Initial bromocriptine did not change mortality in early, mild Parkinson disease

Lees AJ, Katzenschlager R, Head J, Ben-Shlomo Y, on behalf of the Parkinson's Disease Research Group of the United Kingdom. **Ten-year follow-up of three different initial treatments in de-novo PD. A randomized trial.** Neurology. 2001 Nov 13;57:1687-94.

QUESTION

In patients with early, mild Parkinson disease (PD), does the long-term effectiveness of levodopa alone differ from that of levodopa plus selegiline or initial bromocriptine monotherapy?

DESIGN

Randomized {allocation concealed*}†, blinded {data safety and monitoring committee}†,* controlled trial with a mean 9.2-year follow-up.

SETTING

United Kingdom.

PATIENTS

782 patients with a clinical diagnosis of PD. Exclusion criteria were failure to respond to an adequate trial of dopaminergic drugs or incapacitating cognitive impairment.

INTERVENTION

249 patients were allocated to levodopa alone, 271 to levodopa plus selegiline, and 262 to initial bromocriptine. 104 patients in the bromocriptine group were rerandomized to 1 of the other 2 treatment groups after bromocriptine was withdrawn, but all patients were analyzed in the groups to which they were initially randomized.

MAIN OUTCOME MEASURES

Mortality, disability, and adverse effects.

MAIN RESULTS

Analysis was by intention to treat. The groups did not differ for mortality (Table). At 3 years, those assigned to initial bromocriptine had worse disability scores than those assigned to levodopa alone (difference in adjusted mean Webster score 1.3, 95% CI 0.4 to 2.1). This difference was no longer statistically significant at 9 years (0.2, CI –1.5 to 1.5). At a mean of 9.2 years of follow-up, a lower incidence of dyskinesia occurred in patients initially assigned to bromocriptine than in those in the levodopa-alone group (relative risk 0.73, CI 0.57 to 0.93). However, when only moderate-to-severe dyskinesias were analyzed, this difference was no longer statistically significant. The groups did not differ for incidence of dystonia or on-off fluctuations.

CONCLUSIONS

In patients with mild, early Parkinson disease, initial treatment with bromocriptine did not reduce mortality more than levodopa. Disability scores were worse during the first 3 years of treatment with initial bromocriptine.

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*See Glossary.

†Information provided by author.

Initial bromocriptine (IB) vs levodopa alone (L) and levodopa plus selegiline (LS) in early, mild Parkinson disease at a mean 9.2 years

Outcome	Comparisons	Event rates (person-yr at risk)	Unadjusted hazard ratios (95% CI)
Mortality	IB vs L	58% (140) vs 51% (118)	1.15 (0.90 to 1.47)‡
	LS vs IB	61% (148) vs 58% (140)	1.06 (0.84 to 1.34)‡
	LS vs L	61% (148) vs 51% (118)	1.22 (0.95 to 1.55)‡

‡Not significant.

COMMENTARY

The study by Lees and colleagues shows that initiating treatment with bromocriptine or levodopa does not affect mortality rates and that patients who began treatment with levodopa had slightly better motor scores during follow-up but a higher incidence of dyskinesias. The study has methodologic limitations, the main one being that outcome assessment was not blinded to treatment allocation. Potential bias is suggested by the much higher number of deaths from cerebrovascular disease in the bromocriptine group than in the levodopa group. Dyskinesia scores are rather subjective; the distinction between dystonia and dyskinesias is sometimes difficult.

This study describes a larger number of PD patients and has a longer follow-up period than do other studies that compare levodopa and dopamine agonists. These results are in keeping with previous open-label studies on bromocriptine (1) and with more recent controlled studies of new dopamine agonists (2–4). The withdrawal rate in the dopamine agonist group in this study is higher than that reported in the controlled trials of cabergoline (16% at 3 years) and ropinirole (27% at 5 years). In this report, only 3% of patients receiving bromocriptine remained on initial treatment after 10 years.

Remarkably, no clinical differences other than potency have emerged among the various dopamine agonists. Therefore, the question arises on the possible generalization of long-term data on bromocriptine. A recently published meta-analysis acknowledged that determining how to start treatment would depend on the relative effect of improving motor disability compared with lessening motor complications (5). The present study raises further awareness and concern about the pros and cons of starting PD therapy with a dopamine agonist rather than with levodopa. The results are more pro-levodopa than those published in recent series, which may lead clinicians to consider low doses of levodopa as an alternative initial treatment in PD patients.

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