Long-term treatment of Parkinson's disease with bromocriptine

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SUMMARY Bromocriptine (15–75 mg per day) alone or with L-dopa was studied during five to 29 months on 44 patients with Parkinson's disease. Used as sole therapeutic agent, it was found excellent in 12 patients who had never received regular L-dopa treatment either because it was never attempted or because of intolerance from the outset. Its anti-Parkinsonism activity was comparable with L-dopa. The gain was stable in the long term until this report. The side effects of L-dopa were not seen after bromocriptine. In cases where L-dopa had ceased to be active, bromocriptine produced a further improvement if mental deterioration was not associated. In very advanced forms of Parkinson's disease with associated dementia, bromocriptine did not produce durable results. Bromocriptine did not improve the "on-off" effects but reduced a number of the side effects of L-dopa, in particular cardiac, painful contractions, and dyskinesia without "on-off" effects.

The use of L-dopa in the treatment of Parkinsonism represents a great advance but we are becoming increasingly aware of the problems involved with its long-term use—side effects, abnormal involuntary movements, diurnal oscillations in performance ("on-off" effects), and loss of therapeutic efficiency after several years' treatment. Therefore, other substances are being sought to replace or to be used in conjunction with L-dopa. It is for these reasons that dopaminergic agonists have been synthesised: apomorphine, piribedil, lergotril, N-propyl-aporphine and, more recently, bromocriptine (CB 154 Sandoz; Parlodel).

First used for its inhibitory properties on prolactin secretion, bromocriptine also stimulates the postsynaptic (Corrodi *et al.*, 1973) and presynaptic (Snider *et al.*, 1976) central dopaminergic receptors which renders it suitable for the treatment of Parkinson's disease. Bromocriptine also seems to have a stimulating action on the serotonergic receptors (Corrodi *et al.*, 1975; Snider *et al.*, 1976).

Since the first clinical trials done by Calne and co-workers (1974a, b), bromocriptine has been the object of numerous studies. It improves the extrapyramidal symptoms (mainly tremor and rigidity) not only at low doses (20 to 30 mg) in conjunction

with L-dopa (Calne *et al.*, 1974a), but also as the sole treatment at higher doses in patients who had already received L-dopa treatment (Calne *et al.*, 1974b), who could not tolerate L-dopa from the outset, or who had never received treatment of any kind (Lees *et al.*, 1975). In high dosage (80 to 100 mg), its activity seems greater than that of L-dopa (Kartzinel *et al.*, 1976). Numerous authors have reported the favourable effects of bromocriptine in cases where L-dopa had ceased to be active (Kissel *et al.*, 1976; Lieberman *et al.*, 1976a, b; Castaigne *et al.*, 1977; Gron, 1977; Kristensen and Hansen, 1977). Its use appears to be of lesser interest when L-dopa induces "on-off" effects (Frattola *et al.*, 1976; Kartzinel *et al.*, 1976; Petit and Destee, 1977), only bringing about a lowering of their frequency and intensity. Finally, Agnoli *et al.* (1976), Lieberman *et al.* (1976a), and Gautier and Durand (1977) obtained results that improved as the disease progressed. This observation was not confirmed by Parkes *et al.* (1976).

Patients and methods

The study was carried out on 44 subjects (22 men and 22 women aged from 43 to 80 years) with Parkinson's disease (43 idiopathic, one post-encephalitic). The characteristics of the patients are given in Table 1.

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Table 1 Summary of characteristics of patients studied

Age of patients	Duration of disease	Neurological staging (Hoehn and Yahr, 1967)
40 to 50 years— 4 cases	Less than 5 years—10 cases	Stage 2—10 cases
50 to 60 years—11 cases	Between 5 and 10 years—19 cases	Stage 3—23 cases
60 to 70 years—22 cases	Between 10 and 15 years—9 cases	Stage 4— 9 cases
70 to 80 years— 7 cases	More than 15 years—6 cases	

Bromocriptine was prescribed (in tablet form at 2.5 mg per tablet) at 5 mg the first day which was increased by 5 mg every three days. Above a dose of 5 mg, increases were made by daily steps of 2.5 mg until maximum dosage which increased throughout the trial. At the beginning of the study, the maximum dose was fixed at 30 mg, then because of the satisfactory tolerance observed and of data being published, we used higher doses without exceeding 75 mg per day.

