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Bromocriptine in Parkinson Disease

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I. Introduction

THE most important problem in the current treatment of Parkinson disease is the increasingly large number of patients who, after a good response to levodopa (combined with a peripheral decarboxylase inhibitor), fail to maintain this response and become more symptomatic (55, 61). Increasing disability is usually accompanied by diurnal oscillations in performance, predominantly "wearing-off" or end of dose deterioration (60, 61). Occasionally patients exhibit abrupt random oscillations: "on-off" phenomena (60, 61). The increased disability and the decreased response to levodopa may be explained as follows. With disease progression, there is continued loss of the pigmented neurons in the substantia nigra. It is within these neurons that dopa is converted to dopamine, transported to the ipsilateral striatum where it is then released onto specialized postsynaptic receptors (4, 64, 67).

Two separate types of postsynaptic striatal dopamine receptors have been identified: the D_1 receptors that are linked to adenyl cyclase and are localized predominantly to intrastriatal neurons and the D_2 receptors that are not linked to adenyl cyclase and are located predominantly to axons of a descending corticostriatal tract (17, 35, 73, 74). These receptors may exist in low or high affinity binding states. Stimulation of one or both of these receptors is important for controlling the symptoms of Parkinson disease. There are also dopamine receptors on the presynaptic nigrostriatal axons. Stimulation of these receptors results in feedback inhibition of nigrostriatal neurons with decreased dopamine synthesis (16, 17).

In Parkinson disease, symptoms appear after there is an 80% reduction in the number of nigral cells and in the striatal dopamine content (4, 64, 67). In patients with moderately advanced disease, levodopa combined with carbidopa in Sinemet or combined with benserazide in Madopar is the most effective antiparkinsonian treatment. Levodopa compensates for the striatal dopamine deficiency through increased conversion of dopa to dopamine by the remaining nigral neurons (1, 10), and through the development of supersensitivity of the intact but denervated postsynaptic striatal receptors (14, 80). Striatal dopamine receptor supersensitivity has also been invoked as an explanation for the development of choreiform involuntary movements (dyskinesias) in levodopa treated patients. In advanced disease, levodopa administration, although still effective, is not able to fully compensate for the striatal dopamine deficiency because there are too few remaining nigral neurons to synthesize enough dopamine to stimulate the striatal dopamine receptors. In addition, chronic levodopa treatment itself may induce the striatal dopamine receptors to become subsensitive (62). Those investigators who believe that chronic levodopa treatment itself is responsible for the decreased levodopa response and for the dyskinesia and diurnal oscillation in performance advocate delaying levodopa treatment, using low dose levodopa or periodically stopping levodopa (levodopa drug holiday) (12, 42, 68, 77). Those investigators who do not believe that chronic levodopa treatment is responsible for the decreased levodopa response do not advocate delaying levodopa treatment when symptoms warrant its use (57, 63).

Presently, coadministration of a dopamine agonist is the best treatment for those patients whose response to levodopa has decreased, and in whom raising the dose of levodopa results in adverse reactions, or in whom lowering the dose of levodopa results in increased disability. Dopamine agonists bypass the degenerating nigral neurons and stimulate the striatal dopamine receptors directly (9, 21, 22, 23). The most useful dopamine agonists are those derived naturally or synthetically from the ergolene class of ergot alkaloids. Modification of the ergolene molecule has resulted in drugs with more selective properties than the ergots in general medical use which block peripheral alpha adrenergic receptors and constrict smooth muscle. These ergots are useful in obstetrics as uterine smooth muscle constrictors for inducing delivery, and in neurology as vascular smooth muscle constrictors for treating migraine headaches. Bromocriptine is a lysergic acid amide peptide containing ergolene. Bromocriptine and the other ergolene dopamine agonists have a low affinity for alpha adrenergic receptors and are largely devoid of vasoconstricting properties.

The ability to lower serum prolactin was fundamental in screening compounds for dopamine agonist activity (15, 16). Bromocriptine stimulates hypophyseal dopamine receptors which in turn inhibit prolactin release. Because bromocriptine lowers serum prolactin, it has been used successfully as a treatment for several disorders characterized by hyperprolactinemia. These disorders include amenorrhea, galactorrhea, and prolactin secreting pituitary tumors (15, 37, 56). It was subsequently shown that bromocriptine stimulated central dopaminergic receptors (16). This led to its successful introduction as an antiparkinson drug (5, 48). At present bromocriptine is the only dopamine agonist that is therapeutically available on a nonexperimental basis in the United States.

Initially, bromocriptine was used in patients with advanced Parkinson disease who were no longer satisfactorily responding to levodopa (5, 6, 34, 39, 48, 49, 52, 54). In these patients, low dose bromocriptine (5–30 mg/day) added to levodopa had a modest antiparkinsonian effect, while high dose bromocriptine (31–100 mg/day) added to levodopa had a better effect. However, high dose bromocriptine, when added to levodopa, resulted in more adverse reactions. These reactions included orthostatic hypotension, mental changes, and dyskinesias. Later, good responses were obtained with low dose bromocriptine, built up gradually, alone or with levodopa, especially in patients with mild or moderate disease (3, 40, 41, 65, 78). Adverse reactions were infrequent with low dose bromocriptine. Some investigators, because of their experience with the need for high dose bromocriptine in patients with advanced disease, were skeptical about the efficacy of low dose bromocriptine. Because of the questions raised about the use of bromocriptine alone or with levodopa, in a low or in a high dose, in patients with mild, moderate, or advanced disease, we reviewed the pharmacology of bromocriptine, our 10-yr experience with bromocriptine, and the experience of other investigators.

