Optimum Symptomatic Control of Parkinson's Disease with Dopaminergic Therapy

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ABSTRACT: This paper presents a review of the literature on the therapeutic action and the side effects of the two main dopaminergic agents: L-DOPA/decarboxylase inhibitor (L-DOPA/DI) and bromocriptine (Parlodel ®) used either as monotherapy or in combination in patients with Parkinson's disease. The combination of L-DOPA/DI and bromocriptine gives the best therapeutic efficacy (49% improvement) in the total score (bradykinesia, rigidity and tremor). However, treatment by monotherapy or combination gives the same pattern of activity: greatest improvement in tremor, followed by rigidity and bradykinesia. Improvement observed in the short term is not sustained over longer periods of time for monotherapy with either drug. The short-term side effects are similar for each treatment, whereas long-term complications (dyskinesia, end-of-dose deterioration and on-off phenomenon) appear only when levodopa is used, alone (high incidence) or in combination with bromocriptine (low incidence). The overall optimum treatment is obtained with a combination of L-DOPA/DI and bromocriptine.

RÉSUMÉ: Cet article revoit la littérature sur l'effet thérapeutique et le profil des effets secondaires des deux principaux agents dopaminergiques : la L-DOPA associée à un inhibiteur de la décarboxylase (L-DOPA/DI) et la bromocriptine (Parlodel ®) utilisés soit comme monothérapie ou en association chez des patients atteints de la maladie de Parkinson. L'association de la L-DOPA/DI avec la bromocriptine produit la meilleure efficacité thérapeutique (49% d'amélioration) au niveau du score total (bradykinésie, rigidité et tremblement). Ces traitements présentent le même profil d'activité, qu'ils soient administrés en monothérapie ou en association : la plus grande amélioration est notée au niveau du tremblement suivi de la rigidité et de la bradykinésie. Toutefois, l'amélioration observée à court terme diminue en fonction du temps avec l'un ou l'autre agent administré en monothérapie. Le profil des effets secondaires à court terme est similaire pour les deux traitements, alors que les complications à long terme (dyskinésies, détérioration de fin de dose et phénomène "on-off") n'apparaissent qu'en présence de lévodopa, qu'elle soit utilisée seule (incidence élevée) ou en association avec la bromocriptine (incidence faible). L'association de la L-DOPA/DI et la bromocriptine représente le traitement optimal.

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The most significant factor contributing to the control of parkinsonian symptomatology has been the establishment of a rational pharmacological basis for the development of new agents.[1,2] Introduced in 1961,[3,4] the dopamine replacement approach, with the use of levodopa combined with a peripheral decarboxylase inhibitor, has significantly reduced the disability and increased the survival of affected patients.[5,6,7]

However, loss of efficacy and appearance of adverse reactions, including dyskinesia, "end-of-dose" deterioration, and the "on-off" phenomenon, are observed with long-term levodopa therapy.[8,9] The pathogenesis of these adverse reactions is unknown, but they were not reported prior to the introduction of levodopa as treatment for Parkinson's disease. A new therapeutic approach with drugs directly stimulating the brain dopamine receptors was introduced with the advent of the dopamine agonists. Their duration of action is prolonged, their plasma and striatal levels are more stable, and the formation of potentially toxic metabolites of levodopa does not occur.[10,11,12] Bromocriptine is the prototype clinically useful dopamine agonist, and considerable experience has accrued since it was first used to treat Parkinson's disease.[13] Since then, several other dopamine agonists have been tested clinically (lisuride and pergolide;[14,15,16,17] CU 32-085[14,18]) and others are currently in research development.

To assess the optimum strategy for treating Parkinson's disease with dopaminergic therapy, this paper reviews the literature on the use of levodopa and bromocriptine either as monotherapy or in combination, with emphasis on their action on the three cardinal signs.

Therapeutic Activity

Short Term

The studies included in this review are those outlining a well defined population of patients who in most cases had not been

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previously treated with either levodopa or dopamine agonists. These studies had to give a definite percentage change from baseline for each cardinal sign or provide the data allowing its calculation. Treatment duration had to be comparable from one study to the other: approximately three to six months follow-up (for the short term evaluation) which is considered as the "peak" effect period of each treatment. Most studies rated the anti-parkinsonian activity using the Columbia scale. This makes pooling of data an acceptable tool for global evaluation.[19]

Table 1 outlines the authors and the characteristics of their patient populations for the studies used to assess the therapeutic activity of bromocriptine utilized as the initial drug.

