Cost-effectiveness of dopamine agonists and monoamine oxidase B inhibitors in early Parkinson's disease

PD Med Collaborative Group

DOI:
10.1002/mds.28623

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
PD Med Collaborative Group 2021, 'Cost-effectiveness of dopamine agonists and monoamine oxidase B inhibitors in early Parkinson's disease', *Movement Disorders*, vol. 36, no. 9, pp. 2136-2143. https://doi.org/10.1002/mds.28623

RESEARCH ARTICLE

Cost-Effectiveness of Dopamine Agonists and Monoamine Oxidase B Inhibitors in Early Parkinson's Disease

Emma McIntosh, PhD, MSc, BA,[1*] Seamus Kent, PhD, MSc, BA,[2] Alastair Gray, PhD,[2] Carl E. Clarke, MD,[3,4] Adrian Williams, MD,[3,5] Crispin Jenkinson, DPhil,[2] Natalie Ives, MSc,[3] Smitaa Patel, MSc,[3] Caroline Rick, PhD,[6] Keith Wheatley, DPhil,[3] Richard Gray, MA, MSc, and[2] PD MED Collaborative Group

[1]*University of Glasgow, Glasgow, United Kingdom*
[2]*University of Oxford, Oxford, United Kingdom*
[3]*University of Birmingham, Birmingham, United Kingdom*
[4]*Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, United Kingdom*
[5]*Birmingham Hospitals NHS Trust, Birmingham, United Kingdom*
[6]*University of Nottingham, Nottingham, United Kingdom*

ABSTRACT: Background: The PD MED study reported small but persistent benefits in patient-rated mobility scores and quality of life from initiating therapy with levodopa compared with levodopa-sparing therapies in early Parkinson's disease (PD).
Objectives: The objective was to estimate the cost-effectiveness of levodopa-sparing therapy (dopamine agonists or monoamine oxidase type B inhibitors compared with levodopa alone.
Methods: PD MED is a pragmatic, open-label randomized, controlled trial in which patients newly diagnosed with PD were randomly assigned between levodopa-sparing therapy (dopamine agonists or monoamine oxidase type B inhibitors) and levodopa alone. Mean quality-adjusted life-years and costs were calculated for each participant. Differences in mean quality-adjusted life-years and costs between levodopa and levodopa-sparing therapies and between dopamine agonists and monoamine oxidase type B inhibitors were estimated using linear regression.
Results: Over a mean observation period of 4 years, levodopa was associated with significantly higher quality-adjusted life-years (difference, 0.18; 95% CI, 0.05–0.30; $P < 0.01$) and lower mean costs (£3390; £2671–£4109; $P < 0.01$) than levodopa-sparing therapies, the difference in costs driven by the higher costs of levodopa-sparing therapies. There were no significant differences in the costs of inpatient, social care, and institutional care between arms. There was no significant difference in quality-adjusted life-years between those allocated dopamine agonists and monoamine oxidase type B inhibitors (0.02; −0.17 to 0.13 in favor of dopamine agonists; $P = 0.81$); however costs were significantly lower for those allocated monoamine oxidase type B inhibitors (£2321; £1628–£3015; $P < 0.01$) because of the higher costs of dopamine agonists. There were no significant differences between arms for other costs.
Conclusions: Initial treatment with levodopa is highly cost-effective compared with levodopa-sparing therapies. Monoamine oxidase type B inhibitors, as initial levodopa-sparing therapy was more cost-effective, with similar quality-adjusted life-years but lower costs than dopamine agonists. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: cost-effectiveness; Parkinson's disease; dopamine agonists; monoamine oxidase B inhibitors; randomized controlled trial

*__Correspondence to:__ Professor Emma McIntosh, Health Economics and Health Technology Assessment, Institute of Health and Wellbeing, University of Glasgow, Glasgow, G12 8RZ, UK; E-mail: emma.mcintosh@glasgow.ac.uk

__Present address:__ Seamus Kent, Senior Adviser in Data & Analytics, National Institute for Health and Care Excellence, 2nd Floor, 2 Redman Place, London, E20 1JQ.

__Relevant conflicts of interest/financial disclosures:__ All authors report no conflict of interest. Carl Clarke received an honoraria for speaking and advisory board from BIAL; all other authors report no financial disclosures.

