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SYSTEMATIC REVIEW

Modelling the Cost Effectiveness of Treatments for Parkinson's Disease: An Updated Methodological Review

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Abstract

Objective This article systematically reviewed the methodological quality of modelling approaches for economic evaluations of the treatment of motor symptoms in Parkinson's disease in studies published after 2010.

Methods A systematic literature search was undertaken using PubMed, EconLit, the Cochrane Database of Systematic Reviews, National Health Service Economic Evaluation Database and Health Technology Assessment databases of the UK National Health Service Centre for Review and Dissemination (March 2010 to July 2022). Quality was assessed using a checklist from the German Scientific Working Group.

Results A total of 20 studies were evaluated, with the majority based on Markov models ($n = 18$). Studies assessed the cost effectiveness of medical ($n = 12$) or surgical ($n = 8$) treatment, and included costs from a payer or healthcare provider's perspective ($n = 17$). Furthermore, all studies included quality-adjusted life-years as an effect measure. In the quality assessment of the literature, a mean score of 42.1 points (out of 56 points) on the checklist of the German Scientific Working Group was achieved. Seventeen studies concluded the intervention under study was (likely) cost effective. No intervention was classified as cost ineffective.

Conclusions The quality of economic evaluation models in Parkinson's disease has improved in terms of calculating cost and transition parameters, as well as carrying out probabilistic sensitivity analyses, compared with the published literature of previous systematic reviews up to 2010. However, there is still potential for further development in terms of the integration of non-motor complications and treatment changes, the transparent presentation of parameter estimates, as well as conducting sensitivity analyses and validations to support the interpretation of results.

1 Introduction

The treatment of Parkinson's disease (PD) and its comorbidities is economically important, as therapeutic options are often highly specialised and therefore expensive [1–10]. Primary therapy consists of levodopa [11]. If PD progresses, other treatment options are available, for example dopamine agonists to stimulate dopamine production, or enzyme inhibitors to reduce dopamine degradation (e.g. decarboxylase/monoamine oxidase B/catechol-*O*-methyl transferase inhibitors). Combinations of several agents are also available, for example carbidopa (decarboxylase inhibitor) with levodopa (levodopa-carbidopa gastrointestinal gel [LCIG]/Duodopa®). To further improve motor complications (motor fluctuations and dyskinesias, also known as 'off times' during the day), absorption can be improved by infusion/injection (apomorphine) or more continuous administration by a pump (LCIG). In addition, multiple medications can be combined as best medical treatment (BMT). Moreover, surgical treatment options such as the invasive deep brain stimulation (DBS) or the non-invasive magnetic resonance tomography-guided focused ultrasound therapy (MrgFUS) are used when medication fails. In addition to the treatment of PD symptoms and motor complications, as well as consequences of the disease (e.g. falls due to limited mobility), treatment of non-motor complications (e.g. sleep disorders, depression, dementia) is often needed, which places an additional

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Key Points for Decision-Makers

In addition to Parkinson's disease symptoms and motor complications, future models should include non-motor complications and treatment changes.

Methodological quality could be improved by presenting parameter estimates transparently and by critically assessing their influence on the results.

Deterministic, scenario-based, and probabilistic sensitivity analyses and validations of parameters and model designs should be considered in the interpretation of results.

financial burden on the healthcare system [12]. As there is currently no disease-modifying treatment for PD, PD remains a chronic illness and therefore generates high healthcare costs over the long term [13]. Furthermore, the economic burden of PD is expected to increase owing to the older age of patients and an ageing population worldwide [14].

Economic evaluations are used to determine the efficiency of (new) interventions. In a cost-effectiveness analysis, the healthcare costs and effects associated with a new intervention are compared and related to costs and effects of an established treatment by calculating the incremental cost-effectiveness ratio. Effectiveness thereby can be measured based on clinical scales [e.g. Hoehn & Yahr (HY) or the Unified Parkinson's Disease Rating Scale (UPDRS)], as well as quality-adjusted life-years (QALYs), a standard measure for utilities in health economic evaluations, with one QALY representing 1 year of best health-related quality of life, and zero QALYs representing death. The HY scale measures the symptoms of PD, considering unilateral symptoms (HY I), bilateral symptoms (HY II), mild-to-moderate disability with impaired postural reflexes (HY III), severely disabling disease but still able to walk or stand unassisted (HY IV), and confinement to a bed or wheelchair unless aided (HY V). Compared to the HY scale, the UPDRS assesses symptoms through 42 questions in four domains (1) mentation, behaviour, mood, (2) activities of daily living, (3) motor examination and (4) complications of therapy.