Bromocriptine was used as the only treatment whenever possible. In patients who had never received L-dopa treatment, bromocriptine was used alone. In cases where previous treatment had involved the use of L-dopa, with or without inhibitor, substitution was always tried. When the effect of bromocriptine was insufficient, L-dopa was added in moderation until the desired effect was reached.

Each patient was followed by at least two doctors familiar with the therapy being used. The degree of akinesia, rigidity, and tremor and also the functional performance were evaluated, using a staging scale with four increasing levels (0, 1, 2, and 3), before bromocriptine treatment, and during each consultation—that is, every month for three months—then every other month for nine months, and every six months thereafter. At each of these examinations, the main biological constants (blood and urinary) were measured, and an electroencephalogram recorded.

The results were judged using our staging scale: *excellent*—if, regardless of the initial seriousness of the clinical symptoms, the score returned to zero; *good*—if the improvement showed a two-point change without disappearance of clinical signs; *average*—for a one point improvement; *mediocre*—for absence of objective change but with a subjective improvement; *useful*—for a therapeutic value equivalent to that of L-dopa but with reduced side effects; *failure*—corresponding to either intolerance or to ineffectiveness of the drug.

The experiment was begun in October 1975. The study lasted for 5–29 months—that is, six cases of

5–10 months, nine cases of 10–15 months, six cases of 15–20 months, and 13 cases of 20–29 months. All the patients were seen at the end of March 1978. Two patients died of unrelated causes in the third and fifteenth months.

Results

The results are separated into four groups: group 1 included 12 patients who had never received regular L-dopa treatment, either because it was never attempted or because of intolerance from the outset—they are described as non-dopa patients; group 2 was comprised of 18 patients who had shown themselves incompatible with long-term therapy with L-dopa; group 3 included 11 patients with “on-off” effects after long-term treatment with L-dopa; and group 4 contained three patients in whom all anti-Parkinsonism treatment had ceased to be effective.

NON-DOPA PATIENTS

This group was made up of 12 patients (four men and eight women, one of whom had post-encephalitic Parkinson's disease) who had never received L-dopa treatment for any length of time. Six of the patients had never been treated with L-dopa. The six others were intolerant to L-dopa from the outset because of various complications: cardiovascular (one case), digestive (two cases), acute headache (one case), dizziness (one case), attacks of generalised contractions (one case).

The results are shown in Table 2.

We obtained six excellent results using bromocriptine doses of between 20 and 75 mg. These six patients continued their long-term bromocriptine monotherapy without the need to add other treatment. The result is stable and, until the time of reporting, the treatment is still effective. In four cases (6, 7, 28, and 40) the persistence of tremor made the addition of anticholinergics necessary. The levels of bromocriptine were kept moderate (25 to 30 mg) since these were the first patients to be treated, and it was thought best not to raise the dose too high.

Table 2 Summary of results in patients not receiving L-dopa

Reason for trying bromocriptine	Case	Age (yr)	Sex	Duration of illness	Stage*	Dose of bromocriptine (mg)	Results	Later associations	Length of study (months)	Side effects
Never treated by L-dopa	8	66	F	2	3	30	Mediocre	L-dopa (375 mg)		Oedema of the lower limbs + digestive
	26	52	M	4	3	37.5	Excellent	None	3†	None
	27	67	F	3	3	75	Excellent	None	20	Digestive
	28	73	F	3	3	25	Average	Antichol**	20	Slight confusion
	29	67	F	7	4	20	Excellent	None	23	None
	40	74	F	6	2	30	Good	Antichol.	5	None
Intolerant to L-dopa from the outset	5	66	M	5	2	30	Excellent	None	24	Digestive + insomnia
	6	62	F	5	2	30	Good	Antichol.	13	Digestive
	7	80	M	10	3	30	Good	Antichol.	15†	
	10	65	M	1.5	2	25	Failure	None		None
	20	71	F	5	3	30	Excellent	Antichol.	22	Palpitations
	41	69	F	40	4	50	Excellent	Antichol. Amantadine	8	None

*Stage determined using the system of Hoehn and Yahr (1967).

**Antichol = anticholinergics.

†Died during treatment (unrelated illness).

It was with this group that we were able to see the action of this compound on the Parkinsonism symptoms. Using our staging scale, we noticed that akinesia and hypertonia were most favourably affected (+53.5%) and tremor to a lesser degree (+32%). The functional performance was improved by more than 50% on average (Figure).