__Received:__ 26 February 2021; __Accepted:__ 5 April 2021

__Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28623__

Parkinson's disease (PD)[1] is a progressive neurological disorder associated with motor disabilities including tremor, rigidity, slowness, and postural disturbance. In the United Kingdom, 8000 new cases are diagnosed every year, and more than 100,000 people are living with PD.[2,3] Levodopa is the most commonly used class of drug in the treatment of early-stage PD, providing good symptomatic relief for most patients and possibly improving survival.[4,5] However, after a few years of treatment, motor complications ("wearing-off," "on–off," fluctuations, and dyskinesia) often develop.[6] Levodopa-sparing therapies such as dopamine agonists (DAs) and monoamine oxidase type B inhibitors (MAOBIs) have been used, either alone or with reduced doses of levodopa, in an attempt to delay the onset of motor complications. Although, motor complications are seen less frequently with levodopa-sparing therapies, nonmotor side effects such as nausea, hallucinations, edema, and sleep disturbance are more frequent with DAs than with levodopa.[7,8]

The PD MED trial demonstrated that the overall balance of benefits and risks favors levodopa over levodopa-sparing therapies with better patient-rated Health-Related Quality of Life (HRQoL) in both the short and long term. There were no significant differences in the rate of dementia, institutionalization, or mortality.[1] In cases for which levodopa-sparing therapy is deemed appropriate, DAs have traditionally been preferred to MAOBIs, which are perceived as less effective. However, in PD MED, patient-rated HRQoL was marginally better for those allocated MAOBIs.[1] We have extended these analyses by reporting a cost-utility analysis of levodopa versus levodopa-sparing therapies, and of DAs versus MAOBIs carried out alongside the PD MED trial.

Methods

Patients and Procedures

The design of PD MED, a pragmatic, open-label randomized trial, data collection instruments, and the main clinical results have been reported in detail in the trial protocol (http://www.isrctn.com/ISRCTN69812316) and published in a clinical article.[1] Individuals diagnosed with idiopathic PD[9] were eligible if they were previously untreated or had been treated for less than 6 months with dopaminergic drugs and if there were uncertainty about which class of drug to use. Exclusion criteria included dementia and the inability to complete trial questionnaires. Ethical approval was provided by the West Midlands Research Ethics Committee, local approval was obtained at each participating center, and all patients gave written informed consent.

Patients were randomly assigned (1:1:1) to receive levodopa, DA, or MAOBI. Either MAOBI or levodopa could be omitted from the randomization if considered inappropriate for a particular patient. Patients and investigators were not masked to group assignment. Investigators were allowed to start open-label treatment with whichever drug they preferred within the allocated class and to titrate the dose of levodopa and DA within the bounds of the product license. If symptoms were not controlled by the standard dose of MAOBI or the maximum tolerated dose of DA, investigators could add levodopa as needed. Otherwise, adding or switching to a new drug was only permissible if patients' symptoms were not adequately controlled or for adverse effects.

Resource Use Information

The economic analysis was performed from a health and personal social services perspective (PSS), as recommended by the National Institute for Health and Care Excellence (NICE) in the United Kingdom.[10] Information on patients' use of drugs — type of drug and dose — was completed by clinicians at annual follow-up visits. If institutionalization occurred, the type of care (residential or nursing) and the date were recorded on the annual follow-up form, alongside information on whether the patient developed dementia or motor complications. Other health and PSS resource use was self-reported by participants and collected at annual intervals using a short questionnaire. This recorded primary care and outpatient use (contacts with general practitioners, nurse practitioner, Parkinson's disease nurses, health visitors, social workers, physiotherapists, occupational therapists, speech/language therapists, day hospitals, and neurology outpatient departments), hospital stays and respite care, and personal social services (home care/home help, meals on wheels, day care, luncheon clubs, sitting services, and night care). Unit costs were attached to resource use volumes using UK 2011 prices, and both costs and benefits were discounted at an annual rate of 3.5%, consistent with NICE guidance.[10] Unit costs for all resource items are presented in Table S1.

Health-Related Quality of Life

Health-Related Quality of Life (HRQoL) was estimated using the EuroQol EQ-5D 3-level questionnaire.[10,11] EQ-5D utilities were calculated by applying the UK value set,[12] with health state valuations ranging from −0.596 to 1, where 1 represents perfect health, 0 is death, and negative values are health states considered worse than death. EQ-5D questionnaires were distributed to participants for self-completion at baseline, 6 months, 12 months, and annually thereafter.