Results (percentage change from baseline) from a total of 140 patients with idiopathic Parkinson's disease were pooled for assessing the antiparkinsonian effect of bromocriptine. The mean daily dose of bromocriptine was 19 mg (range 10 to 34). The mean age of the patients was 63. The mean duration of the disease was 3.1 years and the mean stage was 2.9 on the Hoehn and Yahr scale.[20]

Table 1: Characteristics of Patients Included for Calculation of the Improvement with Bromocriptine (Monotherapy)

	n	Age (years)	Duration of Illness (years)	Severity (stage)	Daily Dose (mg)
Devathasan, et al., 1984[49]	15	55	2.8	4.5	10
Grimes and Delgado, 1985[50]	20	63	2.9	2.2	13
Olanow and Alberts, 1986[48]	9	61	2.1	3.0	15
Rascol, et al., 1979[33]	12	68	4.6	2.8	34
Rinne and Marttila, 1978[51]	24	64	3.8	3.0	30
Riopelle, et al., 1987[52]	38	67	1.5	2.7	26
Staal-Schreinemachers, et al., 1986[53]	10	59	2.0	1.9	15
Teychenne, et al., 1986[54]	12	66	4.8	2.7	12
MEAN		63	3.1	2.9	19

Duration of treatment: 2 to 12 months (mean: 5.5 months)

Total number of patients: 140

All authors used the Columbia Scale except Rascol, et al. and Staal-Schreinemachers, et al.

Table 2 gives the population parameters for the studies which illustrate the therapeutic activity of L-DOPA with a decarboxylase inhibitor (L-DOPA/DI) as single agent in a total of 74 parkinsonians. The mean age was 62 years. The mean duration of the disease was 3.5 years and the mean stage was 2.6 (Hoehn and Yahr scale). The mean daily dose was 563 mg (range: 263 to 800).

Characteristics of the 86 patients used to assess the therapeutic effect of late combination of L-DOPA (with or without decarboxylase inhibitor) with bromocriptine are shown in Table 3. Patients mean age was 63. The mean duration of the disease was 9.6 years and the mean stage 3.1 (Hoehn and Yahr scale). They received a mean daily dose of 2498 mg of levodopa or 652 mg of L-DOPA/carbidopa for combination with 43 mg of bromocriptine. It is important to note that the duration (9.6 years) and severity (3.1) of the disease were much higher for the combination group than in the two other treatment groups in which patients had had the disease for significantly less time.

Figure 1 illustrates, for each of the three therapeutic strategies, the weighted mean change (%) from baseline observed during the treatment and calculated by pooling the results for bradykinesia, rigidity, tremor and the total of the three cardinal signs from the above mentioned studies.

The mean improvement in the total score (bradykinesia + rigidity + tremor) is 41%, 41% and 49% with bromocriptine, L-DOPA/DI and the combination of both, respectively. The

Table 2: Characteristics of Patients Included for Calculation of the Improvement with L-DOPA/DI (Monotherapy)

	n	Age (years)	Duration of Illness (years)	Severity (stage)	Daily Dose (mg)
Caraceni, et al., 1977[55]	14	60	5.4	2.5	625
Rinne and Marttila, 1978[51]	21	64	3.8	3.0	800
Riopelle, et al., 1987[52]	39	62	1.3	2.3	263
MEAN		62	3.5	2.6	563

Duration of treatment: 3 to 6 months

Total number of patients: 74

Table 3: Characteristics of Patients Included for Calculation of the Improvement with L-DOPA/DI + Bromocriptine (Combination)

	n	Age (years)	Duration of Illness (years)	Severity (stage)	Daily Dose (mg)
Jansen, 1978[56]	10	59	8.8	3.8	L-Dopa: 2900 Bromocriptine: 70
Jellinger, 1982[57]	22	65	7.7	NA	L-Dopa/Carbidopa: 493 Bromocriptine: 40
Kartzinel, et al., 1976[10]	20	61	11.6	NA	L-Dopa: 1700 or L-Dopa/Carbidopa: 600 Bromocriptine: 34
Lieberman, et al., 1976[41]	14	64	9.6	2.6	L-Dopa/Carbidopa: 950 Bromocriptine: 57
Teychenne, et al., 1986[54]	20	67	10.1	3.0	L-Dopa: 2893 or L-Dopa/Carbidopa: 565 Bromocriptine: 11
MEAN		63	9.6	3.1	L-Dopa: 2498 or L-Dopa/Carbidopa: 652 Bromocriptine: 43

Duration of treatment: 5 to 7.5 months

Total number of patients: 86

All authors used the Columbia Scale except Jansen and Lieberman, et al.