II. Studies in Animals

Several techniques are available to study the efficacy and mode of action of the antiparkinson drugs. These techniques depend upon the development of an animal model of parkinsonism. Such models may be made by inducing a selective degeneration of the nigrostriatal dopamine neurons in rats and in monkeys (17, 21, 67). In rats unilateral intranigral injection of 6-hydroxydopamine results in contralateral circling behavior when the rats are challenged with drugs that stimulate dopamine receptors. Bilateral intranigral injection of 6-hydroxydopamine into rats causes severe akinesia, aphagia, and adipsia. These rats cannot survive without intensive support. Unilateral surgical lesions of the ventromedian mesencephalon in monkeys cause ipsilateral nigrostriatal tract degeneration with resultant contralateral hypotonia and resting tremor. The circling behavior of the rats can be quantitated. Monkeys with unilateral mesencephalic lesions lose their contralateral tremor (9, 17, 21–23) and may develop dyskinesias when challenged with drugs that stimulate dopamine receptors. The striatal dopamine receptors on the denervated side of these animals become supersensitive and react strongly to dopamine agonists. These actions of the dopamine agonists can be blocked by dopamine receptor antagonists. Conversely, drugs, like amphetamine, that release dopamine from presynaptic nerve terminals release it only from the intact side where the dopamine acts as an agonist and results in circling toward the denervated side. Recently, systemic administration of the meperidine analog, 1-methyl-4 phenyl-1,2,5,6-tetrahydropyridine (MPTP), has caused parkinsonism in man and monkeys (38). Animals with parkinsonism induced by unilateral surgical lesions, unilateral 6-hydroxydopamine injections, or by MPTP are now used in screening antiparkinson drugs.

Animals with appropriately induced nigrostriatal lesions may be pretreated with alpha-methyl-*p*-tyrosine (AMPT), a compound that inhibits presynaptic dopamine synthesis. Antiparkinson drugs, whose activity is blocked by pretreatment with AMPT, require a relatively intact nigrostriatal system to be effective. Such drugs are likely to be useful in patients with mild or moderate Parkinson disease where the presynaptic nigrostriatal neurons are relatively well preserved. Such drugs are less likely to be effective in patients with advanced disease where the presynaptic nigrostriatal neurons are not well preserved (21–23, 26, 33, 59, 76). Stimulation of the presynaptic dopamine receptors can be measured by pretreatment with gamma butyrolactone (GBL) which inhibits impulse flow in the presynaptic neurons, resulting in increased striatal dopamine synthesis. Drugs that stimulate the presynaptic dopamine receptors block the

ability of GBL to elicit increased dopamine synthesis (21–23, 26, 59, 76). Binding of drugs to striatal dopamine agonist receptor sites can be measured by using a radiolabeled dopamine receptor ligand such as [^{3}H]dopamine. Binding of drugs to striatal dopamine antagonist receptor sites can be measured by using a radiolabeled dopamine receptor antagonist such as [^{3}H]haloperidol or [^{3}H]spiroperidol. Striatal dopamine receptors can be visualized by *in vitro* light microscopic autoradiography using [^{3}H] spiroperidol. Receptor binding is demonstrated by placing tritium-sensitive film in contact with treated brain sections. The film is then developed, and the autoradiograms are analyzed by computerized densitometry and image enhancement (17, 21–27, 33, 59, 71, 76). Measurement of released cyclic adenosine monophosphate (AMP) after dopamine receptor stimulation indicates whether a receptor is or is not linked to adenyl cyclase (24, 26, 27, 33, 35, 58, 59, 71, 73, 74, 76). Intrastriatal injection of kainic or ibotenic acid, neurotoxins which selectively destroy neurons, indicates whether or not receptors are localized to intrastriatal neurons. Decortication, which severs the descending corticostriatal tract, indicates whether receptors are or are not localized to axons of the descending tract.

III. Pharmacology

Bromocriptine is an ergopeptine derivative and exerts some pharmacological properties which are different from those of other ergolenes and of classical dopamine agonists. The findings that the antiparkinsonian activity of bromocriptine is diminished by pretreatment with the dopa synthesis inhibitor AMPT (24–27, 33, 58, 71, 76) suggest that some intact nigrostriatal dopamine neurons are required for its therapeutic action. With respect to the presynaptic dopamine receptors, bromocriptine has some properties of a mixed "agonist-antagonist" (24–26, 33, 58, 59, 71, 75, 76). Thus, bromocriptine, at high concentrations, inhibits synaptomal tyrosine hydroxylase activity, but it also partially reverses the agonist apomorphine-elicited inhibition of tyrosine hydroxylase activity. Bromocriptine predominantly stimulates the D_2 dopamine receptors, but it has mixed "agonist-antagonist" properties at these receptors. Bromocriptine, unlike other dopamine agonists, does not differentiate between the low and high affinity D_2 receptor binding states. The binding affinities of dopamine agonists are decreased by exposure of striatal membranes to higher temperatures or by addition of guanine nucleotides (26, 27), while the binding affinities of dopamine antagonists and of bromocriptine are not affected by these treatments (26, 27). Heat treatment mimics the effects of guanine nucleotide, suggesting that both modalities have a common mechanism. Indeed, some evidence has been obtained that exposure of membranes to higher temperatures inactivates the guanine nucleotide binding protein which regulates the dopamine agonist binding affinities (31). Thus, bromocriptine has some binding characteristics of dopamine antagonists, and unlike other dopamine agonists, it does not induce conformational changes in the receptor which leads to the formation of a ternary complex between agonist receptor binding proteins and the guanine nucleotide binding protein (2, 31, 75).