Statistical Analysis

Two comparisons were made: (1) levodopa was compared with levodopa-sparing therapies, incorporating

TABLE 1 *Demographic and baseline characteristics by randomization option and by protocol comparison*

	Randomization option			Levodopa versus levodopa-sparing comparison		Levodopa-sparing comparison (dopamine agonist vs MAOBI)	
	3-way (levodopa vs dopamine agonist vs MAOBI), n = 1057	2-way (levodopa vs dopamine agonist), n = 335	2-way (dopamine agonist vs MAOBI), n = 201	Levodopa (n = 522)	Levodopa-sparing (n = 870)	Dopamine agonist (n = 451)	MAOBI (n = 454)
Age (y)	71 (8)	71 (8)	63 (9)	71 (8)	71 (8)	69 (9)	69 (9)
Men	686 (65%)	218 (65%)	137 (68%)	335 (64%)	569 (65%)	282 (63%)	313 (69%)
Patients with regular carer	664 (63%)	196 (59%)	114 (57%)	324 (62%)	536 (62%)	289 (64%)	269 (59%)
Duration of Parkinson's disease (y)	0.6 (1.1)	0.5 (0.9)	0.7 (1.0)	0.6 (1.1)	0.6 (1.0)	0.6 (0.9)	0.6 (1.2)
Hoehn and Yahr stage 1–1.5	479 (45%)	186 (56%)	140 (70%)	253 (48%)	412 (47%)	229 (51%)	231 (51%)
Hoehn and Yahr stage 2	319 (30%)	95 (28%)	43 (21%)	154 (30%)	260 (30%)	126 (28%)	129 (28%)
Hoehn and Yahr stage 2.5–5	259 (25%)	54 (16%)	18 (9%)	115 (22%)	198 (23%)	96 (21%)	94 (21%)
Previously received antiparkinsonian treatments	88 (8%)	28 (8%)	13 (6%)	44 (8%)	72 (8%)	35 (8%)	37 (8%)
EQ-5D utility score	0.65 (0.24)	0.65 (0.25)	0.69 (0.23)	0.65 (0.23)	0.65 (0.25)	0.65 (0.26)	0.68 (0.22)
Missing EQ-5D information	19 (2%)	5 (1%)	5 (2%)	9 (2%)	15 (2%)	11 (2%)	7 (2%)

Data are mean (SD) or n (%).
Data exclude the 27 participants recruited in the Czech Republic or Russia.
MAOBI, monoamine oxidase type B inhibitor.

TABLE 2 *QALYs and costs over mean 4 years of follow-up by treatment allocation and differences for the levodopa versus levodopa-sparing comparison*

	Levodopa	Levodopa-sparing	Difference[a]
Quality-adjusted life-years			
Unadjusted	2.27 (0.05)	2.10 (0.04)	−0.17 (−0.30 to −0.04); $P = 0.01$
Adjusted			−0.18 (−0.30 to −0.05); $P < 0.01$
Costs (UK 2011 £)			
Levodopa	493 (15)	307 (11)	−186 (−223 to −150); $P < 0.01$
Dopamine agonists	1107 (187)	3879 (146)	2773 (2308 to 3238); $P < 0.01$
MAOBIs	89 (25)	294 (20)	206 (143–268); $P < 0.01$
Other drugs	207 (23)	144 (17)	−63 (−120 to −6); $P = 0.03$
Drug subtotals	1896 (194)	4624 (151)	2729 (2248–3210); $P < 0.01$
Primary care and outpatient use	3187 (185)	3848 (145)	661 (193–1130); $P < 0.01$
Inpatient and respite care	9442 (2918)	6991 (1955)	−2452 (−9032 to 4129); $P = 0.46$
Personal social services	4561 (641)	4965 (482)	403 (−1192–1999); $P = 0.62$
Institutionalization	2675 (532)	3177 (402)	502 (−807–1811); $P = 0.45$
Total costs[b]	5083 (287)	8473 (225)	3390 (2671–4109); $P < 0.01$

Values are mean (standard error) or mean (95% confidence interval).
[a]Positive values indicate higher costs and higher QALYs for those allocated levodopa-sparing.
[b]Includes only those cost components for which there is a significant difference ($P < 0.05$) between arms.
MAOBI, monoamine oxidase type B inhibitor.

information from those randomized among all 3 treatments and those randomized between only levodopa and DA, and (2) DA was compared with MAOBIs, utilizing information from those randomized among all 3 treatments and those randomized between only DAs and MAOBIs.

