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

PD MED Collaborative Group*

Summary

Background Whether initial treatment for Parkinson’s disease should consist of levodopa, dopamine agonists, or monoamine oxidase type B inhibitors (MAOBI) is uncertain. We aimed to establish which of these three classes of drug, as initial treatment, provides the most effective long-term control of symptoms and best quality of life for people with early Parkinson’s disease.

Methods In this pragmatic, open-label randomised trial, patients newly diagnosed with Parkinson’s disease were randomly assigned (by telephone call to a central office; 1:1:1) between levodopa-sparing therapy (dopamine agonists or MAOBI) and levodopa alone. Patients and investigators were not masked to group assignment. Primary outcomes were the mobility dimension on the 39-item patient-rated Parkinson’s disease questionnaire (PDQ-39) quality-of-life scale (range 0–100 with six points defined as the minimally important difference) and cost-effectiveness. Analysis was intention to treat. This trial is registered, number ISRCTN69812316.

Findings Between Nov 9, 2000, and Dec 22, 2009, 1620 patients were assigned to study groups (528 to levodopa, 632 to dopamine agonist, 460 to MAOBI). With 3-year median follow-up, PDQ-39 mobility scores averaged 1·8 points (95% CI 0·5–3·0, p=0·005) better in patients randomly assigned to levodopa than those assigned to levodopa-sparing therapy, with no increase or attrition of benefit during 7 years’ observation. PDQ-39 mobility scores were 1·4 points (95% CI 0·0–2·9, p=0·05) better in patients allocated MAOBI than in those allocated dopamine agonists. EQ-5D utility scores averaged 0·03 (95% CI 0·01–0·05; p=0·0002) better with levodopa than with levodopa-sparing therapy; rates of dementia (hazard ratio [HR] 0·81, 95% CI 0·61–1·08, p=0·14), admissions to institutions (0·86, 0·63–1·18; p=0·4), and death (0·85, 0·69–1·06, p=0·17) were not significantly different, but the upper CIs precluded any substantial increase with levodopa compared with levodopa-sparing therapy. 179 (28%) of 632 patients allocated dopamine agonists and 104 (23%) of 460 patients allocated MAOBI discontinued allocated treatment because of side-effects compared with 11 (2%) of 528 patients allocated levodopa (p<0·0001).

Interpretation Very small but persistent benefits are shown for patient-rated mobility scores when treatment is initiated with levodopa compared with levodopa-sparing therapy. MAOBI as initial levodopa-sparing therapy was at least as effective as dopamine agonists.

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Introduction Parkinson’s disease is a common cause of disability in older people with 8000 new cases diagnosed every year in the UK, and more than 100 000 people living with the disease.12 Of the three classes of drug widely used as initial therapy, levodopa achieves somewhat better control of motor symptoms of Parkinson’s disease than do dopamine agonists and monoamine oxidase type B inhibitors (MAOBI), but abnormal involuntary movements (dyskinesias) and fluctuations in motor control develop after long-term use or high-dose treatment.14 Motor complications are seen less frequently with dopamine agonists and MAOBI than with levodopa, suggesting that longer-term symptomatic control could be better with levodopa-sparing therapy than with levodopa. However, non-motor side-effects such as nausea, hallucinations, oedema, and sleep disturbance are more frequent with dopamine agonists than with levodopa,18 and could be more important for patients and carers than are motor complications.1 Safety is another issue, with higher mortality reported with the MAOBI, selegiline, than with levodopa alone in the UKPDRG study,7 although this has not been confirmed in other studies.6 Conversely, the DATATOP study8 raised the possibility that selegiline slows functional decline. Because most previous studies included too few patients, had short follow-up, and assessed motor symptoms rather than the effect of the drugs on the patient’s self-rated overall quality of life, uncertainty remains regarding the comparative balance of risks and
benefits of initiation of treatment with these different classes of drugs for Parkinson’s disease. Costs vary substantially; the new dopamine agonists and MAOBI s cost more than do either levodopa or selegiline, and large, long-term randomised studies are needed to compare the clinical and cost-effectiveness of the different drug classes, detect any neuroprotective effects, and clarify how they should best be used in clinical practice.

We aimed to establish which class of drug results in the best patient-rated quality-of-life scores, in both early and later Parkinson’s disease. We describe the first results of the early disease randomisation, which addressed two questions: (1) does initial treatment with levodopa-sparing therapy (either a dopamine agonist or an MAOBI) delay deterioration in patient-rated quality of life compared with levodopa alone; and (2) which class of levodopa-sparing treatment is preferable (dopamine agonists or MAOBI)?