In two cases (8 and 10), the use of low doses of bromocriptine (25 and 30 mg) did not bring about a satisfactory control of extrapyramidal symptoms. In one of them (10), bromocriptine treatment was stopped while in the other patient

(8) L-dopa was added (375 mg daily). At the time of this experiment, we never exceeded 25 to 30 mg of bromocriptine per day. The treatment was not continued at higher doses. In the light of present experience, the question could be asked if higher doses would have brought about a more favourable response.

These results are comparable with those obtained in similar populations by Lees *et al.* (1975) (11 patients) and Parkes *et al.* (1976) (10 patients). These authors had few failures—for Lees, two cases, one of whom had Shy-Drager syndrome, and none for Parkes. In their experiments, the average dose was 40 mg which is slightly higher than the one we used. We were unable to find a correlation between the effectiveness of bromocriptine and the degree or duration of illness. Parkes *et al.* (1976), however, state that they obtained better results with less severe forms, and Lieberman *et al.* (1976a) observed greater effectiveness of bromocriptine on more recently contracted conditions. Bromocriptine was effective for long-term treatment in the six patients treated over a year (and up to 24 months). None of these patients ever showed any abnormal movements or "on-off" effects.

Figure Main symptoms and functional performance in 12 non-dopa patients.

PATIENTS INCOMPATIBLE WITH L-DOPA

This group comprised 18 patients who were prescribed bromocriptine after having received L-dopa treatment over a long period (Table 3), either because of lack of effectiveness, drop in efficiency after three to six years (four cases), non-effectiveness of L-dopa given alone (4 g per day) (one case), insufficient action of L-dopa (600 mg daily (one case), or because of side effects of L-dopa, such as acute confusion (two cases), digestive disorders (one case), tachycardia and

Table 3 Summary of results in patients with L-dopa side effects

Reason for using bromocriptine	Case	Age (yr)	Sex	Duration of illness (yr)	Length of L-dopa + IDD† treatment (yr)	Stage*	Dose of bromocriptine (mg)	Results	Subsequent decrease in L-dopa	Length of study (months)	Side effects
Exhaustion of L-dopa action	3	60	M	15	3	2	30	Excellent	Stop	21	None
	14	70	M	5	6	3	30	Excellent but transitory (8 months)	Stop then 600 mg	20	None
	30	70	M	10	4	3	62.5	Good	25%	14	Dizziness + orthostatic hypotension
	32	65	F	15	4	3	40	Failure			Nausea-vomiting: stop treatment
Ineffectiveness of L-dopa	39	71	M	10		4	30	Average	Stop	18	None
Insufficient L-dopa action	42	50	F	3		3	30	Average	12%	11	None
L-dopa side effects											
Confusion	34	71	F	22	2	4	15	Good	Stop		None
	35	74	F	4	3	4	50	Failure	—		Asthenia
Digestive	31	55	F	2	3	3	50	Failure	—		Inconvenient dyskinesia: stop treatment
Cardiac	11	62	M	3	5	3	25	Good	33%	21	Hypersomnia
	4	57	F	20	4	3	30	Mediocre	60%	29	0
	16	57	M	1.5	5	2	22.5	Good	Stop	22	Slight digestive disorders
Dyskinesia moderate	2	43	F	6	6	3	35	Good	50%	23	None
	12	54	F	10	6	3	40	Excellent	Stop	22	None
	19	53	F	3	5	2	40	Excellent	Stop	15	None
intense	1	56	M	17	5	4	30	Mediocre	50%		None
	22	50	F	5	5	3	30	Excellent	50%		None
	24	54	M	10	6	3	70	Good	66%		Orthostatic hypotension. Increased libido

*Stage determined using the system of Hoehn and Yahr (1967).

†IDD = Dopa-decarboxylase inhibitors.

palpitations (one case), painful contractions of the lower limbs (two cases), or serious dyskinesia without "on-off" effects (six cases). When bromocriptine treatment was started, L-dopa was discontinued whenever possible.

A summary of the results is given in Table 3.

In the subgroups who showed loss in efficiency the one "failure" (case 32) was caused by digestive intolerance with 40 mg of bromocriptine. There were two "excellent" results after stopping L-dopa treatment, bromocriptine alone being very effective for several months. One of the cases (3) showed further improvement which is still maintained after more than 21 months with the same quality. In the other (14), the improvement was only transitory since after eight months the effect of bromocriptine was insufficient at 30 mg, and it became necessary to add L-dopa (600 mg).