A small number of individuals recruited from outside the United Kingdom were excluded from analysis. Aggregated QALYs and costs were estimated for each trial participant up to 7 years from randomization or death if earlier. QALYs for each individual were estimated using the area under the curve approach with linear interpolation between times.[13] Total costs were calculated by first comparing costs by treatment arm within each resource use category, class of drugs, and institutionalization status, then excluding components of cost for which there was no evidence of difference between arms, and finally, summing the remaining components.

Incremental costs and QALYs were calculated for each comparison within a linear regression framework, adjusting QALYs for baseline levels.[14] The probability of being cost-effective at a range of commonly accepted UK threshold values for an incremental QALY was estimated by resampling the patient population 2000 times using bootstrapping with replacement to generate a joint distribution of cost-effect pairs. Cost-effectiveness was calculated for each iteration, and the proportion of iterations in which a particular treatment is cost-effective provides an estimate of the probability of cost-effectiveness.[15]

Missing data were handled using multiple imputation (MI) methods.[16] MI using chained equations was applied to drug costs, costs for each of the self-reported resource use questions, institutionalization costs, and the EQ-5D utility score using predictive mean matching. Forty imputed data sets were created and averaged using Rubin's rule.[17] Included as covariates in the imputation equations were patients' baseline characteristics (age and sex), health outcomes, and health status measures (dementia, motor complications, and Hoehn and Yahr score), and a 1-period lagged value of the outcome variable. Imputation was performed separately by treatment allocation at randomization in accordance with guideline recommendations.[18] Two-part models were used for all cost items owing to the high frequency of zero observations. The probability of positive costs was estimated in the first part and the cost conditional on observing positive costs in the second, and from these expected cost was computed.[19] Predicted costs and QALYs for the period in which death occurred were adjusted for the proportion of the year survived.

To assess whether the differences in total costs and QALYs between levodopa and levodopa-sparing therapies differed for individuals older and younger than 70 years, an age effect and an interaction with treatment allocation were included in the linear regression models.

In the primary analysis, costs were attached to each drug based on the observed drug within each class (ie, levodopa, DA, MAOBI). However, the costs of drugs within class differ substantially, and there is no evidence of differential effectiveness by drug. Sensitivity analyses were therefore undertaken to explore the impact of using the cheapest drug within each class on cost-effectiveness (ie, ropinirole for patients receiving DA and oral selegiline for patients receiving MAOBI), assuming the choice of drug within class had no effect on HRQoL.

Results

One thousand six hundred and twenty people with early-stage PD were assigned to treatment groups in PD MED. The 27 individuals recruited in the Czech Republic or Russia were excluded from this analysis. Of the remainder, 1057 (66%) were randomly assigned 3 ways among DA, MAOBI, and levodopa, 335 (21%) were assigned 2 ways between DA and levodopa, and 201 (13%) were assigned 1 ways between DA and MAOBI. In total 1392 were randomized between levodopa-sparing therapy and levodopa and 905 between the 2 levodopa-sparing therapies, DA and MAOBI. Patients assigned only between DA and MAOBI had less severe disease and higher HRQoL and were younger than those in other assignations. Baseline EQ-5D utility was higher for those assigned MAOBI than for those assigned DA (0.68 vs 0.65; *P* for difference = 0.03). Other patient characteristics were balanced between randomization and treatment groups (Table 1). Rates of withdrawal (n = 33) and loss to follow-up (n = 5) were low; most censoring was because of the end of trial follow-up. The percentages of missing data in each year were similar across different types of resource