Methods

Study design and participants

For this pragmatic, open-label randomised trial (PD MED), people diagnosed with idiopathic Parkinson’s disease by movement disorder specialists using UK Brain Bank Diagnostic Criteria were eligible if they were previously untreated, or had been treated for less than 6 months with dopaminergic drugs and if there was uncertainty as to which class of drug to use. Exclusion criteria included dementia and inability to complete trial questionnaires. Ethics approval was provided by the West Midlands Research Ethics Committee, local approval was obtained at each participating centre, and all patients gave written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1:1) to receive either levodopa, dopamine agonists, or MAOBI by telephone call to the central randomisation service at the University of Birmingham (Birmingham, UK). Either MAOBI or levodopa could be omitted from the randomisation if considered inappropriate for a particular patient. Randomisation was minimised by previous levodopa therapy (none, <1, 1–2, 3–5 months), Hoehn and Yahr disease stage, and age (<50, 50–59, 60–69, 70–79, ≥80 years). Patients and investigators were not masked to group assignment.

Procedures

The pragmatic trial design aimed to facilitate large-scale recruitment of a heterogeneous group of patients, allowing investigators to start open-label treatment with whichever drug they preferred within the allocated class and to titrate the dose of levodopa and dopamine agonists within the bounds of the product licence. If symptoms were not controlled by the standard dose of MAOBI or the maximum tolerated dose of dopamine agonist, investigators could add levodopa as needed. Otherwise, adding or switching to a new drug from another drug class was only permissible if patients’ symptoms were still not adequately controlled, or for adverse effects.

Outcomes

One primary outcome was patient-rated functional status on the mobility subscale of the 39-item Parkinson’s Disease Questionnaire (PDQ-39). The PDQ-39 assesses the effect of Parkinson’s disease on quality of life, and is sensitive to changes regarded as important to patients, but not identified by clinical rating scales. The second primary outcome was quality-adjusted life-years (QALYs) derived from the EuroQol EQ-5D generic quality-of-life measure and a resource usage questionnaire. Cost utility analyses will be reported separately. Secondary outcome measures included the other PDQ-39 domains and overall score (summary index), compliance, cognition

<table>
<thead>
<tr>
<th>Randomisation option</th>
<th>Levodopa vs levodopa sparing comparison</th>
<th>Levodopa-sparing comparison (dopamine agonist vs MAOBI)</th>
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<tr>
<td>Age (years)</td>
<td></td>
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</tr>
<tr>
<td>71 (34–94)</td>
<td>71 (44–93)</td>
<td>71 (34–94)</td>
</tr>
<tr>
<td>69 (27–92)</td>
<td>69 (36–92)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>686 (65%)</td>
<td>225 (65%)</td>
<td>328 (64%)</td>
</tr>
<tr>
<td>284 (62%)</td>
<td>315 (68%)</td>
<td></td>
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<tr>
<td>Patients with regular carer</td>
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</tr>
<tr>
<td>664 (63%)</td>
<td>199 (57%)</td>
<td>324 (61%)</td>
</tr>
<tr>
<td>289 (63%)</td>
<td>269 (58%)</td>
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<tr>
<td>Duration of Parkinson’s disease (years)</td>
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<tr>
<td>0.6 (0–13)</td>
<td>0.6 (0–6)</td>
<td>0.6 (0–6)</td>
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<td>0.6 (0–6)</td>
<td>0.6 (0–6)</td>
<td>0.6 (0–6)</td>
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<tr>
<td>479 (45%)</td>
<td>189 (54%)</td>
<td>254 (48%)</td>
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<tr>
<td>232 (51%)</td>
<td>235 (51%)</td>
<td></td>
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<tr>
<td>Hoehn and Yahr stage 1-1.5</td>
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<td>0.6 (0–13)</td>
<td>0.6 (0–13)</td>
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<td>479 (45%)</td>
<td>189 (54%)</td>
<td>254 (48%)</td>
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<td>232 (51%)</td>
<td>235 (51%)</td>
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<tr>
<td>Hoehn and Yahr stage 2</td>
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<td>189 (54%)</td>
<td>254 (48%)</td>
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<tr>
<td>232 (51%)</td>
<td>235 (51%)</td>
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<tr>
<td>Previously received anti-Parkinsonian treatments</td>
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<tr>
<td>479 (45%)</td>
<td>189 (54%)</td>
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<tr>
<td>232 (51%)</td>
<td>235 (51%)</td>
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<tr>
<td>PDQ-39 mobility score</td>
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<tr>
<td>30.3 (25–8)</td>
<td>32.2 (26–4)</td>
<td>31.2 (25–5)</td>
</tr>
<tr>
<td>28.3 (26–5)</td>
<td>27.7 (26–6)</td>
<td></td>
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<tr>
<td>PDQ-39 summary index</td>
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<td></td>
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<td>22.3 (13–7)</td>
<td>22.8 (13–9)</td>
<td>22.6 (13–2)</td>
</tr>
<tr>
<td>21.7 (13–5)</td>
<td>21.4 (13–2)</td>
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</tbody>
</table>

Data are mean (range), n (%), or mean (SD). PDQ=Parkinson’s disease questionnaire. MAOBI=monoamine oxidase type B inhibitor.