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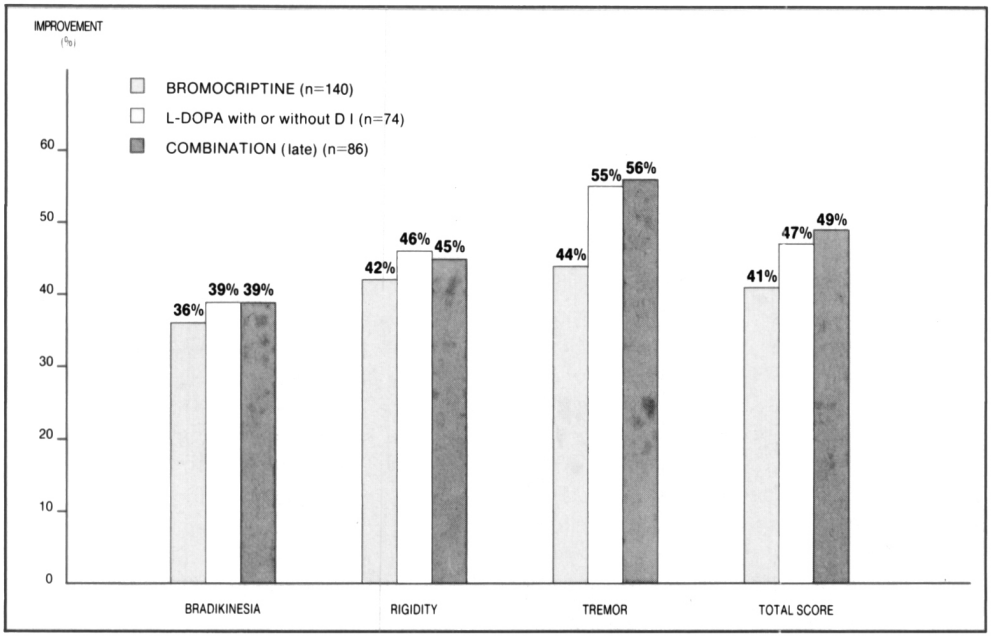

Figure 1 — Weighted mean improvement (%) calculated from studies outlined in Tables 1, 2 and 3 for each treatment.

greatest improvement is observed in tremor (44%, 55% and 56%) followed by rigidity (42%, 46% and 45%) and bradykinesia (36%, 39% and 39%). The three treatments exhibit a similar pattern of activity in relation to each parkinsonian sign indicating no specificity of action on the three signs for any of the treatments used. It is therefore difficult to draw any conclusion linking the profile of therapeutic activity of drugs within and between different classes with their mechanism of action. In fact, Rinne[14] found no definite relationship between the therapeutic profile of several different dopamine agonists and their specificity of action on the receptors.

A combination of levodopa with bromocriptine produces more improvement in the total score than levodopa or bromocriptine alone. However, the improvement observed in each clinical sign is similar for both the combination and levodopa alone, with bromocriptine producing slightly less improvement. Taking into account that the combination group was more severely disabled and had had the disease for a longer period of time (three times longer than the two other treatment groups), the data outlined in Figure 1 might represent an underevaluation of the efficacy of the combination therapy. The combination treatment group consisted of patients who were experiencing several difficulties on levodopa therapy before bromocriptine was added (late combination) and thus had more advanced and severe Parkinson's disease. The only "early" combination study published in the literature[21] could not be included in this group since no data are given for the short term efficacy (six months).

Long Term

The percentage of patients treated with L-DOPA/DI or bromocriptine as monotherapy who can maintain an acceptable improvement of the parkinsonian symptoms decreases with time (Figure 2). It is generally appreciated that basal and treated Parkinson's disease disability progresses with time[22] and that this factor accounts for some and perhaps all of the loss of effectiveness of antiparkinsonian treatment. However, Fahn and Bressman[23] suggest that prolonged treatment with levodopa could also be in part responsible for this unfavorable development by inducing hypersensitivity of the receptors.[24] Although it is well recognized that the initial benefit from levodopa therapy lessens with time,[9,25,26,27,28] there is some controversy regarding the long term loss of efficacy of bromocriptine. Lees and coworkers,[29,30] Lieberman et al.[31] and Goetz[32] reported loss of effectiveness of bromocriptine with time whereas Rascol[33] followed patients for up to six years and demonstrated a sustained benefit of the treatment.