The results obtained in the subgroups showing side effects were four "good" results—cardiac disorders (case 11), painful muscle contractions (case 16), acute confusion (case 34) caused by L-dopa.

In these patients, the effectiveness of bromocriptine was equivalent to that of L-dopa and the side effects of the latter did not reappear.

There were two "failures". In one case (31) there were digestive complications (nausea, acidity, and vomiting) and in the other (35) acute confusion under L-dopa. These side effects continued under bromocriptine treatment.

The dyskinesia group consisted of six patients showing after L-dopa treatment from two months to five years (with or without inhibitors) serious dyskinesia of the choreic or ballistic type, almost constantly or for several hours a day, with neither fixed periodicity nor association with "on-off" effects. These cases of dyskinesia were not usefully improved by modifying the dose of L-dopa nor by redistributing administration during the day. In three cases, bromocriptine was used alone in substitution for L-dopa. Dyskinesia was considerably reduced. In the three other cases, 35 to 70 mg bromocriptine was not enough to stabilise the patient, and it was, therefore, necessary to add

L-dopa but at low doses. These were cases of extremely intense dyskinesia. The combination of bromocriptine in conjunction with small quantities of L-dopa brought about a food equilibrium in the patient with an excellent reduction of the frequency and intensity of dyskinesia.

In the cases studied, bromocriptine has brought about fresh therapeutic activity in patients where L-dopa had ceased to be active. It should be stressed that none of the patients presented any associated dementia. The results are similar to those of Lieberman *et al.* (1976a) who reported 10 "excellent" results in 14 patients receiving an average daily dose of 70 mg. It is possible that the benefit of bromocriptine in these cases can be explained by its direct action on the striatal post-synaptic dopaminergic receptors, and this would add weight to the hypothesis that decreased effectiveness of L-dopa is due to the destruction of the striatal neurones required to transform L-dopa into dopamine (Marsden and Parkes, 1977).

The failure of bromocriptine in the two cases where L-dopa was shown to be ineffective or insufficient (cases 39, 42) in spite of several months' trial, poses a problem that we cannot resolve. Whether it be a problem of L-dopa synthesis, of deterioration of the cholinergic or gabaminergic striatonigral pathways, a change in dopaminergic receptor, or even a different extrapyramidal illness, we have no way of proposing an answer.

In patients showing disagreeable side effects of L-dopa, bromocriptine was extremely useful in allowing the total withdrawal of L-dopa. The side effects were greatly reduced, in particular cardiac problems and muscular contractions. There is, therefore, a new therapeutic capacity that should

not be neglected in these subjects. It must be stressed that cases of dyskinesia (without "on-off" effects) showing the most successful results were the moderate forms.

In our population, the quality of the improvement is maintained in 14 of the 15 patients still under treatment. In just one case (14), a drop in the effectiveness of bromocriptine after eight months made necessary the addition of 600 mg L-dopa (with inhibitor). Lieberman *et al.* (1976a) reported four such decreases in effectiveness in a group of 10 patients after six months of treatment.

PATIENTS WITH "ON-OFF" EFFECTS

"On-off" effects are defined as the sudden appearance of impossibility of movement (the "off" effect corresponding to akinesia) followed by an equally sudden renewed possibility of movement ("on" effect) often accompanied by dyskinesia (Lieberman *et al.*, 1976a). The distribution and characteristics of the 11 patients (nine classic "on-off" cases and two "on-off" cases with shuffling) are given in Table 4.

Observation of case 13 ended after 10 months because of death from an unrelated illness. On the whole, for daily doses between 15 and 75 mg of bromocriptine, it was possible in seven cases to reduce the frequency and intensity of the on-off effects but not to make them disappear. L-dopa administration was reduced in all cases from 30 to 90% and totally stopped in one case. The three failures were caused by two types of intolerance—cardiac at 15 mg (case 18) and psychological at 40 mg (case 43). Finally, in one patient, the slight improvement brought about by bromocriptine dis-

Table 4 Summary of results in patients with "on-off" effects after long-term therapy with L-dopa