Table 1: Demographic and baseline characteristics by randomisation option and by protocol comparison
using mini-mental state examination (MMSE), onset of dementia, dyskinesias and motor fluctuations, admissions to hospital or institutional care, and mortality. Patients completed study forms before randomisation and, by post, at 6 months, 1 year, and thereafter annually. The MMSE was administered at baseline, 5 years, and 10 years. Information about disease status (Hoehn and Yahr stage, any change in Parkinson’s disease diagnosis), motor complications, treatment compliance, side-effects, dementia diagnoses, and admissions to institutions was collected systematically at annual clinical assessments and on serious adverse event forms. Mortality was monitored through the National Health Service Information Centre.

Statistical analysis

We designed PD MED to detect a six-point minimum clinically meaningful difference between groups in the PDQ-39 mobility domain at any one timepoint. We assumed a SD of 18·6, which required 300 patients in each arm for 90% power at p<0·01. To allow for a 10% withdrawal rate and for the two-way randomisation options, target recruitment was 1500 patients. The study closed to recruitment, with 1620 randomised, when the parallel randomisation in later disease reached its 500-patient recruitment target.

Analyses were by intention to treat, including all available data irrespective of treatment compliance, and stratified by randomisation option. Continuous outcome measures were analysed with mixed effect repeated measures models with baseline scores included as a covariate. Missing items in PDQ-39 domain scores were imputed with an expectation maximisation algorithm. Missing assessments were not imputed. Time-to-event data were compared with log-rank methods. MMSE scores were compared with t tests. Side-effects and serious adverse events were compared with Fisher’s exact test. Comparisons of overall drug doses use levodopa equivalent doses (LED). p values do not allow for multiple significance testing. Variability in treatment effect across protocol-specified stratification parameters was explored with tests of heterogeneity or trend.

Figure 1: Trial profile
MAOBI=monoamine oxidase type B inhibitors. COMTI=catechol-0-methyl transferase inhibitors. *Reasons for discontinuing drug class are not mutually exclusive, some patients had more than one reason for stopping drug class usually side-effects and absence of efficacy. †14 patients withdrew or were lost to follow-up then later died (five for levodopa group, eight for dopamine agonist, one for MAOBI). ‡Other reason normally comorbidity
We used SAS version 9.2 for analyses. Interim analyses of unmasked efficacy and safety data were reviewed annually by an independent data monitoring committee. The trial is registered, number ISRCTN69812316.

Role of the funding source
The funders had no role in study design, conduct, or reporting. The writing committee had full access to all data, and were responsible for the decision to publish.

Results
Between Nov 09, 2000, and Dec 22, 2009, 1620 people with early Parkinson’s disease were assigned to treatment groups in PD MED from 89 UK neurology and geriatric clinics, one Czech, and one Russian site. 1058 (65%) of 1620 were randomly assigned three ways between dopamine agonists, MAOBI, and levodopa. 348 (21%) were assigned two ways between dopamine agonists and levodopa, and 214 (13%) were assigned two ways between dopamine agonists and MAOBI (table 1; figure 1). Thus, in total, 1406 were randomised between dopamine agonists and levodopa, and 919 between the two levodopa-sparing therapies, dopamine agonists and MAOBI. Patients assigned only between dopamine agonists and MAOBI had less severe disease and were younger, with a mean age of 62 years compared with 71 years in the other two randomisation options. Other patient characteristics were balanced between randomisation and treatment groups. 136 (8%) of 1620 patients had previously received dopaminergic treatment. If allocated dopamine agonists, clinicians for 348 (21%) of 1620 to use pramipexole, and less than 5% of 1620 patients intended to use ropinirole, 887 (55%) of 1620 patients intended to use ropinirole, 628 (39%) of 1620 to use selegiline for 842 (66%) of 1620, rotigotine [17/1620], and lisuride [1/1620]. The intended MAOBI was oral selegiline for 842 (66%) of 1272 patients, sublingual selegiline for 142 (11%) of 1272, and rasagiline for 266 (21%) of 1272 patients.

Median follow-up was 3 years (range 0–9). The diagnosis of idiopathic Parkinson’s disease was revised for 79 (5%) of 1620 patients, most to Parkinson’s disease-plus syndrome. 1601 (99%) of 1620 patients had complete PDQ-39 data at baseline, 1521 (95%) of 1601 at 6 months, 1479 (94%) of 1581 at 1 year, 1258 (91%) of 1379 at 2 years, 970 (88%) of 1101 at 3 years, 698 (85%) of 821 at 4 years, 525 (83%) of 636 at 5 years, 330 (76%) of 443 at 6 years, and 204 (75%) of 271 at 7 years. We noted no significant differences between randomisation arms in numbers with missing assessments (figure 1, appendix). Few patients had assessments beyond 7 years and, accordingly, analyses of continuous outcome measures (eg, PDQ-39) include data up to 7 years only.