Economic evaluations are often conducted based on clinical trials investigating the efficacy of a new intervention [15]. These "piggyback" studies benefit from the existing structure of the main trial such that health economic data are available at the same time as efficacy data with low additional costs for the health economic evaluation and data highly adapted to the research objective. However, clinical trials are generally limited to shorter follow-up periods, making it difficult to obtain long-term results. Furthermore, scenarios beyond the study protocol, such as younger/older patients with more/less symptoms or treatment changes, cannot be evaluated. To overcome these limitations, mathematical models can be used to determine the course of the disease for different time horizons by combining data from multiple sources [15].

Because economic evaluations based on modelling approaches cannot draw conclusions based on empirical data, a critical assessment of methodological quality is needed to determine the influence of model design, model assumptions, and parameter estimates, and to interpret results reasonably [16]. Systematic reviews of the literature on modelling the cost effectiveness of treatments for PD before 2010 showed major weaknesses in adherence to good modelling practice recommendations [17–19]. The authors criticized the predominant use of a healthcare payer's perspective and insufficient consideration of adverse events (other than motor complications) and comorbidities. Furthermore, sensitivity analyses to deal with statistical uncertainty, and validations of model design and parameter estimates were often inadequate. Therefore, the authors concluded that interpretation of the results may be limited. The current systematic review therefore updated previous reviews [17–19] by assessing the methodological quality of modelling approaches for economic evaluations of the treatment of motor symptoms in PD published after 2010.

2 Methods

2.1 Literature Review and Assessment

2.1.1 Literature Search

A literature search was conducted in PubMed, EconLit, the Cochrane Database of Systematic Reviews, National Health Service Economic Evaluation Database and Health Technology Assessment databases of the UK National Health Service Centre for Review and Dissemination (March 2010 to July 2022). The starting date for the date range of the literature search of March 2010 corresponded to the end date of literature searches of published reviews on the same subject [17, 18]. The search was based on the following keywords: 'Parkinso's disease', 'economic evaluation', 'decision analysis', 'health care model', 'Markov model', 'discrete event simulation' and 'QALY' [see Electronic Supplementary Material (ESM)]. This search was supplemented by a hand search of the reference lists of the included literature. A detailed description of search terms can be found in the ESM.

Included studies had to (1) address patients with PD, (2) present an economic evaluation (i.e. costs and effects of at least two interventions had to be compared and related), (3) compare treatment of motor symptoms and (4) be based on a mathematical modelling approach. Studies were excluded if they (1) were not original research, (2) were not published in English or (3) were published before 2010.

Literature was reviewed, the data extracted and the quality assessed by two independent authors (JD, JZ). Discrepancies were solved through discussion between the two authors.

2.1.2 Data Extraction and Assessment

Data extraction of the included evidence covered the following domains:

- Table 1. 'Summary of analytic framework and model features': reference, country, funding, study type, comparators, target population, perspective, time horizon, discount rate, outcomes, analytic approach, sensitivity analyses and validations, conclusions (by the authors).
- Table 2. 'Summary of input parameters of published cost-effectiveness models': reference, transition probabilities, efficacy, utilities, costs.

As international quality checklists such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [16] or the checklist by Drummond et al. [20] do not focus on modelling aspects of economic evaluations (such as the choice of model design, parameter estimation, dealing with uncertainties especially in the context of modelling) and thus do not contribute to all relevant aspects of the current study objective, a checklist of the German Scientific Working Group was used to assess the study quality [21]. This comprises 56 questions on context (two questions), evaluation framework (eight questions), analytic approach (four questions), health outcomes (seven questions), costs (nine questions), discounting (four questions), presentation of results (seven questions), uncertainty (six questions), discussion (seven questions) and conclusions (two questions). Each of the questions could be rated as 1 = 'criterion fulfilled', ½ = 'criterion partially fulfilled' and 0 = 'criterion not fulfilled', thus a maximal of 56 points could be achieved.

3 Results

The literature search resulted in 430, 23, 22 and 51 hits in PubMed, the National Health Service database, the Cochrane Library and EconLit, respectively (Fig. 1). In addition, eight studies were identified via screening of the references of included economic evaluations and systematic reviews. A total of 534 hits were found, of which 34 were duplicates. After screening the title and abstract, 51 full-text articles were reviewed. Of these, two were excluded that did not relate to PD, 13 were not health economic evaluations, two did not compare treatment of motor symptoms and six did not use a modelling approach. In addition, eight systematic reviews whose literature was screened were excluded. In sum, 20 original papers were included.

3.1 Treatment Options and Target Population

All studies evaluated the cost effectiveness of symptomatic treatment options after the onset of motor complications (Table 1) [22–41]. These included the dopamine agonist ropinirole [40] and the monoamine oxidase B inhibitor rasagiline [29, 31], as well as entacapone [31] and opicapone [32] as catechol-O-methyl transferase inhibitors. Furthermore, treatment with LCIG [24, 33, 35, 36] and extended-release carbidopa/levodopa [22] as a decarboxylase inhibitor as well as apomorphine [23, 39, 41] were evaluated. In addition to medical treatment, surgical interventions such as DBS [25–28, 30, 34, 38] and MRgFUS [37] were investigated.