This long term decreased efficacy might be explained by a possible post-synaptic neuronal deterioration as Parkinson's disease progresses or by a progressive decrease in the endogenous dopamine pool which, according to the postulate of

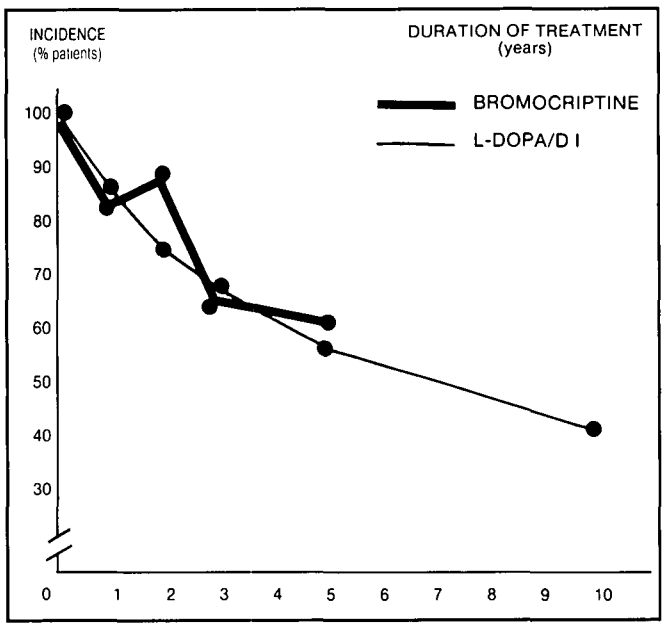

Figure 2 — Incidence (%) of patients exhibiting sustained benefits in long-term therapy.
BROMOCRIPTINE: from Lees and Stern,[24,30]
L-DOPA/DI: from Barbeau,[28]; Hunter, et al.,[26]; Sweet, et al.[25]

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Goldstein, et al.[34] would be required to enhance the D2 agonistic activity of bromocriptine (via stimulation of D1 receptors by dopamine).

Thus, the unsustained therapeutic activity observed in more than 20% of patients after one year of monotherapy with levodopa or bromocriptine suggests that, in order to maintain satisfactory benefit, treatment should include a combination of both L-DOPA/DI and bromocriptine. Long term sustained effectiveness of combination therapy has been reported by Caraceni.[35]

Adverse Effects

Short Term

Table 4 outlines the side effects encountered most frequently during the first year of treatment with either L-DOPA/DI or bromocriptine, irrespective of the dosage. Data were obtained from published reports in which the incidence of side effects was given or could be calculated.

The reported side effects are dose related and are therefore reduced with lower dosages. The incidence and type of side effects are similar with both treatments[24,36] except for dyskinesia which appears in almost half of the patients treated with levodopa at a daily dosage of 500 to 950 mg.[7,28,37,38,39] Only one case of dyskinesia was reported in short term treatment with bromocriptine.[30] Gastric disturbances including nausea and vomiting are reported in 30% of patients treated with L-DOPA/DI and 42% with bromocriptine. Domperidone, which blocks peripheral dopamine receptors, has been used successfully to decrease nausea and vomiting in patients treated with bromocriptine[40] and can also be used with levodopa.

Table 4: Most Frequent Side Effects Encountered in Short-term Therapy

	L-DOPA/DI	Bromocriptine
Dyskinesia	44%	1 case *
Gastric Disturbances	30%	42%
Confusion	14%	6%
Sedation	10%	15%
Postural Hypotension	9%	12%
Hallucinations	5%	12%

Incidence (% patients) calculated from the literature (≤12 months of treatment)

* Lees and Stern, 1981[30]

Table 5: Long Term Complications

	L-DOPA/DI		Bromocriptine		Combination	
	≤700mg (0 to 3 years)	≥700mg (up to 10 years)	≤30mg (0 to 3 years)	≥30mg (0 to 3 years)	≤700mg ≤30mg (0 to 3 years)	≥700mg ≥30mg (6 months)
Dyskinesia	27%	63%	2 cases	1 case	15%	50%**
End-of-Dose Deterioration	22%	47%	0%	0%	4%	NA
On-off Phenomenon	13%	65%	0%	0%	8%	57%

Incidence (% patients; 0 to 12 years treatment) calculated from the literature (Barbeau[28]; Caraceni, et al.[55]; Kartzinel, et al.[10]; Lieberman, et al.[41]; Lees and Stern[30]; Markham and Diamond[39]; Rajput, et al.[38]; Rinne[21]; Sweet and McDowell[58]; Teychenne[59]).

* From Rinne[21] (early combination).

** From Lieberman, et al.[41] (late combination in moderately to markedly affected patients).

Other adverse effects include mental disturbances (confusion and hallucinations) which occur in approximately 19% of patients treated with either L-DOPA/DI or bromocriptine. Sedation and postural hypotension are observed in 9% to 15% of patients.