For compliance, participants allocated MAOBI or dopamine agonists were significantly more likely to discontinue their allocated drug class than those allocated levodopa: 7-year probabilities were 72% for MAOBI, 50% for dopamine agonists, and 7% for levodopa (p<0.0001, figure 2). This difference was mainly attributable to side-effects with 179 (28%) of 632 allocated dopamine agonists and 104 (23%) of 460 allocated MAOBI discontinuing because of side-effects compared with 11 (2%) of 528 allocated levodopa (p<0.0001, appendix). The side-effects (mainly psychological, sleep disturbance, and gastrointestinal) were usually mild, only 16 patients (nine given dopamine agonists, four given MAOBI, and three given levodopa) had serious adverse events believed to be possibly related to trial treatment. 35 (6%) of 362 allocated dopamine agonists and 78 (17%) of 460 allocated MAOBI were stopped because of an absence of efficacy compared with five (1%) of 528 in the levodopa group (p<0.0001). Of those patients who stopped dopamine agonists, 169 (78%) of 218 switched to levodopa, ten (5%) of 218 switched to MAOBI, and 17 (8%) of 218 to catechol O-methyltransferase inhibitors (COMT). Of those stopping MAOBI, 102 (48%) of 215 changed to levodopa, 88 (41%) of 215 to dopamine agonists, and nine (4%) of 215 to COMT. In the levodopa group, 11 (39%) of 28 switched to dopamine agonists.

Participants allocated and still taking MAOBI or dopamine agonists were also significantly more likely than those allocated levodopa to need a drug from another class added to their treatment: 2-year probabilities were 64% for MAOBI, 40% for dopamine agonists, and 20% for levodopa (p<0.0001, appendix). Of 333 patients in the dopamine agonist group, 311 (93%) added levodopa alone, 12 (4%) added MAOBI, and ten (3%) added COMT. However, of 287 in the MAOBI group, 194 (67%) added levodopa, 91 (32%) added dopamine agonists, and two (1%) added COMT. Finally, of 203 patients in the levodopa group, 103 (51%)
added dopamine agonists, 33 (16%) added MAOBI, and 67 (33%) added COMT inhibitors. Exposure to levodopa was, however, similar in the dopamine agonists and MAOBI groups: averaging in all patients at 1 year, 96 mg/day (SD 157) for dopamine agonists and 131 mg/day (172) for MAOBI, rising at 7 years to 526 mg/day (266) for dopamine agonists and 489 mg/day (246) for MAOBI. The mean daily dose in patients allocated levodopa was 347 mg (SD 139) at 1 year rising to 531 mg (229) at 7 years (appendix). For patients allocated dopamine agonists and taking ropinirole, mean dose was 9 mg/day (SD 4·5) at 1 year rising to 13 mg/day (6·7) at 7 years. For pramipexole, mean dose was 2·2 mg/day (1·1; salt) at 1 year rising to 3·4 mg/day (SD 1·5) at 7 years. The mean doses for MAOBI remained constant: 8·4 mg/day (SD 3·1) for selegiline and 1·0 mg/day (0·1) for rasagiline at 1 year compared with 8·6 mg/day (2·7) for selegiline and 1·0 mg/day (0·0) for rasagiline at 7 years. Converting drug doses into LED,18 showed that LED was similar at 1 year in the dopamine agonists (269 mg/day [SD 155]) and MAOBI groups (247 mg/day [154]), but significantly (p<0·001) higher in the levodopa group (354 mg/day [136]). By 7 years, LED had risen to 636 mg/day (SD 298) in the levodopa group, 695 mg/day (329) in the MAOBI group, and 768 mg/day (387) in the dopamine agonist group (figure 3).

PDQ-39 mobility scores did not differ significantly between the levodopa group and levodopa-sparing group at any follow-up assessment (figure 4A). However, the average score during the first 7 years of follow-up was 1·8 points (95% CI 0·5–3·0; p=0·005) better with levodopa than with levodopa-sparing therapy, with no significant divergence or convergence in this efficacy estimate (p=0·19). Scores on the activities of daily living (ADL), stigma, cognition, communication, and bodily discomfort subscales were also significantly (p<0·05 without allowance for multiple significance testing) better with levodopa than with levodopa-sparing therapy (table 2). The levodopa group averaged 1·0 points higher in PDQ-39 summary index than did the levodopa-sparing group (95% CI 0·3–1·7; p=0·008) with no significant increase or attrition of benefit during follow-up (figure 4B). Scores for the EuroQol EQ-5D utility measure averaged 0·03 (95% CI 0·01–0·05; p=0·0002) better with levodopa than with levodopa-sparing therapy (table 2, appendix). The clinically rated Hoehn & Yahr disease stage scores were also on average 0·07 (95% CI 0·03–0·12, p=0·0009) points better with levodopa than with levodopa-sparing therapy (appendix).