The antiparkinson activity of bromocriptine is longer than that of levodopa, because bromocriptine has a longer half-life than levodopa. Bromocriptine's long duration of action might be due to the unique interaction of the cyclic peptide side chain of the ergopeptines with additional sites of the dopamine receptors (2, 31, 75). It has also been suggested that bromocriptine's long duration of action occurs because bromocriptine interacts with the receptor in an irreversible fashion (2). There is a delay in the onset of bromocriptine's antiparkinsonian activity, indicating that this activity depends on the formation of one or more active metabolites (24–27, 33, 58, 59, 71, 76). In man, following a 1-mg oral dose, bromocriptine is absorbed within 0.12 h, and peak plasma levels are achieved within 1–2 h (72). The half-life of bromocriptine is 3 h. The degradation of bromocriptine proceeds through a process of first pass metabolism by the liver. The first pass metabolism of bromocriptine is 94%; *i.e.*, 6% of the absorbed dose of bromocriptine reaches the systemic circulation. Two types of bromocriptine metabolites have been identified. Type I metabolites are formed by cleavage of the peptide portion of bromocriptine. Subsequent metabolism leads to further scission of the peptide. Type II metabolites are formed by cleavage of the indole portion of the ergolene moiety through debromination and oxygenation.

IV. Studies in Humans

To assess the role of bromocriptine in the treatment of Parkinson disease, we reviewed 27 papers encompassing 790 patients representing most of the published studies on bromocriptine. The review included 3 of our own papers encompassing 124 patients. In the 27 studies, patients were selected for bromocriptine treatment for several reasons. Among patients already on levodopa, the reasons included a decreased response to levodopa, no response to levodopa, adverse effects on levodopa, or diurnal oscillations in performance on levodopa. Many patients received bromocriptine as their initial treatment because of concern that chronic levodopa therapy itself might lead to a decreased levodopa response or the appearance of diurnal oscillations in performance.

A. Study Groupings

The studies were divisible into two main groups: patients on bromocriptine without levodopa and patients on bromocriptine with levodopa. The first group, patients on bromocriptine without levodopa, consisted mainly of patients who received bromocriptine as their initial antiparkinson drug. This group also included some patients who received bromocriptine without levodopa because previous attempts to use levodopa resulted in adverse

effects. This group also included a few patients in whom levodopa was discontinued during the course of bromocriptine treatment. The second group consisted of patients who were treated with bromocriptine with levodopa. This group consisted mainly of patients whose response to levodopa had decreased considerably. The group also consisted of some patients whose response to levodopa had decreased minimally or not at all.

The two main groups could then be divided into two subgroups. These two subgroups consisted of those patients who were treated with low dose bromocriptine (5–30 mg/day) and those patients who were treated with high dose bromocriptine (31–100 mg/day). In those studies which included patients in more than one of the above groups, the number of patients in the study in the particular group were analyzed with the patients from the other studies who were also in that group.

B. Efficacy Evaluation Methodology

Most studies started out evaluating bromocriptine in Parkinson disease regardless of dose. The number of evaluable study patients listed is the number who completed the study plus the number who discontinued bromocriptine because of adverse reactions. The following parameters were analyzed for each of the groups: the mean age of the patients; the mean duration of Parkinson disease; the number of patients who had never been treated with levodopa; the number of patients who had been treated with levodopa but in whom levodopa was discontinued prior to or during bromocriptine treatment; the number of patients who had mild or moderate Parkinson disease (Stages 0, 1, 2, or 3); and the number of patients who had advanced disease (Stages 4 or 5). To evaluate treatment efficacy, the number and percentage of patients in a particular study who were judged by the investigators to be improved over base line were noted. This method of evaluating efficacy is necessary because the different investigators used different Parkinson disease disability scales to assess disability (11). These disability scales include the Columbia University Scale, the Cornell University-UCLA Disability Scale, the Hoehn and Yahr Scale, the N. Y. U. Disability Scale, the University of British Columbia Scale, and the Webster Scale. These scales evaluate the primary symptoms of Parkinson disease: rigidity; tremor; bradykinesia; gait disturbance; and postural instability. Some disability scales include some of the secondary symptoms such as mental changes, seborrhea, dysphagia, and speech disturbances. Weighting factors are often assigned to each of the disease symptoms and different points from 0 to 4 are assigned for symptom severity. Thus, the disability scales are not strictly comparable.

In evaluating diurnal oscillations in performance, the investigators used different methods to assess these oscillations. However, the most common method was to review a diary patients were instructed to keep of the number of hours they were "on" or "off" during a 24-h period. The patients' assessments and the diaries were regularly checked by the investigator. Efficacy in reducing diurnal oscillations was evaluated by noting the number of patients with oscillations who, in the opinion of the study investigator, were considered improved. This was usually determined by noting the increase in the number of hours patients were "on."

In addition to assessing disability through an examination given at the time patients were seen in the office and in instructing patients to keep a diary, some investigators also assess disability through a functional disability rating scale. On the functional disability rating scale, patients rate themselves in their ability to complete the activities of daily living. A number of different functional disability scales are used including the N. Y. U. Functional Disability Scale, the Northwestern University Scale, and the Schwab and England Scale. As many investigators of bromocriptine did not use a functional disability scale, this method of rating disability was not used in assessing treatment efficacy. Adverse reactions which resulted in drug discontinuation were noted. The major adverse reactions were mental changes including confusion, disorientation, hallucinations, paranoid ideations, and affective disturbances. Other adverse reactions included dyskinesias, orthostatic hypotension, gastrointestinal disturbances (nausea), and peripheral (lower extremity) edema. All adverse reactions were reversible upon drug discontinuation.