Reason for using bromocriptine	Case	Age (yr)	Sex	Duration of illness (yr)	Length of L-dopa +IDD treatment (yr)	Stage*	Dose of bromocriptine (mg)	Results	Subsequent decrease in L-dopa	Length of study (months)	Side effects
Classic on-off effects with shuffling	9	67	M	5	7	2	30	Useful	50%	16	None
	13	58	F	12	6	3	50	Transitory	66%	10†	None
	17	64	M	10	6	3	50	Good	75%	21	Slight acute confusion
	18	48	M	13	7	3	15	Failure	55%	—	Cardiac intolerance. Stop treatment
	25	69	M	9	7	3	40	Failure	Stop	—	Acute confusion. Stop treatment
	33	58	M	9	6	2	50	Good	65%	16	None
	36	66	F	6	5	3	25	Useful	50%	12	Dyskinesia
	37	52	F	6	5	2	35	Useful	50%	12	None
	40	73	F	7	4	3	32.5	Useful	90%	18	None
	43	64	M	29	8	2	75	Failure	Stop	—	Digestive
	44	62	F	6	6	2	75	Useful	30%	9	None

*Stage determined by the system of Hoehn and Yahr (1967).

†Died during treatment.

appeared after eight to nine months of treatment (case 13). Of particular interest was patient 44 who was treated with extremely low levels of bromocriptine (7.5 mg per day). Any attempt at stopping all treatment, however, was impossible since this led to the reappearance of striatal symptoms.

In these experiments, it can be seen that bromocriptine had a very moderate beneficial action on the on-off effects, inducing, at best, a decrease in their frequency and intensity. These results agree well with those found in other published reports. Where Parkes *et al.* (1976) (two patients) and Frattola *et al.* (1976) (five patients) did not notice any significant differences, Kartzinell *et al.* (1976) (nine patients), Lieberman *et al.* (1976b) (14 patients), and Kristensen and Hansen (1977) (11 patients) did observe, as in our case, a slight reduction of the qualitative characteristics of the on-off effects with higher doses (70 and 100 mg per day).

Various mechanisms have been proposed to explain the on-off effects: variations in gastrointestinal absorption of L-dopa during nyctemeresis, appearance of abnormal L-dopa metabolites such as tetrahydropapaveroline (Simon *et al.*, 1971) or of methoxylated derivatives (Lhermitte *et al.*, 1977), and finally variation in receptor sensitivity (Pycock and Marsden, 1977). The persistence of on-off effects with bromocriptine leads us to think that there is a variation in the sensitivity (or a hypersensitivity) of the striatal dopaminergic receptors which must play an important role in the physiopathology of the effects.

PATIENTS WITH ADVANCED PARKINSONISM

These three patients, aged between 62 and 68 years, had had the illness from five to 18 years, were all rated 4 on the Hoehn and Yahr (1967) scale, were no longer receiving any beneficial effects from L-dopa nor from other anti-Parkinsonism therapies, and had all shown

dementia for several months.

In all three cases, the administration of 30–32.5 mg of bromocriptine and withdrawal of L-dopa brought about only a very partial improvement that was at best transitory (three to six months). In spite of continued bromocriptine treatment, the therapeutic effect was reduced to zero after this period. In two cases, the patients died after the end of the trials (Table 5).

In this small group the substitution of L-dopa for bromocriptine was not effective for an adequate period. It should be noted, however, that the doses used (30–32.5 mg) are low compared to those used by Lieberman *et al.* (1976b) (75–100 mg) who obtained good results in two patients incapacitated while under L-dopa treatment. Castaigne *et al.* (1977) reported a case of this type where there was obvious effectiveness of bromocriptine. On the physiopathological level, the ineffectiveness of L-dopa and of bromocriptine could represent not only alterations of the neurones and of the striatal dopaminergic receptors but also the spread of lesions in the basal ganglia and the motor neurones as proposed by Marsden and Parkes (1977).

SIDE EFFECTS OF TREATMENT WITH BROMOCRIPTINE

There was a low incidence of side effects brought about by bromocriptine treatment. Out of 44 patients, four had to interrupt treatment because of inconvenient dyskinesia with 50 mg bromocriptine (case 31), cardiovascular intolerance with increased blood pressure with tachycardia and sweating with 15 mg (case 18), acute confusion with 40 mg (case 25), and digestive disorders with 40 mg (case 32) (nausea and vomiting). In 14 cases, transitory and spontaneously regressive side effects not necessitating therapeutic modifications appeared—digestive disorders (nausea, heartburn, hypersalivation) in seven cases, cardiovascular disorders in three cases (orthostatic hypotension and palpitations), psychological disorders in five cases (slight acute confusion, increased libido,