Patients in the levodopa group were more likely to develop dyskinesias than those in the levodopa-sparing group (hazard ratio [HR] 1·52, 95% CI 1·16–2·00, p=0·003; figure 5), but there was no difference in motor fluctuations (1·11, 0·90–1·37, p=0·3; appendix). 5-year decline in MMSE was similar (1·9 [SD 4·1] with levodopa and 1·9 [4·4] with levodopa-sparing therapy p=0·9), and although fewer patients in the levodopa than in the levodopa-sparing group developed dementia (HR 0·81, 95% CI 0·61–1·08, p=0·14, appendix); fewer entered institutional care (0·86, 0·63–1·18; p=0·4, appendix); and fewer died (0·85, 0·69–1·06, p=0·17, appendix), none of these differences were statistically significant.
Treatment efficacy, as measured by PDQ-39 mobility subscale, did not differ according to baseline stratification variables (age, Hoehn and Yahr stage, and duration of Parkinson’s disease symptoms). In particular, the advantage of levodopa compared with levodopa-sparing therapy was similar in patients younger than and older than 70 years (appendix).

PDQ-39 mobility scores averaged 1.4 points (95% CI 0.0–2.9, p=0.05) better in patients initiating therapy with MAOBI than those initiating dopamine agonists (figure 6A). Significantly better scores on the cognition subscales were also seen with MAOBI compared with dopamine agonists (table 2), and PDQ-39 summary index averaged 0.8 points (95% CI 0.0–1.7, p=0.05) better in participants allocated MAOBI as initial therapy than in those allocated dopamine agonists (figure 6B). There was no difference in scores on the EuroQol EQ-5D generic quality-of-life measure: 0.004 (95% CI 0.01 to 0.02; p=0.6; table 2), appendix. Hoehn and Yahr disease stage scores averaged 0.05 (95% CI 0.00–0.10, p=0.05) points better with MAOBI than with dopamine agonists (appendix).

Rates of dyskinesia were similar (HR 0.85, 95% CI 0.60–1.22, p=0.4), but motor fluctuations were higher (HR 1.32, 95% CI 1.01–1.72, p=0.04) in the dopamine agonist group than in the MAOBI group (appendix). 5-year decline in MMSE was greater in participants allocated dopamine agonists than in those allocated MAOBI (2.4 [SD 4.4] vs 1.3 [3.7], p=0.04), but there was no significant difference in the number of patients developing dementia (HR 1.11, 95% CI 0.77–1.59, p=0.6; appendix), entering institutional care (1.08, 0.70–1.64, p=0.7, appendix), or dying (0.96, 0.73–1.28, p=0.8, appendix).

**Discussion**

Generally, levodopa is accepted to provide better short-term control of the motor symptoms of newly diagnosed Parkinson’s disease and fewer side-effects than dopamine agonists or MAOBI, but motor complications are increased and symptom control is poorer (panel). We show that the overall balance of benefits and risks favours levodopa over levodopa-sparing therapy with better patient-rated quality of life both in the short and long

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**Table 2: Estimated average differences between levodopa and levodopa-sparing groups, and between dopamine agonist and MAOBI, in the different PDQ-39 subscales and in EQ-5D utility score**

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Levodopa vs levodopa-sparing</th>
<th>Dopamine agonist vs MAOBI</th>
<th>MID†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate† (95% CI)</td>
<td>p value</td>
<td>Estimate‡ (95% CI)</td>
</tr>
<tr>
<td>Mobility</td>
<td>1.8 (0.5 to 3.0)</td>
<td>0.005</td>
<td>1.4 (0.0 to 2.9)</td>
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<tr>
<td>ADL</td>
<td>1.9 (0.7 to 3.0)</td>
<td>0.002</td>
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<td>Emotional wellbeing</td>
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<td>0.7</td>
<td>0.3 (-0.8 to 1.4)</td>
</tr>
<tr>
<td>Stigma</td>
<td>1.3 (0.2 to 2.3)</td>
<td>0.02</td>
<td>1.3 (0.0 to 2.5)</td>
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<tr>
<td>Social support</td>
<td>0.1 (-0.6 to 0.8)</td>
<td>0.8</td>
<td>0.8 (-0.1 to 1.7)</td>
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<tr>
<td>Cognition</td>
<td>1.0 (0.0 to 2.0)</td>
<td>0.05</td>
<td>1.7 (0.5 to 2.9)</td>
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<tr>
<td>Communication</td>
<td>0.9 (0.0 to 1.8)</td>
<td>0.05</td>
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<td>Bodily discomfort</td>
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<td>0.01</td>
<td>0.7 (-0.6 to 2.0)</td>
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<tr>
<td>Summary index</td>
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<td>0.008</td>
<td>0.8 (0.0 to 1.7)</td>
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<tr>
<td>EQ-5D utility score</td>
<td>0.03 (0.01 to 0.05)</td>
<td>0.0002</td>
<td>0.004 (-0.01 to 0.02)</td>
</tr>
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</table>

PDQ=Parkinson’s disease questionnaire. MAOBI=monoamine oxidase type B inhibitor. ADL=activities of daily living. *MID=minimally important difference. †Positive numbers favour levodopa. ‡Positive numbers favour MAOBI.