C. Results

1. Therapeutic efficacy. The results of treatment with low dose bromocriptine in patients not on levodopa are summarized in Table 1. There were 79 patients in 4 studies (20, 28, 70, 78). Fifty-six (71%) of the patients had never been treated with levodopa. Twenty-three patients (29%) had been treated with levodopa, but levodopa was stopped prior to or during bromocriptine treatment. Most of the patients (63%) had mild or moderate Parkinson disease. Forty-six patients (58%) improved on low dose bromocriptine alone. Bromocriptine was discontinued in only seven patients (9%) because of adverse effects.

The results of treatment with high dose bromocriptine in patients not on levodopa are summarized in Table 2. There were 143 patients in 7 studies (7, 18, 34, 41, 48, 65, 69). The mean dose of bromocriptine was 56 mg/day. Ninety-seven patients (68%) had never been treated with levodopa. Forty-six patients (32%) had been treated with levodopa, but levodopa was stopped prior to or during bromocriptine treatment. In 132 patients, information on disease severity was available. In these 132 patients, 102 patients (77%) had mild or moderate disease. Eighty-eight of 143 patients (62%) improved on high dose bromocriptine alone. Bromocriptine was discontinued in 39 patients (27%) because of adverse effects.

In comparing these two studies, predominantly involving patients with mild or moderate disease, a higher dose

TABLE 1
Bromocriptine alone: low dose

Study	Patients	Bromocriptine (mg)	Age (yr)	Duration of Parkinson disease (yr)	Never on levodopa		Stop levodopa		Mild/moderate Parkinson disease		Advanced Parkinson disease		Improvement		Adverse effects	
					Patients	%	Patients	%	Patients	%	Patients	%	Patients	%	Patients	%
Grimes (28)	20	13			20	(100)	0	0	0	0	20	(100)	13	(65)	4	
Godwin (20)	24	23	62		1	(4)	23	(96)	19	(79)	5	(21)	7	(29)	0	(0)
Rinne (70)	24	13	64	3.8	24	(96)	0	0	20	(83)	4	(17)	16	(67)	2	(8)
Teychenne (78)	11	15	65	5.3	11	(100)	0	0	11	(100)	0	0	10	(91)	1	(9)
Mean		16	63	4.3												
Total	79				56	(71)	23		50	(63)	29	(37)	46	(58)	7	(9)

35/79 Patients (44%) evaluated double blind

TABLE 2
Bromocriptine alone: high dose

Study	Patients	Bromocriptine (mg)	Age (yr)	Duration of Parkinson disease (yr)	Never on levodopa		Stop levodopa		Mild/moderate Parkinson disease		Advanced Parkinson disease		Improvement		Adverse effects	
					Patient	%	Patient	%	Patient	%	Patient	%	Patient	%	Patient	%
Caraceni (8)	14	60	60	5.4	3	(21)	11	(79)	11	(79)	3	(21)	13	(93)	2	(14)
Gerlach (18)	20	30	65	8.0	0	0	20	(100)	10	(50)	10	(50)	10	(50)	1	(5)
Kartzinel (34)	12	46	57	9.1	4	(33)	8	(67)	8	(75)	4	(25)	8	(67)	1	(8)
Lees (40)	50	70	57	2.0	50	(100)	0	0	45	(90)	5	(10)	28	(56)	25	(50)
Lieberman (48)	7	70	64	9.6	0	0	7	(100)	0	0	7	(100)	4	(57)	2	(29)
Parkes (65)	11	35	62	—	11	(100)	0	0					6	(55)	4	(36)
Rascol (69)	29	56	66	5.5	29	(100)	0	0	28	(97)	1	(3)	19	(66)	4	(14)
Mean		56	61	5.1	97	(68)	46	(32)	102/132	(77)	30/132	(23)	88	(62)	39	(27)
Total	143															

93/143 Patients (65%) evaluated double blind

TABLE 3
Bromocriptine/levodopa: low dose

Study	Patients	Bromocriptine (mg)	Age (yr)	Duration of Parkinson disease (yr)	Duration of levodopa (yr)	Levodopa (mg)	Mild/ moderate Parkinson disease		Advanced Parkinson disease		Levodopa (% of decrease)	Improvement		Adverse effects	
							Patients	%	Patients	%		Patients	%	Patients	%
Carceni (7)	12	25	60	5.2	3.0	700	10	(83)	2	(17)	(50)	10	(83)	2	(17)
Fahn (13)	53	23	61	9.2	5.8	640	13	(25)	40	(65)	(20)	26	(49)	31	(58)
Grimes (28)	37	24	67	9.0	5.0		0	0	37	(100)	(34)	37	(100)	4	(16)
Gron (20)	15	22	64	8.5	4.0	590	13	(87)	2	(13)	(0)	12	(80)	0	(0)
Hoehn (30)	18	20									(0)	14	(78)	0	(0)
Lieberman (48)	11	26	62	8.9			8	(73)	3	(27)	(0)	6	(55)	1	(9)
Parkes (65)	20	26	62	12.9	3.9						(0)	12	(60)	5	(25)
Pfeiffer (66)	21	29	65								(0)	14	(67)	7	(33)
Teychenne (78)	14	12	70	8.5	4.5	620					(0)	12	(86)	3	(20)
Mean		23	63	8.8	4.5		44/128	(35)	84/128	(65)		143	(71)	53	(26)
Total	201														

88/164 Patients (54%) evaluated double blind

of bromocriptine (56 mg *versus* 16 mg) resulted in only slightly more improvement (62% *versus* 58%), but with more adverse effects (27% *versus* 9%). From these studies, it is clear that bromocriptine alone at a low or a high dose has an antiparkinsonian effect. The need for a higher dose of bromocriptine probably depends on disease severity.