Table 5 Summary of results in three cases of very advanced Parkinsonism. The patients were rated 4 on the scale of Hoehn and Yahr (1967)

Reason for using bromocriptine	Case	Age (yr)	Sex	Duration of illness (yr)	Length of L-dopa + IDD treatment (yr)	Stage	Dose of bromocriptine (mg)	Results	Subsequent modification in L-dopa	Associated condition
Very advanced forms no longer responding to treatment	15	66	M	16	5	4	30	Transitory (3mo)	Stop	Dementia
	21	68	F	8	7	4	30	Transitory (3mo)	Stop	Dementia
	23	62	M	5	7	4	32.5	Transitory (10 mo)	Stop	Dementia

hypersomnia, and insomnia), intense asthenia in one case, and intense dyskinesia in one case when using L-dopa. The on-off effects persisted when the bromocriptine L-dopa association was used. These effects, resembling those observed with L-dopa, are in agreement with those reported by Calne *et al.* (1974a, b), Agnoli *et al.* (1976), Kartzinel *et al.* (1976), Parkes *et al.* (1976) and Kristensen and Hansen (1977). We did not, however, observe, as did Gautier and Durand (1977) any cutaneous disorders, sensations of ocular discomfort, or constipation. There was no effect on blood pressure. Bromocriptine administration did not induce any modifications in the biological constants of the blood or of the urine. The EEG was unchanged.

Discussion

Bromocriptine was found to be effective in 34 out of 44 cases (22 "excellent" or "good" results, and 12 "useful" or "mediocre" results). In 10 cases bromocriptine treatment failed. These results should, however, be viewed with respect to the group treated.

Bromocriptine, a dopaminergic agonist, has an effective action against Parkinson's disease in man. Used as sole therapeutic agent in 12 patients, it was found to be effective in 10. In our series of experiments, bromocriptine was seen to be active on akinesia and rigidity (an average improvement of 53.5%) and to a lesser degree on tremor (+32%). The functional capacity of the patients was improved by an average of 55%. The best results were obtained with the highest doses of bromocriptine. The two failures were observed at the start of the trials in patients who only received low doses, and the possibility that higher doses would have been effective cannot be excluded. In our opinion, bromocriptine, at high enough doses, is currently the best anti-Parkinsonism treatment for patients intolerant to L-dopa since it is more effective than the anticholinergics or amantadine. What is more, it would appear to be useful as a first treatment before L-dopa administration. These results confirm those of Lees *et al.* (1975) and Parkes *et al.* (1976). We have not hitherto observed any falling-off of effect, variations in performance, or abnormal movements in the population studied (some of whom have been under observation for two years). It is, therefore, possible that the improvement is durable. If this is so, this treatment would then show considerable advantages over other dopaminergic agonists and over L-dopa. Tolerance was satisfactory; there was a minimum of accidents and side effects.

Bromocriptine reduced a number of the inconveniences of L-dopa—improvement of certain side effects (in particular cardiac and painful contractions), reduction of dyskinesia, and renewed response in patients where L-dopa no longer had any useful action but before the onset of intellectual deterioration. Bromocriptine would, therefore, seem to be particularly useful when the effect of L-dopa starts to diminish before the appearance of physical and intellectual decay. In very advanced stages of the illness, however, (psychological and physical decay with ineffectiveness of L-dopa) bromocriptine does not give very useful results.

In the very difficult problem of the treatment of Parkinson's disease with on-off effects, with or without a shuffling walk, bromocriptine reduced their frequency and their intensity and allowed the dose of L-dopa to be reduced by 30–90%. It was, however, no more than an attenuation and the use of this drug does not provide a solution to this problem.

Pharmacologically, the advantages of the dopaminergic agonist bromocriptine over L-dopa indicates two important mechanisms: (1) its action on the postsynaptic dopaminergic receptor, and (2) a saving in the intraneuronal consumption of dopa-decarboxylase. For these reasons bromocriptine could be useful as the first treatment in Parkinson's disease. As the illness develops and the transformation of exogenous L-dopa to dopamine striatal neurones becomes insufficient, bromocriptine can take over by acting at another pole of the synaptic complex. At a more advanced stage, it may be postulated that L-dopa and bromocriptine are no longer effective because of the degeneration of the neurones and the dopaminergic receptors.

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