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**Figure 5: Risk of developing dyskinesia in levodopa and levodopa-sparing groups**

**Figure 6: 39-item patient-rated Parkinson’s disease questionnaire mobility score (A) and summary index (B) with time in dopamine agonist and MAOBI groups**

MAOBI=monoamine oxidase type B inhibitors.
Levodopa treatment achieved better scores than did dopamine agonists or MAOBI treatment on the primary PDQ-39 mobility outcome, and a range of other patient-rated outcome measures, including ADL and overall quality of life as measured by the PDQ-39 disease-specific and EQ-5D generic quality-of-life measures. Clinician-rated disease status by Hoehn and Yahr staging was also significantly improved. These benefits were seen despite levodopa-treated patients developing more involuntary movements though, notably, no more motor fluctuations.

The 1·8 PDQ-39 mobility and 1·0 summary index points favouring initial levodopa compared with levodopa-sparing treatment are, however, below the predefined six-point threshold thought, when PD MED was designed, to be the minimum clinically important difference (MCID), and below a subsequent, smaller MCID estimate of 3·2 points. The corresponding standardised effect sizes are 0·09 SD and 0·07 SD, below the 0·2 SD threshold categorised as a small treatment effect. Expressed in relation to rate of decline, these treatment benefits correspond to around 5 months and 4 months progress of the disease, respectively—less than the 6-month disease progress MCID threshold cited in dementia studies using annual decline methods. Thus, the benefits of levodopa compared with levodopa-sparing are unquestionably small.

A clinically relevant finding, though, is that during 7 years of follow-up, we showed no indication of any cumulative adverse effect of levodopa therapy, with no loss of benefit with time. The lower rates of admissions to institutions, dementia, and death were not statistically significant, but the upper CI preclude any substantial increase with levodopa compared with levodopa-sparing therapy. Thus, there seems to be no grounds for concerns that use of levodopa as first-line therapy results in worse long-term outcome. The better quality-of-life scores with levodopa at earlier assessments might be partly explained by higher LED dose treatment in the levodopa group than in the dopamine agonists and MAOBI groups. However, by 7 years, the dopamine agonists group was receiving higher LED treatment than were the levodopa and MAOBI groups, yet there was no suggestion that the advantage of initial treatment with levodopa and MAOBI over dopamine agonists diminished over 7 years of follow-up.

In cases for which levodopa-sparing therapy is deemed appropriate, dopamine agonists are generally preferred to MAOBI, which are perceived as less effective. However, we noted small—ie, below MCID thresholds—but significant benefits favouring initial treatment with MAOBI compared with dopamine agonists in PDQ-39 mobility, cognition, and summary index scores, but not in EQ-5D. Although more patients discontinued MAOBI than did dopamine agonists, the benefits of MAOBI compared with dopamine agonists are not explained by readier addition of other drugs because the LED was higher in the dopamine agonists group than in the MAOBI group throughout the first 7 years of treatment. A possible explanation for the lesser efficacy of dopamine agonists, despite the higher LED, is that levodopa could be less effective when added to dopamine agonists than MAOBI, because dopamine agonists and levodopa both act on D2 class receptors—with levodopa also stimulating dopamine D1 receptors—so the efficacy of the combination might be less than additive. Notably, the onset of dyskinesia was not significantly higher with MAOBI than with dopamine agonists, and fewer motor fluctuations were reported with initial MAOBI therapy, so avoiding motor complications should not be a reason to prefer dopamine agonists over MAOBI therapy.

A full cost-utility analysis will be reported separately. However, because other outcome measures—including major cost-drivers such as admissions to institutions and development of dementia—consistently favour levodopa over levodopa-sparing therapy the economic analyses are also likely to favour the substantially less expensive levodopa therapy. Similarly, because MAOBI, particularly selegiline, cost less than do dopamine agonists and achieved at least as good results, they are likely to be shown in cost-utility analyses to be more cost effective.