The results of treatment with low dose bromocriptine and levodopa are summarized in Table 3. There were 201 patients in 9 studies (7, 13, 28–30, 54, 65, 66, 78). The mean dose of bromocriptine was 23 mg/day. The mean duration of levodopa treatment was 5 yr. The mean daily dose of levodopa (in Sinemet) varied from 590–700 mg. In 128 patients, information on disease severity was

available. Forty-four (35%) had mild or moderate disease, while 84 patients (65%) had advanced disease. From the description of the patients in terms of duration of disease, duration of levodopa treatment, and presence of diurnal oscillations, it is assumed that most of the patients for whom no direct information on disease severity was available also had advanced disease. The dose of levodopa was decreased from 0–50% during bromocriptine treatment. Bromocriptine, in low doses, when added to levodopa, resulted in improvement in 143 of 164 evaluable patients (71%). Bromocriptine was discontinued in 55 patients (27%) because of adverse effects.

The results of treatment with high dose bromocriptine with levodopa are summarized in Table 4. There were 367 patients in 7 studies (6, 19, 32, 34, 40, 52, 70). The mean dose of bromocriptine was 48 mg. The mean duration of levodopa treatment was 6.5 yr. The mean dose of levodopa (in Sinemet) ranged from 700–1150 mg. In 256 patients, information was available on disease severity. Thirty-eight of 256 patients (15%) had mild or moderate disease, while 218 patients (85%) had advanced disease. From the description of the patients in terms of duration of disease, duration of levodopa treatment, and presence of diurnal oscillations, it is assumed that most of the patients for whom no direct information on disease severity was available also had advanced disease. The dose of levodopa was decreased from 18–74% during bromocriptine treatment. Bromocriptine in high doses, when added to levodopa, resulted in improvement in 212 of 367 patients (58%). Bromocriptine was discontinued in 118 patients (32%) because of adverse reactions. More patients in the low dose bromocriptine (23 mg/day) plus levodopa group improved than in the high dose bromocriptine (48 mg/day) plus levodopa group, 71% of patients improving *versus* 58%. Fewer patients in the low dose bromocriptine plus levodopa group experienced adverse effects, 26% of patients *versus* 32%. The need for a higher dose of bromocriptine with levodopa probably depends on disease severity, because the patients on the higher dose of bromocriptine had more advanced disease as manifested by a longer mean disease duration (10.7 *versus* 8.8 yr), longer mean duration of levodopa treatment (6.5 *versus* 4.5 yr), and a higher percentage of diurnal oscillations (34% *versus* 25%).

The results of treatment with bromocriptine in low doses plus levodopa in patients with diurnal oscillations in performance are summarized in Table 5 (7, 13, 28–30, 50, 65, 66, 78). In 51 of 201 patients (25%), specific mention is made of the presence of diurnal oscillations. Forty-two of the 51 patients (82%) were improved during bromocriptine treatment. The results of treatment with bromocriptine in high doses plus levodopa in patients with diurnal oscillations are summarized in Table 6 (6, 19, 32, 34, 40, 52, 69). In 123 of 367 patients (34%), specific mention is made of the presence of diurnal oscillations. Seventy-eight of the 124 patients (63%) improved. Several mechanisms may be responsible for the efficacy of bromocriptine in patients with diurnal oscillations in performance. Diurnal oscillations do not occur in patients on bromocriptine who have not been treated with levodopa (41). In some patients who have been treated with levodopa and in whom diurnal oscillations appear, replacing some of the patient's levodopa with bromocriptine, which has a lesser propensity to induce oscillations, may itself decrease the diurnal oscillations. Alternately, bromocriptine may interact synergistically with dopamine at the postsynaptic striatal dopamine receptors to prolong the effect of dopamine at these receptors.

2. Adverse reactions. The adverse effects experienced with bromocriptine are summarized in Table 7. The adverse effects consisted mainly of mental changes and were more likely to occur in patients with an underlying organic dementia. The next most frequent adverse effects

TABLE 4
Bromocriptine/levodopa: high dose

Study	Patients	Bromocriptine	Age	Duration of Parkinson disease (yr)	Duration of levodopa (yr)	Levodopa (mg)	Mild/moderate Parkinson disease		Advanced Parkinson disease		Levodopa (% of decrease)	Improvement		Adverse effects	
							Patients	%	Patients	%		Patients	%	Patients	%
Calne (6)	79	53	61	10.8		700					(41)	44	(56)	29	(37)
Glantz (19)	23	51	61	12.5	7.6		1	(4)	22	(96)	(60)	9	(39)	10	(43)
Kartzinel (34)	32	79	61	11.6							(74)	17	(53)	4	(13)
Jansen (32)	12	71	59	8.8	4.6	590	0	0	12	(100)		9	(75)	0	(0)
Lees (40)	33	30	64	10.0	10.0		0	0	33	(100)		30	(91)	17	(52)
Lieberman (52)	106	41	62	11.0	6.3	1150	9	(8)	97	(92)	(18)	55	(52)	54	(51)
Rascol (69)	82	40	61	9.4	4.9		28	(34)	54	(66)	(50)	48	(775)	4	(13)
Mean		48	62	10.7	6.5		38/256	(15)	218/256	(85)		212	(58)	118	(32)
Total	376														