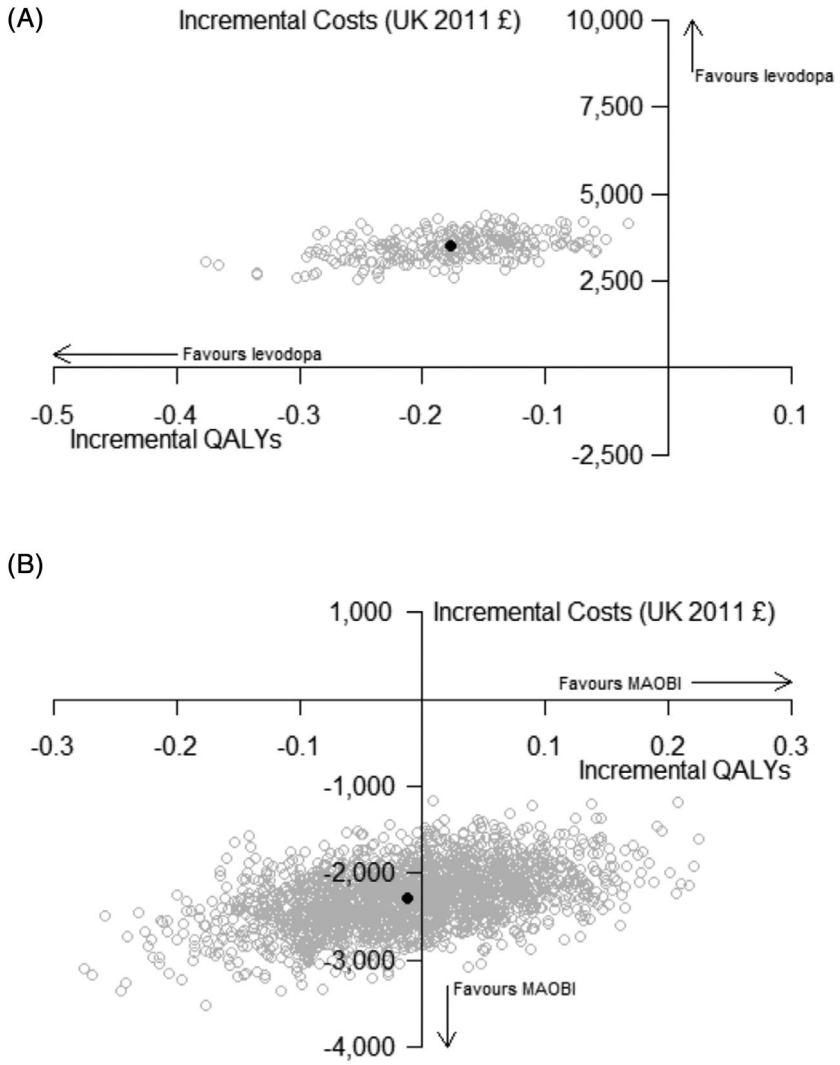

FIG. 1. Cost-effectiveness scatterplots for (**A**) levodopa versus levodopa-sparing and (**B**) dopamine agonists versus MAOBIs. (**A**) Levodopa versus levodopa-sparing. (**B**) Dopamine agonists versus MAOBIs. The gray circle represents the joint estimated distribution of cost and quality-of-life differences between treatment allocations based on 2000 bootstrapped samples. The black circle gives means of these differences.

use and HRQoL and increased with follow-up time (Table S2).

Levodopa Versus Levodopa-Sparing

The mean follow-up time in the comparison of levodopa versus levodopa-sparing was 4 years. Total QALYs were higher among those allocated levodopa (2.27 ± 0.05 QALYs) than those allocated levodopa-sparing therapy (2.10 ± 0.04 QALYs), and the unadjusted difference of 0.17 QALYs (95% CI, 0.04–0.30 QALYs; $P = 0.01$) was significant. Adjusting for QALYs at recruitment had little effect on the difference (0.18 QALYs; 95% CI, 0.05–0.30 QALYs; $P < 0.01$); see Table 2.

The mean aggregate cost of levodopa therapy received over the mean 4 years of follow-up was £186 (95% CI, £150–£223; $P < 0.01$) higher among those allocated levodopa than those allocated levodopa-sparing therapies. The costs of DAs and MAOBIs were higher among those allocated levodopa-sparing therapies than those allocated levodopa, with differences of £2773 (£2308–£3238; $P < 0.01$) and £206 (£143–£268; $P < 0.01$), respectively. The cost of other drugs received was higher among those allocated levodopa (£63; 95% CI: £6–£120; $P = 0.03$). In total, drug costs were £2729 (£2248–£3210; $P < 0.01$) higher in those allocated levodopa-sparing therapies compared with those allocated levodopa. Mean incremental costs for primary and outpatient care were £661 (£193–£1130; $P < 0.01$) higher among those allocated levodopa-sparing therapies. There was no evidence of significant differences in costs of inpatient care, home care, or in institutional care between treatment arms. Including drug costs and outpatient care costs, mean aggregate costs were £3390 (£2671–£4109; $P < 0.01$) higher among those allocated levodopa-sparing therapies (Table 2).