In present clinical practice, patients younger than 60 years are treated initially with either a dopamine agonist or MAOBI to avoid levodopa-related motor complications. Levodopa tends to be used in patients older than 70 years for whom long-term complications are judged less important. Subgroup comparisons in PD MED noted no difference in treatment efficacy in those younger than and older than 70 years and hence do not support age-specific treatment recommendations. However, as seen in studies of Parkinson’s disease incidence, few participants (12%) were younger than 60 years at randomisation, particularly in the levodopa versus levodopa-sparing comparison, so the trial provides little direct evidence for how such patients should be treated.
The significant benefits of initial therapy with MAOBI compared with dopamine agonists in PDQ-39 cognition score and decline in MMSE, but not in development of dementia, could reflect a disease-modifying effect—long hypothesised for MAOBI treatment—but might also be explained by an altering effect of the amphetamine metabolites of selegiline, or an antidepressant effect of MAOBI, or chance. Longer-term follow-up of PD MED will be informative.

Missing data can be a source of bias in studies with symptom ratings as outcome, particularly if levels of missing outcome data differ between treatment groups. Although reasons for stopping treatment differed across the drugs in PD MED, patients who stopped their randomised treatment still continued to complete patient questionnaires, and outcome data were available for most such patients. Also, the repeated measures analyses include all available data so patients who miss some assessments still contribute to estimates of treatment efficacy. Hence, given the low level of missing data, we do not consider that any bias from missing data could be of sufficient size to materially alter the study conclusions.

Another potential weakness of PD MED was open-label treatment, which could have introduced assessment bias. However, any such bias is probably small because all patients received active treatment, and would also be likely to favour levodopa-sparing therapy, particularly dopamine agonists, because the results are opposite to the a-priori expectations of most clinicians and patients. Open-label treatment, and patient-rated outcome measures, reduce trial costs and complexity, and this helped PD MED to recruit more patients than any previous trial of Parkinson’s disease treatment.

Patient-reported outcome measures have not been widely used previously—an omission in previous trials—but similar treatment differences were seen with clinician-rated disease status and patient-rated outcomes, as previously reported with PDQ-39 and the clinician-rated UPDRS in the PD SURG trial. Also, with few eligibility restrictions, a fairly typical group of patients with Parkinson’s disease who would be candidates for dopaminergic treatment in a clinical setting were included, diagnostic accuracy was high, and compliance similar to that in previous studies. The large sample enhances statistical reliability and the so-called real world trial design arguably provide results that are more generalisable to typical patients and, as a result, more valuable in clinical practice than are less pragmatic studies.

Another potential limitation of the study was the long period between initiation and availability of the results. However, the findings remain highly relevant for, with example, National Institute for Health and Care Excellence awaiting the findings before updating their with, for example, National Institute for Health and Care Excellence awaiting the findings before updating their guidance on levodopa-sparing therapy.

Contributors
RG, CEC, AG, CJ, KW, and AW designed the trial. RG, CEC, KW, AW, NI, SP, and CR ran the trial and CEC and AW recruited patients. NI and SP analysed the data. RG, CEC, AG, NI, CJ, EM, SF, CR, KW, and AW interpreted the data and wrote the paper. The authors assume responsibility for the accuracy and completeness of the data and for the overall content and integrity of the paper.

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Initiating dopaminergic treatment in Parkinson’s disease

In The Lancet, Richard Gray and the UK PD MED Collaborative Group report the highly anticipated results of a very large, pragmatic trial assessing outcomes during a median follow-up of 3 years and maximum 7 years in patients with early Parkinson’s disease. A total of 1620 patients were managed with three different initial treatment regimens: levodopa (528 patients) or two levodopa-sparing approaches, either a dopamine agonist (632 patients) or a monoamine oxidase type B inhibitor (MAOBI; 460 patients). The findings of the study show small but persistent benefits from initial therapy with levodopa compared with the alternatives, and initial MAOBI treatment was at least as effective as a dopamine agonist. The study had two primary outcome measures. The first was the mobility subscale of the Parkinson’s Disease Questionnaire-39 (PDQ-39), and patients assigned to levodopa scored 1.8 points (95% CI 0.5–3.0) higher on the PDQ-39 mobility subscale on average than those assigned to levodopa-sparing therapy. The study’s second primary outcome involved a cost-utility analysis that will be reported separately.

Perhaps the most important questions we should ask related to this report are: first, how important or clinically meaningful were the outcome differences between the study groups; second, are the results of the study unexpected; and finally, will these results change clinical practice? First, on the importance of outcome differences between study groups, although the differences in favour of initial levodopa treatment were significant and persistent, they were very small and failed to even approach the study’s predetermined minimum clinically important differences (defined as six points on the PDQ-39 mobility subscale). The authors emphasise that by 7 years the advantage of initial treatment with levodopa or MAOBI compared with a dopamine agonist did not diminish (despite the dopamine agonist group receiving higher levodopa equivalent doses). Perhaps an alternative conclusion also should be voiced that the apparent disadvantage, in terms of the difference in the primary outcome measure with levodopa-sparing therapy, was not associated with an important short-term or long-term detrimental effect. Thus, physicians choosing these alternative treatments in their practice cannot be faulted on the basis of poorer outcomes.

