2-bromo-alpha-ergocryptine) on paralysis agitans compared with Madopar in a double-blind, cross-over trial. Acta Neurol Scand 53:189–200, 1976
10. Godwin-Austen RB, Smith NJ: Comparison of the effects of bromocriptine and levodopa in Parkinson's disease. J Neurol Neurosurg Psychiatry 40:479–482, 1977
11. Kartzinel R, Perlow M, Teychenne PF, et al: Bromocriptine and levodopa (with or without carbidopa) in parkinsonism. Lancet 2:272–275, 1976
12. Kebabian JW, Calne DB, Kebabian PR: Lergotrile mesylate: an *in vivo* dopamine agonist which blocks dopamine receptors *in vitro*. Psychopharmacol Commun 1:311–318, 1977
13. Kebabian JW, Clement-Cormier YC, Petgold GL, et al: Chemistry of dopamine receptors. Adv Neurol 9:1–11, 1975
14. Lieberman AL, Kupersmith M, Estey E, et al: Treatment of Parkinson's disease with bromocriptine. N Engl J Med 295:1400–1404, 1976
15. Lieberman AL, Miyamoto T, Battista AF, et al: The antiparkinsonian efficacy of lergotrile. Neurology (Minneap) 25:459–462, 1975
16. Lieberman AL, Zolfaghan M, Boal D, et al: The antiparkinsonian efficacy of bromocriptine. Neurology (Minneap) 26: 405–409, 1976
17. Parkes JD, Debono AG, Marsden CD: Bromocriptine in parkinsonism: long term treatment, dose response and comparison with levodopa. J Neurol Neurosurg Psychiatry 39:1101–1108, 1976
18. Parkes JD, Debono AG, Marsden CD, et al: Clinical pharmacology of bromocriptine in parkinsonism, in Bayliss RIS, Turner P, Maclay WP (eds): Pharmacological and Clinical Aspects of Bromocriptine. Tunbridge Wells, Engl, MCS Consultants, 1976, pp 27–33
19. Parkes JD, Marsden CD, Donaldson A, et al: Bromocriptine treatment in Parkinson's disease. J Neurol Neurosurg Psychiatry 39:184–193, 1976
20. Schmidt MJ, Hill L: Effects of ergots on adenylate cyclase activity in the corpus striatum and pituitary. Life Sci 20:789–798, 1977
21. Shaw KM, Lees AJ, Kohout V, et al: Bromocriptine in parkinsonism, in Bayliss RIS, Turner P, Maclay WP: Pharmacological and Clinical Aspects of Bromocriptine. Tunbridge Wells, Engl, MCS Consultants, 1976, pp 98–102
22. Silbergeld E, Pfeiffer RF: Differential effects of three dopamine agonists: apomorphine, bromocriptine and lergotrile. J Neurochem 28:1323–1326, 1977
23. Teychenne PF, Calne DB, Leigh PN, et al: Idiopathic parkinsonism treated with bromocriptine. Lancet 2:473–476, 1975
24. Teychenne PF, Calne DB, Lewis PJ, et al: Interactions of levodopa with inhibitors of monoamine oxidase and L-aromatic amino acid decarboxylase. Clin Pharmacol Ther 18:273–277, 1975
25. Teychenne PF, Kartzinel R, Calne DB, et al: Long term experience with bromocriptine in parkinsonism, in Bayliss RIS, Turner P, Maclay WP (eds): Pharmacological and Clinical Aspects of Bromocriptine. Tunbridge Wells, Engl, MCS Consultants, 1976, pp 27–33
26. Teychenne PF, Plotkin CN, Rosin AJ, et al: Cross tolerance between two dopaminergic ergot derivatives—bromocriptine and lergotrile. Neurology (Minneap) 27:405–406, 1977
27. Trabucchi M, Spano PF, Tonon GC, et al: Effects of bromocriptine on central dopaminergic receptors. Life Sci 19:225–231, 1976