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What is the best initial treatment in Parkinson's disease?

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TITLE Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial

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SUMMARY

The PD MED study[1] was a large open-label pragmatic randomised trial that aimed to determine which initial treatment is best in Parkinson's disease (PD) for long-term control of motor symptoms and quality of life.

A total of 1620 recently diagnosed PD patients were assigned to one of three starting regimens: levodopa (n=528), monoamine oxidase B inhibitors (MAOBI; n=460) or dopamine agonist (n=632) (the latter two referred to as 'dopamine-sparing' regimens) and followed for a median of three years and up to seven. Patients and investigators were not masked to group allocation. Primary outcome measures were the mobility subscale of the Parkinson's disease Questionnaire (PDQ-39) and quality-adjusted life years (QALYs).

Over the course of the trial, medications for motor symptoms were added as needed: by year 2, 64% of patients in the MAOBI group and 40% in the dopamine agonist group required an additional drug class. By year 7, total levodopa equivalent doses were highest in the dopamine agonist group and lowest in the levodopa group.

The main result was that there were no significant differences between groups at each of the time points in the primary outcome measures: mobility and quality of life scores were not significantly different whether treatment began with levodopa, a dopamine agonist, or a MAOBI. Furthermore, the rate of decline in mobility and quality of life over the course of follow-up was no different between groups. Interestingly, when the scores were averaged across all years, there was a small advantage of levodopa. This advantage, however, was small: the difference in patient-rated mobility – 1.8 points – was smaller than the 3.2-point minimally important difference for the scale, and smaller still than the study's pre-determined 6-point minimum clinically meaningful difference. The advantage of levodopa over dopamine-sparing therapies remained when the analysis was limited to patients less than 70 years old.

Patients who were initially assigned levodopa had higher overall rates of dyskinesias (hazard ratio 1.52, 95% CI 1.16–2.0) but by the year 7 follow-up, the proportion with dyskinesias was similar (36% for the levodopa arm and 33% for dopamine-sparing groups), which likely reflects the fact that levodopa doses, by year 7, were similar across groups (526 and 489 mg/day in the agonist and MAOBI groups, respectively, compared to 531 mg/day in the levodopa group). The risk of developing motor fluctuations was no different across groups. MAOBIs were associated with slightly better mobility scores and better scores on the cognition subscale of the PDQ-39, compared to dopamine agonists.

OPINION

Over the last decades, practitioners and patients alike have felt compelled to delay initiation of levodopa due to concerns, supported by multiple studies,[2] that earlier levodopa was associated with earlier dyskinesias, worse fluctuations and, therefore, worse quality of life. The results of the PD MED study indicate that this delay does not benefit patients.

The result that is most relevant to clinical decision-making is the *non-inferiority* of initial treatment with levodopa over the 7-year follow-up period, compared to dopamine-sparing strategies. Although initial therapy with levodopa was associated with a higher risk of dyskinesias, side-effect burden was lower. These two findings may have had a balancing effect on the study's primary outcome measures.

One concern is that the scales used may not have been sufficiently sensitive to capture the negative effects of dyskinesias on quality of life. For instance, the items on the mobility subscale of the PDQ-39 assess the ability to walk certain distances, get around the house, or cook, all of which could remain intact despite bothersome dyskinesias. Stratifying analyses based on the presence of dyskinesias would have addressed the possibility that the non-inferiority of levodopa was driven by better quality of life scores in non-dyskinetic patients.

Another weakness of the study, pointed out in the accompanying editorial,[3] is that it did not directly address the possibility that levodopa delay might be specifically beneficial to younger patients. Analyses were stratified according to the age cut-off of 70 years. A lower cut-off age would have been more informative because younger patients are more prone to developing dyskinesias and have a longer remaining lifespan.

Nonetheless, the take-home message is clear: levodopa should be included among first-line therapy options in newly diagnosed patients with PD. Whether additional factors, such as younger age, make one regimen more appropriate than another remains to be determined.

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