Second, in response to the expectedness of results, it is widely appreciated and accepted that levodopa is the most effective treatment for Parkinson’s disease. Why then is there such an emphasis on the concept of levodopa-sparing therapies? This concern has resulted in an unfortunate so-called levodopa phobia, causing many physicians (and subsequently many patients) to resist the use of the best treatment for the disease. The issue dates back to a time when there was a concern that levodopa was toxic to remaining dopaminergic neurons, possibly by increasing dopamine turnover and accentuating resultant oxidative damage. These fears have largely dissipated, leaving the main concern related to the established increased risk of motor complications (dyskinesias and motor fluctuations) with levodopa therapy compared with dopamine agonists.

One important outcome of PD MED is that patients receiving initial levodopa did as well as or better than the other groups, despite the greater incidence of involuntary movements. However, younger age is possibly the most important predisposing factor for levodopa-induced dyskinesias. This finding has encouraged a revision of the question of how best to initiate treatment in Parkinson’s disease, to how best to initiate treatment in patients younger than 60 years. After stratification of the analysis by age (older and younger than 70 years), levodopa sparing strategies offered similar disadvantages in...
younger patients compared with older patients. In view of the present state of clinical uncertainty, examination of the group of patients younger than 60 years could have been more interesting. The large difference in dyskinesia rates in groups receiving roughly 400 mg of levodopa between this study (16% at 3 years; mean age 71 years) and the STRIDE-PD trial (35% at 3 years; mean age 60 years) suggests that exploration of lower age cutoffs is important. Although only 12% of the PD MED study population were younger than 60 years, this amounts to roughly 200 participants and therefore could have been quite informative.

What is unexpected about the study results is the persistence of a small but statistically significant difference between outcomes in the levodopa group versus levodopa-sparing groups even as long as 7 years after randomisation, with no suggestion of a reduction in size of this difference with time. This finding is surprising in view of the progressive adoption of levodopa treatment in the sparing groups. This observation suggests that either the difference in outcomes is driven largely by adverse effects of dopamine agonists, which are often continued in the presence of the added levodopa, or that there is a barrier to achievement of true clinically equivalent efficacy (despite calculated levodopa equivalent doses) in the presence of polypharmacy or by investigators who are predisposed to spare levodopa throughout the course of treatment. In the absence of a clear explanation, a careful examination of the baseline characteristics of those lost to follow-up versus those continuing, and also reasons for dropout, would be important.

Finally, will the results of this study change clinical practice? Since PD MED was initiated in 2000, important developments in the field have been made and treatment has changed. Results of longer-term follow-up of patients originally participating in levodopa versus dopamine agonist trials have shown remarkably similar outcomes with respect to both parkinsonian features and motor complications independent of how treatment was initiated. It is now generally acknowledged that a delay or reduction in incidence of dyskinesias through initiation of dopamine agonists as opposed to levodopa in the early years, when these are generally mild and not disabling, does not necessarily translate into a better outcome in the long term when patients are typically on levodopa combined with other drugs (independent of how treatment was initiated). Furthermore, only after the initiation of this study did the first reports of impulse control disorders with dopamine agonists begin to appear. It is now widely recognised that this is a major limitation to dopamine agonist therapy that has a strong effect on the choice of these drugs as initial therapy.

Since PD MED was launched, a large proportion of the neurological community have espoused the choice of dopamine agonists over levodopa as initial therapy, which was supported by several studies showing delay in the development of motor complications. This choice was encouraged by aggressive pharmaceutical marketing. In recent years, a major shift in this treatment approach is occurring, at least in North America, on the basis of results of longer follow-up of earlier trials and also a recognition of important differences in side-effect profiles. If this is the case, the results of PD MED might not be “opposite to the a priori expectations of most clinicians and patients” as the authors suggest. We look forward to validated surveys of prescribing practices to learn whether the results of PD MED will be practice changing or simply practice validating.

The crucial question of how best initially to manage younger patients with Parkinson’s disease remains unresolved, and many experts will continue to initiate treatment with a dopamine agonist in most patients with disease onset in their 40s and 50s. PD MED provides reassuring data showing that in most patients with Parkinson’s disease, who have an older age of onset, how treatment is initiated generally does not matter because outcomes are very similar. The results of the cost analysis will add another important factor for physicians to weigh when judging how to initiate treatment. Finally, and perhaps most importantly, the results of this study will help to persuade physicians and reassure patients that fears have served as the groundwork in establishing levodopa phobia—that often results in patients experiencing unnecessary and easily managed disability and reduction in quality of life in the early years of their disease—are unfounded.

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1 PD MED Collaborative Group. 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. Lancet 2014; published online June 11. http://dx.doi.org/10.1016/S0140-6736(14)60683-8.