Allocation to levodopa was associated with significantly higher mean QALYs and lower mean costs than levodopa-sparing therapies. The probability that levodopa is cost-effective was estimated at 100% for all threshold values for a QALY considered (Fig. 1A). There was no evidence that the costs (P for interaction = 0.32), QALYs ($P = 0.80$), or cost-effectiveness differed for individuals younger than 70 years. Assuming all patients receiving DA and MAOBI receive ropinirole (mean daily dose, 11.4 mg) and oral selegiline (mean daily dose, 8.3 mg), respectively, the mean cost difference between levodopa and levodopa-sparing therapy fell by £876 to £1853, but still favored levodopa. Comparing levodopa with only MAOBI, assuming all patients received oral selegiline, the difference was smaller (£571) but still favored levodopa. This difference reflects greater treatment switching to DAs among those allocated MAOBIs than among those allocated placebo.[1] Hence, cost-effectiveness is not materially affected by the use of the least costly levodopa-sparing therapies, even assuming no difference in effectiveness between drugs within class.

TABLE 3 *QALYs and costs over mean 4 years of follow-up by treatment allocation and comparison of differences for dopamine agonists versus MAOBIs*

	Dopamine agonists	MAOBI	Difference[a]
Quality-adjusted life-years			
Unadjusted	2.11 (0.06)	2.14 (0.06)	0.03 (−0.13 to 0.19); $\underline{P} = 0.71$
Adjusted			−0.02 (−0.17 to 0.13); $\underline{P} = 0.79$
Costs (UK 2011 £)			
Levodopa	302 (16)	285 (15)	−16 (−60 to 27); $\underline{P} = 0.46$
Dopamine agonists	5620 (245)	2793 (244)	−2827 (−3507 to −2148); $\underline{P} < 0.01$
MAOBI	57 (31)	652 (32)	595 (507–684); $\underline{P} < 0.01$
Other drugs	172 (22)	109 (21)	−63 (−123 to −3); $\underline{P} = 0.04$
Durg subtotals	6151 (253)	3840 (252)	−2311 (−3014 to −1609); $\underline{P} < 0.01$
Primary care and outpatient use	3759 (201)	3700 (198)	−59 (−612 to 493); $\underline{P} = 0.83$
Inpatient and respite care	6809 (2516)	7039 (2514)	230 (−6715 to 7175); $\underline{P} = 0.95$
Personal social services	4516 (640)	4014 (616)	−502 (−2260 to 1255); $\underline{P} = 0.58$
Institutionalization	2370 (546)	2850 (544)	479 (−1039 to 1998); $\underline{P} = 0.54$
Total costs[b]	5849 (250)	3554 (249)	−2295 (−2989 to −1601); $\underline{P} < 0.01$

Values are mean (standard error) or mean (95% confidence interval).
[a]Positive values indicate higher costs and higher QALYs for those allocated MAOBIs.
[b]Includes only those cost components for which there is a significant difference ($\underline{P} < 0.05$) between arms.
MAOBI, monoamine oxidase type B inhibitor.

DA versus MAOBI

Mean follow-up time in the comparison of DA versus MAOBI was 4 years. Mean QALYs were similar for those allocated MAOBIs (2.14 ± 0.06) and DA (2.11 ± 0.06), with a nonsignificant difference of 0.03 QALYs (95% CI, −0.13 to 0.19 QALYs; $P = 0.70$). Adjusting for baseline QALYs, the difference (−0.02 QALYs; 95% CI, −0.17 to 0.13 QALYs; $P = 0.79$) remained nonsignificant (Table .3).

Mean aggregate costs of DA were £2827 (95% CI, £2148–£3507; $P < 0.01$) higher for those allocated DA than for those allocated MAOBI. Costs for MAOBIs were £595 (95% CI, £507–£684; $P < 0.01$) higher amongst those allocated to the MAOBI arm. There was no significant difference in the costs of levodopa between arms ($P = 0.46$). Costs of other drugs were higher among those allocated DA (difference, £63; 95% CI, £3–£123; $P = 0.04$). There were no significant differences in costs for primary care and outpatient care, hospital admissions, personal social services, or institutional care. Including those components of costs for which there were significant differences between arms, total costs were £2295 (95% CI, £1601– £2989; $P < 0.01$) higher for those allocated DA (Table .3).