144/367 Patients (39%) evaluated double blind

TABLE 5
Bromocriptine/levodopa: low dose oscillations

Study	Patients	Bromocriptine (mg)	Oscillations		Improvement in oscillations	
			Patients	%	Patients	%
Caraceni (7)	12	25	2/12	(17)	1/2	(50)
Fahn (13)	53	23	15/53	(28)	7/15	(47)
Grimes (83)	37	24	28/37	(76)	28/28	(100)
Gron (29)	15	22				
Hoehn (30)	18	20	2/18	(11)	2/2	(100)
Lieberman (48)	11	26	2/11	(18)	2/2	(100)
Parkes (65)	20	26	0		0	
Pfeiffer (66)	21	29				
Teychenne (78)	14	12	2/14	(14)	2/2	(100)
Mean		23				
Total	201		51/201	(25)	42/51	(82)

TABLE 6
Bromocriptine/levopoda: high dose oscillations

Study	Patients	Bromocriptine (mg)	Oscillations		Improvement in oscillations	
			Patients	%	Patients	%
Calne (6)	79	53	29	(37)	19	(66)
Glantz (19)	23	51	23	(100)	9	(39)
Kartzinel (34)	32	79	8	(25)	8	(25)
Jansen (32)	12	71	5	(42)	0	(0)
Lees (40)	33	30	0	(0)	0	(0)
Lieberman (52)	106	41	41	(39)	34	(82)
Rascol (69)	82	40	18	(22)	8	(44)
Mean		48				
Total	367		124	(34)	78	(63)

were orthostatic hypotension and nausea. A small number of patients experienced vasospastic phenomena: Raynaud's phenomena, angina. All adverse effects were reversible. Among the 790 patients treated with bromocriptine, 217 (28%) experienced adverse effects. The fewest adverse effects occurred with low dose bromocriptine without levodopa (9%). More adverse effects occurred with high dose bromocriptine without levodopa (27%) or with low dose bromocriptine with levodopa (26%). The most adverse effects occurred with high dose bromocriptine and levodopa (32%). This suggests that many of the adverse effects that occur with bromocriptine are related to the dose of bromocriptine and the coadministration of levodopa. However, patients treated with high dose bromocriptine and levodopa had more advanced disease, and it is possible that they are more susceptible to mental changes and dyskinesias.

3. Dose determinants. Among these 790 patients, 360 (46%) were evaluated in a double blind manner. Bromocriptine, when used alone in low or in high dose, or when combined with levodopa in low or in high dose, resulted in improvement in 489 patients (61%), while 217 patients (27%) experienced adverse reactions. Bromocriptine without levodopa in low or high dose is a useful treatment in patients with mild or moderate disease. Low dose bromocriptine is associated with fewer adverse effects (9% *versus* 27%). The main reason that patients with mild or moderate disease need a higher dose of bromocriptine than others may be that the disease, although mild or moderate, is nonetheless more advanced in the patients needing the higher dose (39). Thus, the mean disease duration was longer in patients on high dose bromocriptine without levodopa than in patients on low dose bromocriptine without levodopa: 5.1 yr *versus* 4.3 yr. Another reason that some patients with mild or moderate disease need a higher dose of bromocriptine than other patients may be related to the treatment preferences of the individual investigators. Some investigators seek complete symptom resolution despite adverse effects, but others seek partial symptom resolution with fewer adverse effects. A third reason some patients need a higher bromocriptine dose may be related to individual differences in drug absorbtion and metabolism (72). The same dose of bromocriptine may in different individuals result in different plasma levels of active drug. Patients with mild or moderate disease who respond to high dose bromocriptine may, because of decreased absorption or increased metabolism, achieve only a low plasma level of active drug even though they received a high oral dose. Conversely, other patients with mild or moderate disease who respond to low dose bromocriptine may, because of increased absorption or de-

TABLE 7
Bromocriptine adverse effects

Study (no.)	Patients	Bromocriptine (mg)	Levodopa	Adverse effects		Mental changes	Dyskinesia	Orthostatic hypotension	Gastrointestinal	Other
				No.	%					
4*	79	16	0	7	(9)	1			5	1
7†	143	56	0	39	(27)	20	1	7	7	4
9‡	201	23	+	53	(26)	21	7	9	11	5
7§	367	48	+	118	(32)	48	12	24	17	17
Total	790			217	(28)	90	20	40	40	27

* References 20, 28, 70, and 78.
† References 8, 18, 34, 40, 48, 65, and 69.
‡ References 7, 13, 28–30, 48, 65, 66, and 78.
§ References 6, 19, 32, 34, 40, 52, and 69.

creased metabolism, achieve a high plasma level of active drug even though they received a low oral dose.

D. Timing Considerations

Debate has arisen as to the dose of bromocriptine required to treat patients with Parkinson disease. The debate is needless as the bromocriptine dose is based on the patient's response to treatment. However, it is important for physicians to realize that, in many patients, a good therapeutic effect (with few adverse reactions) can be achieved on a low dose of bromocriptine, particularly when it is built up slowly and gradually. To further define the role of low or high dose bromocriptine without or with levodopa, we compared the results of treatment with bromocriptine low dose without and with levodopa with bromocriptine high dose without and with levodopa in Table 8. More patients treated with low dose bromocriptine without or with levodopa had mild or moderate disease. Fewer patients treated with high dose bromocriptine without or with levodopa had mild or moderate disease. The same percentage of patients treated with low or high dose bromocriptine improved. This again suggests that disease severity is a factor in determining the dose of bromocriptine (39).