Long Term

The reported incidence of adverse reactions during long term treatment with L-DOPA/DI or bromocriptine either as monotherapy or in combination is outlined in Table 5. Dyskinesia occurred in 27% to 63% of patients on L-DOPA/DI and in 15% to 50% of patients treated with a combination of L-DOPA/DI and bromocriptine. Concerning patients receiving bromocriptine as monotherapy, there have been only three cases of dyskinesia reported.[21,41] Dyskinesia has been related to the formation of free radicals generated from levodopa metabolism and to stimulation of D1 receptors.[42,43] Since bromocriptine has D2 agonistic activity and D1 antagonistic action, it might not be expected to produce dyskinesia.

End-of-dose deterioration occurs in 22% to 47% of patients receiving L-DOPA/DI and in 4% of patients receiving bromocriptine.[21] Neither end-of-dose deterioration nor on-off phenomenon are reported in patients treated with bromocriptine alone, whereas 13% to 65% of patients on L-DOPA/DI, and 8% to 57% of patients on combination therapy do exhibit on-off phenomenon.

Thus, there is a clear difference in the occurrence of long term complications between treatments involving the use of levodopa and of bromocriptine as single therapy. The combination of both agents produces an intermediate level of complications. Adverse long term complications are the major problems encountered with levodopa treatment and therefore limit its usefulness in Parkinson's disease.

Summary and Conclusions

Figure 3 summarizes arbitrarily the results reported in the literature and provides an overall picture of the therapeutic activity and the occurrence of adverse reactions. From the efficacy point of view, the most effective therapy is the combination of L-DOPA/DI and bromocriptine (score: 6 (+)) followed by the use of L-DOPA/DI alone (score: 4) and bromocriptine alone (score: 3 (+)). The best adverse reaction profile is observed with bromocriptine (score: 5) followed by the combination (score: 4) and the L-DOPA/DI alone (score: 3). The overall optimum treatment combining efficacy and side effects profiles is the combination of L-DOPA/DI and bromocriptine (score: 10 (+)), which therefore appears to be the best avail-

	EFFICACY		COMPLICATIONS		TOTAL
	SHORT TERM	LONG TERM	SHORT TERM	LONG TERM	
DOPA/DI	+++	+	++	+	7
BROMOCRIPTINE	++(+)	+	++	+++	8(+)
DOPA/DI+ BROMOCRIPTINE	+++(+)	+++	++	++	10(+)

Figure 3 — Overall summary
Arbitrary rating from results calculated from the literature.

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able treatment for Parkinson's disease. However, there are several ways in which such a regimen could be initiated.

Therapy could be initiated with L-DOPA/DI, adding bromocriptine later when L-DOPA/DI begins to lose efficacy, or side effects necessitating dose reduction occur. Alternatively, one may initiate therapy with bromocriptine and add L-DOPA/DI when initial benefit starts fading. A third approach would be to initiate therapy with a combination of L-DOPA/DI and bromocriptine, adjusting the dosages in order to maintain optimal therapeutic activity and reduce the occurrence of adverse reactions. Although these three strategies are all theoretically acceptable, the problem of induction of long term complications by levodopa treatment must be taken into account. Should levodopa be delayed and should the dosage be kept low? These two very important questions have been addressed in the literature.

Lees and Stern[44] and Rajput[38] suggest keeping levodopa dosage as low as possible, but Fahn[23] observed a wearing off effect in some patients in whom the dosage of levodopa was kept low. McDonald and Sweet,[45] Fahn[23] and Rajput[38] have demonstrated that postponing the onset of levodopa therapy can delay the onset of the disabling long term problems. However, Markham[39,46] and Agid[22] bring some controversy to this by suggesting that the late-occurring fluctuations in response to levodopa therapy are due to progression of the disease rather than to the therapy. Fahn and Bressman[23] do not agree with Markham's[39,46] results, and challenge the scale which was utilized and the lack of linearity in the scores.

This objection of using low doses of levodopa can be fulfilled with either of the three combination strategies outlined above. Some researchers[12,21,47] recommend the "early combination" strategy. However, if one wishes to delay the use of levodopa, then the only strategy left will be the one suggested by Rascol[36] and Olanow,[48] accepting the possibility of slightly lesser level of initial response by initiating treatment with bromocriptine, and adding L-DOPA/DI when required to control parkinsonian symptoms with a low incidence of side effects. Further studies with current dopaminergic drugs and new therapeutic agents should bring new insights with regard to the optimum therapy to improve the quality of life of parkinsonians.

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