Allocation to MAOBIs was associated with significantly lower costs than allocation to DAs, with no evidence of a difference in QALYs. For UK threshold values of £20,000 and £30,000 per incremental QALY, the probability that allocation to MAOBI is cost-effective compared with DA was 92% and 81%, respectively (Fig. 1B). Assuming all patients on DA receive ropinirole and all patients on MAOBI receive oral selegiline, the mean cost difference between DA and MAOBI remains very similar at £2133, favoring MAOBI. Hence, MAOBI remains the more cost-effective option even when compared with using the least costly DA.

Discussion

Allocation to levodopa was found to slightly improve HRQoL and reduce health care costs relative to allocation to the more expensive levodopa-sparing therapies. Levodopa is therefore deemed to be a highly cost-effective alternative to levodopa-sparing therapies. These results are consistent with the main clinical results, which reported better patient-rated HRQoL in the short- and long term with allocation to levodopa despite these patients developing more involuntary movements.[1]

The higher cost of levodopa-sparing therapy was predominantly a result of the high costs of DA. Assuming patients allocated to DAs and MAOBIs used the lowest-cost drug within class with no detrimental impact on quality of life, levodopa remained the cost-effective option. However, the rate of treatment switching from MAOBIs to DAs observed in this study is likely to be lower in current clinical practice following the results of the PD MED trial; this would further reduce the cost difference between levodopa and MAOBI therapies.

Previous analyses of PD MED identified a small advantage of MAOBIs over DAs in PDQ-39 mobility and summary index scores, but no significant difference in EQ-5D utility value.[1] Our area under the curve analyses similarly identified no difference in QALYs between levodopa-sparing treatment arms. However, because DAs are substantially more costly than MAOBIs, treatment with MAOBIs is the cost effective option when treatment with levodopa is not considered appropriate.

In clinical practice, patients younger than 60 years are typically initially treated with either a DA 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 to be less important. However, the PD MED clinical article identified no difference in treatment efficacy in those younger and older than 70 years. Similarly, no evidence was found in these analyses for a difference in QALYs, costs, or cost-effectiveness between age groups. However, the incidence of PD among individuals younger than 60 years is low,[2,20] and only 12% of patients in PD MED and fewer in the levodopa versus levodopa-sparing comparison were younger than 60 years at randomization. Further research — including longer follow-up of PD MED — is therefore needed to assess any age-related differences with greater certainty.

Resource use information across broad-ranging health and PSS was collected using self-reported questionnaires, raising the possibility of measurement error and leading to a substantial amount of missing data. Missingness was not related to treatment allocation but was found to be related to onset of dementia. Because dementia is likely to be an important cost driver, reported costs for use of health care services may underestimate true costs. However, differences in rates of dementia were not significantly different between treatment arms. Indeed, observed differences favored levodopa and so would be unlikely to contradict the conclusions of this analysis. Similarly because of the self-reported nature of resource use, costs in the period prior to death are likely to be underestimated; however, there is a nonsignificant difference in mortality favoring levodopa, so any bias is not expected to materially affect the conclusions. Further work is required to assess the extent of any bias resulting from inaccuracies in patient self-reported resource use, although we would expect any such bias to have equal effects across randomized treatment arms. Following NICE guidance,[10] we have not taken into account locally negotiated price discounts that may reduce the list price of some of the therapies considered here. Nor have we included costs other than those falling on the health and PSS systems, for example, patient and family expenditure on institutional care.

A further potential limitation of PD MED was the use of open-label treatment, which could have

promoted assessment bias. However, any such bias is probably small because all patients received active treatment and might also be likely to favor levodopa-sparing therapy insofar as the clinical results of PD MED were counter to the a priori expectations of most clinicians and patients. In comparing classes of drugs, we assumed equal efficacy of drugs within class in the absence of data to the contrary. Future assessments of cost-effectiveness between classes of drugs would benefit from further head-to-head comparisons between agents within each class.

In conclusion, allocation to levodopa was found to be associated with higher QALYs and reduced costs compared with allocation to levodopa-sparing therapies. Furthermore, if levodopa-sparing therapy is used, MAOBI therapy might be preferred, as it was associated with similar QALYs but substantially reduced costs.