A reasonable question is whether bromocriptine should be used as the initial treatment for Parkinson disease. If it is true that the duration of the optimal response to levodopa before diurnal oscillations in performance appear (the levodopa honeymoon) is a function of the duration of levodopa treatment (regardless of disease severity), then bromocriptine should be considered as a first treatment (along with anticholinergics and amantadine). Bromocriptine has been successfully used as a first treatment for Parkinson disease (7, 18, 20, 28, 34, 41, 48, 65, 69, 70, 78). Patients may be started on low doses, but eventually many require higher doses, and ultimately all require levodopa (40, 41). Patients treated with bromocriptine alone do not develop diurnal oscillations in performance and experience few dyskinesias. As it is not now clear that the duration of the levodopa honeymoon is a function of the duration of levodopa treatment, bromocriptine, anticholinergics, amantadine, and levodopa may all be considered as a first treatment for Parkinson disease depending upon individual patient circumstances and physician preferences.

Few studies examined bromocriptine's long term efficacy. Bromocriptine's efficacy, like that of the other ergolenes or levodopa, eventually declines (51). When bromocriptine is begun in low doses and built up slowly, peak efficacy occurs within the first 6 mo of treatment and then may decline. The decreased efficacy is more pronounced in patients with advanced disease treated with high doses of bromocriptine than in patients with mild or moderate disease treated with low doses. Our own long-term experience with bromocriptine is summarized in 28 patients with Parkinson disease who were treated with bromocriptine for at least 2 yr [mean, 2.8 yr; range, 2–5 yr (51)]. All of them had first been treated with levodopa (alone or combined with carbidopa, as Sinemet) for 7.4 yr (range, 1–10 yr). At the time bromocriptine was started, all were showing increasing disability. Bromocriptine (mean daily dose, 56 mg) was added to levodopa and resulted in improvement in 21 of the patients. After 2 yr, 5 of these patients continued to maintain their original improvement. The remaining patients, although there has been deterioration, maintained some of their original improvement. Thus, bromocriptine, when added to levodopa, results in improvement that is maintained, in part, for at least 2 yr.

The decreased efficacy or, in some patients, the failure to respond to bromocriptine at all may result from decreased postsynaptic striatal receptor sensitivity which, in turn, may result from a decrease in the number of receptors or from a confirmational change in the receptors. The decreased receptor sensitivity may occur as a result of disease progression or as a result of tolerance to chronic drug treatment (through a process of down regulation of the receptors).

TABLE 8

A comparison of bromocriptine alone minus bromocriptine/levodopa (BC/LD) minus bromocriptine: low dose minus bromocriptine: high dose

	Patients	Duration of Parkinson disease	Mild/moderate Parkinson disease (%)	Improvement (%)	Adverse effects (%)
BC alone*	222	4.8	72	60	21
BC/LD†	568	10.0	21	63	30
BC: low‡	280	7.5	45	68	21
BC: high§	510	9.1	36	59	31

* References 8, 18, 20, 28, 34, 40, 48, 65, 69, 70, and 78.
† References 6, 7, 13, 19, 28–30, 32, 34, 40, 48, 52, 65, 66, 69, and 78.
‡ References 7, 13, 20, 28–30, 48, 65, 66, 70, and 78.
§ References 6, 18, 19, 32, 34, 40, 48, 52, and 69.

E. Bromocriptine versus Other Ergolines

The efficacy of bromocriptine was compared to the other ergolines: lergotrile; pergolide; lisuride; and mesulergine. Studies in which an investigator treated one group of patients with bromocriptine and a second group with another agonist were reviewed (8), but analysis was undertaken only of those studies in which both agonists were used in the same patients.

Two studies compared bromocriptine with lergotrile. In one, patients were treated first with bromocriptine, and then after a suitable washout period with lergotrile (79). The study was done double blind. All of the patients were on levodopa which was held constant during the study. Mean daily dose of bromocriptine or lergotrile was 50–150 mg. Five patients improved more on bromocriptine, 1 improved more on lergotrile, 8 improved equally on both drugs, and 6 did not improve on either drug. The 2 drugs were considered to be equally effective. In a second, retrospective study, 24 patients with advanced disease were treated at different times with bromocriptine or lergotrile (plus levodopa) (47). Three patients

improved equally on both drugs, and 8 did not improve on either drug. Bromocriptine was discontinued in 8 patients because of adverse effects. Lergotrile was discontinued in 16 patients because of adverse effects including hepatotoxicity in 11. Hepatotoxicity did not occur with bromocriptine. Bromocriptine and lergotrile were judged equally effective.

The efficacy of bromocriptine was compared to pergolide. In one study, 27 patients were randomly assigned to treatment with either bromocriptine or pergolide (in addition to levodopa) and then were crossed over to the other drug after an appropriate washout period (45). Seven patients were more improved on bromocriptine, 11 were more improved on pergolide, 4 were equally improved on both drugs, and 5 were not improved on either drug. Mean daily dose of bromocriptine was 43 mg. Mean daily dose of pergolide was 3.3 mg. Bromocriptine and pergolide were judged to be equally effective. In a second, retrospective study, patients who had been treated with bromocriptine were treated with pergolide (53). By the time patients were treated with pergolide, they were, on average, 3 yr older than they had been at the time they were treated with bromocriptine. Eleven patients improved more on bromocriptine, and 14 improved more on pergolide. Diurnal oscillations improved more on pergolide than on bromocriptine. The number of hours "on" increased by 62% on bromocriptine. The number of hours "on" increased by 224% on pergolide. Adverse effects were comparable on both drugs with 9 patients discontinuing bromocriptine and 8 patients discontinuing pergolide because of such reactions. Mean dose of bromocriptine was 50 mg. Mean dose of pergolide was 2.1 mg. Bromocriptine and pergolide were equally effective in decreasing disability.