Acknowledgments: PD MED was supported by funding from the UK National Institute for Health Research Health Technology Assessment Programme (project number 98/03/02). The University of Birmingham Clinical Trials Unit also received support from the UK Department of Health. Richard Gray is funded by the UK Medical Research Council, Emma McIntosh was partly funded by Parkinson's UK, and Alastair Gray was an NIHR Senior Investigator during the study. The views and opinions expressed in this article are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS, or the Department of Health. We thank all investigators who contributed to the trial, the patients who agreed to enter the study, and the Dementia and Neurodegenerative Disease (DeNDRoN) Clinical Research Network for their help with recruitment.

Writing Committee

S. Kent (University of Oxford), E. McIntosh (University of Glasgow), A. Gray (University of Oxford), C. E. Clarke (University of Birmingham; Sandwell and West Birmingham Hospitals NHS Trust), R. Gray (University of Oxford), A. Williams (University of Birmingham; Birmingham Hospitals NHS Trust), Natalie Ives (University of Birmingham), Smitaa Patel (University of Birmingham), Crispin Jenkinson (University of Oxford), Caroline Rick (University of Nottingham), Keith Wheatley (University of Birmingham).

UK PD MED Collaborative Group

A complete list of collaborators in the UK PD MED Collaborative Group is available elsewhere.[1]

References

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;384(9949):1196–1205.
2. Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. Mov Disord 2003;18(1):19–31.
3. Schrag A, Ben-Shlomo Y, Quinn NP. Cross sectional prevalence survey of idiopathic Parkinson's disease and Parkinsonism in London. BMJ 2000;321(7252):21–22.
4. Oertel WH, Quinn NP. Parkinson's disease: drug therapy. Baillieres Clin Neurol 1997;6(1):89–108.
5. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004;351(24):2498–2508.
6. Caillava-Santos F, Margis R, de Mello Rieder CR. Wearing-off in Parkinson's disease: neuropsychological differences between on and off periods. Neuropsychiatr Dis Treat 2015;11:1175–1180.
7. Ives NJ, Stowe RL, Marro J, et al. Monoamine oxidase type B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525 patients. BMJ 2004;329(7466):593.
8. Stowe RL, Ives NJ, Clarke C, et al. Dopamine agonist therapy in early Parkinson's disease. Cochrane Database Syst Rev 2008;(2):CD006564. https://doi.org/10.1002/14651858.CD006564.pub2.
9. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51(6):745–752.
10. National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal. London: National Institute for Health and Care Excellence; 2013.
11. Szende A, Oppe M, Devlin N, eds. EQ-5D Value Sets: Inventory, Comparative Review and User Guide. The Netherlands: Springer; 2007.
12. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35(11):1095–1108.
13. Richardson G, Manca A. Calculation of quality adjusted life years in the published literature: a review of methodology and transparency. Health Econ 2004;13(12):1203–1210.
14. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ 2005;14(5):487–496.
15. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. Br J Psychiatry 2005;187:106–108.
16. Noble SM, Hollingworth W, Tilling K. Missing data in trial-based cost-effectiveness analysis: the current state of play. Health Econ 2012;21(2):187–200.
17. Rubin D. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons; 1987.
18. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. Pharmacoeconomics 2014;32(12):1157–1170.
19. Burton A, Billingham LJ, Bryan S. Cost-effectiveness in clinical trials: using multiple imputation to deal with incomplete cost data. Clin Trials 2007;4(2):154–161.
20. Caslake R, Taylor K, Scott N, et al. Age-, gender-, and socioeconomic status-specific incidence of Parkinson's disease and parkinsonism in northeast Scotland: the PINE study. Parkinsonism Relat Disord 2013;19(5):515–521.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

SGML and CITI Use Only
DO NOT PRINT

Author Roles

R.G., C.E.C., A.G., C.J., K.W., and A.W. designed the trial. R.G., C.E.C., K.W., A.W., N.I., S.P., and C.R. ran the trial, and C.E.C. and A.W. recruited patients. A.G. and E.M. wrote the protocol for the economic analysis, performed interim analysis, and oversaw the economic evaluation. S.K. analyzed the data. S.K., E.M., and A.G. interpreted the data and wrote the manuscript. All listed authors contributed to revisions of the manuscript. The authors assume responsibility for the accuracy and completeness of the data and for the overall content and integrity of the paper.