The efficacy of bromocriptine was compared to lisuride. In one study, 28 patients were randomly assigned to treatment with either bromocriptine or lisuride (in addition to levodopa) and then were crossed over to the other drug (44). Twelve patients were more improved on bromocriptine, 4 were more improved on lisuride, and 10 were improved equally on both drugs. The mean dose of bromocriptine was 57 mg. The mean dose of lisuride was 4.5 mg. Bromocriptine and lisuride were judged to be equally effective. In a second, retrospective study, 25 patients who had been treated with bromocriptine were treated with lisuride (46). At the time the patients were treated with lisuride, they were, on average, 2 yr older than they had been at the time they were treated with bromocriptine. Nine patients improved more on bromocriptine, 11 improved more on lisuride, and 5 improved equally on both drugs. Diurnal oscillations improved more on lisuride than on bromocriptine. The number of hours "on" increased by 33% on bromocriptine, and by 128%. Eleven patients discontinued bromocriptine because of adverse effects. Eight patients discontinued lisuride because of adverse effects. Bromocriptine and lisuride were equally effective in decreasing parkinsonian disability. Lisuride was more effective than bromocriptine in reducing diurnal oscillations. The greater efficacy of lisuride in decreasing diurnal oscillations, in patients with advanced disease, may relate to its ability, unlike bromocriptine's, to stimulate striatal dopamine receptors independently of the declining activity of the presynaptic dopamine neurons (16, 17, 25, 71).

Mesulergine and bromocriptine were compared in 18 parkinsonian patients who completed a randomized, double-blind, crossover study (36). There were no significant differences between mesulergine (mean dose, 27.4 mg/day) and bromocriptine (mean dose, 40.8 mg/day) during each agent's optimal treatment phase.

In general, the dopamine agonists, despite their structural and pharmacological differences, when used with levodopa in patients with advanced disease, result in improvement in disability in the same percentage of patients and, with the exception of lergotrile, result in the same percentage of adverse effects. However, it is noteworthy that individual patients react differently to the different agonists with some patients improving on one agonist, and not another; and some patients developing adverse effects on one agonist and not another. Moreover, when the response to one agonist decreases, another agonist may usually be substituted with good effect.

V. Mode of Action

Bromocriptine, in low doses, alone or with levodopa, is effective in patients with mild to moderate Parkinson's disease. On the other hand, in patients with advanced Parkinson's disease, the combination of bromocriptine with levodopa is more effective than either drug alone. Studies in animal models of Parkinson's disease have shown that the pharmacological response elicited by bromocriptine is, in part, dependent on the nigrostriatal dopamine activity (25). It has been suggested that bromocriptine acts as a "mixed DA agonist-antagonist," and that partial blockade of the striatal dopamine receptors may increase in the release of dopamine from the remaining nigrostriatal neurons. In light of recent findings, we would like to offer another hypothesis that could explain the partial dependency of the antiparkinsonian action of bromocriptine on dopamine neurotransmission and the enhanced effect of bromocriptine in combination with levodopa. Bromocriptine by itself does not discriminate between the low and high affinity states of the dopamine receptors. However, dopamine formed from administered levodopa will induce a conformational change of the dopamine receptor, resulting in a shift to the high affinity state and thereby allowing bromocriptine to interact with the high affinity state. Thus, the administration of levodopa may trigger a change in the dopamine receptor state which then permits bromocriptine to act more effectively.

VI. Summary

Bromocriptine is an ergopeptine derivative and dopamine agonist that predominantly stimulates the striatal D_2 non-adenyl cyclase-linked dopamine receptors. Bromocriptine, unlike other dopamine agonists, has mixed "agonist-antagonist" properties at these receptors. The striatal dopamine receptors exist in two different affinity states: a low and a high affinity state. Bromocriptine, unlike other dopamine agonists, does not differentiate between the low and the high affinity state of the D_2 receptors, and bromocriptine does not induce a conformational change in these receptors. Bromocriptine, in low doses, is effective in patients with mild to moderate Parkinson's disease, while bromocriptine in higher doses is needed in patients with advanced disease. Both in low doses and in high doses, bromocriptine combined with levodopa is usually more effective than bromocriptine alone.

The efficacy of low dose (5–30 mg/day) and high dose (31–100 mg/day) bromocriptine alone and with levodopa was examined in 27 studies encompassing 790 patients. Forty-six % of the studies were done in a double blind manner. In four studies of 79 patients, low dose bromocriptine (16 mg/day) without levodopa resulted in improvement in 58% of the patients. Only 9% of the patients experienced adverse effects. Most of the patients (63%) and mild or moderate Parkinson disease. In seven studies of 143 patients, high dose bromocriptine (56 mg/day) without levodopa resulted in improvement in 62% of patients, but with 27% having adverse effects. Most of these patients (77%) had mild or moderate disease. Diurnal oscillations in performance, the "wearing off" or "on-off" effect, were not seen during treatment with bromocriptine alone. In nine studies of 201 patients, low dose bromocriptine (23 mg/day) and levodopa resulted in improvement in 71% of patients with 26% having adverse effects. Most of these patients (66%) had advanced disease, and many had diurnal oscillations in performance. In seven studies of 367 patients, high dose bromocriptine (48 mg/day) and levodopa resulted in improvement in 58% with 37% having adverse effects. Most of these patients (85%) had advanced disease.

The increased effectiveness of bromocriptine in combination with levodopa may be explained as follows. Bromocriptine by itself does not discriminate between the low and the high affinity states of the dopamine receptors. However, the dopamine that is formed from the administered levodopa will induce a conformational change in the dopamine receptor, resulting in a shift from the low to the high affinity state thus allowing bromocriptine to interact with the high affinity state, a change which results in bromocriptine being a more effective antiparkinson agent.

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