The initial age of the patients varied between 52 [25, 30] and 65 [28, 40] years, depending on the treatment and its intended administration during the course of PD (Table 1). Accordingly, the model design was adjusted to the severity of the disease of the target population depending on the treatment under study. For the treatment of early motor complications, patients were assumed to be aged 52–63 years and frequently in HY I–III [25, 29, 30, 39]. For the treatment of motor complications in advanced stages of PD, patients were assumed to be aged 59–65 years with the majority being in HY II–IV and with higher 'off times' per day compared with patients with early motor complications [22–24, 26–28, 31–38, 40, 41].

The majority of studies took place in the UK [24, 27, 30, 33, 35, 36, 41] und USA [22, 29, 31, 32, 38, 39] healthcare systems. Three studies pertained to the Germany [25, 26, 41], and two to Canada [23, 37]. Remaining studies pertained to the Netherlands [40], Taiwan [28] and Japan [34] (Table 1).

3.2 Modelling Approach and Transition Probabilities

In all but three publications [29, 30, 37], disease progression was modelled by the disease-specific symptom scales HY [23–28, 33–36, 38, 40, 41] and 'off times' because of

Table 1 Summary of analytic framework and model features

Study, country (funding (F))	Study type (S) and comparators (C)	Target population: age (A), male gender (G), disease severity (DS)	Perspective (P), modelling time horizon (MTH), discount rate (D)	Outcomes	Analytic approach	Statistical analysis (A), uncertainty (U), model validation (V)	Most sensitive parameters of deterministic SA (D), results of probabilistic SA (P)	Conclusions (by the authors)
Medical treatment								
Apomorphine								
CADTH 2018, Canada (F: Canada's federal, provincial and territorial governments; exposé summited) [23]	S: CUA C: apomorphine injection vs BMT	A: 60 years G: representative for the Canadian population DS: 22%, 60%, 17% and 0.4% in HY states I–IV (5.86 hours per day spent with 'off time')	P: payer's perspective MTH: 5 years D: 1.5%	ICUR (CAN$/ QALY)	Markov model five health states: HY I–IV distinguished by 'off time' per day (0–25%, 26–50%, 51–75%, 76–100%) and death	A: deterministic cohort simulation U: deterministic and probabilistic SA V: n.r.	D: efficacy, dosage P: 27%/67% probability of cost effectiveness for apomorphine at WTP of CAN$ 50,000/100,000 per QALY *Reanalysis by CADTH common drug review* P: 0% probability of cost effectiveness for apomorphine at WTP of CAN$ 100,000 per QALY	Apomorphine injection is a cost-effective treatment strategy *Reanalysis by CADTH common drug review* A price reduction of almost 50% would be required for an apomorphine injection to achieve an ICUR less than $100,000 per QALY, and 65% to cost less than $50,000 per QALY
Thach et al. 2021, USA (F: Sunovion Pharmaceuticals Inc.) [39]	S: CUA/CEA C: apomorphine injection vs apomorphine sublingual film vs levodopa inhalation powder	A: 62.7 years G: n.r. DS: 1%, 73%, 26% in HY I–III (3.90 hours per day spent with 'off time')	P: payer's perspective MTH: 10 years D: 3% R: 2020	ICUR (USD/ QALY); ICER (USD/ 'off time' in hours; LY)	Microsimulation model 'off time' per day was simulated based on distributions informed by clinical outcomes for each comparator arm	A: microsimulation U: scenario-based SA V: external validation of results	Scenario analyses confirmed results of base-case analysis	Apomorphine sublingual film represents a cost-effective option compared with apomorphine injection or levodopa inhalation powder

Table 1 (continued)

Study, country (funding (F))	Study type (S) and comparators (C)	Target population: age (A), male gender (G), disease severity (DS)	Perspective (P), modelling time horizon (MTH), discount rate (D)	Outcomes	Analytic approach	Statistical analysis (A), uncertainty (U), model validation (V)	Most sensitive parameters of deterministic SA (D), results of probabilistic SA (P)	Conclusions (by the authors)
Walter et al. 2015, UK and Germany (F: EVER Neuro Pharma) [41]	S: CUA C: CSAI vs DBS/ LCIG/BMT	A: 59.1 years G: n.r. DS: 25%, 50%, 25% in HY III–V (50% of waking time in 'off time' state)	P: UK/German healthcare provider's perspective MTH: lifetime D: 3.5%/3%	ICUR (£/QALY or €/QALY)	Markov model three health states: HY III–V distinguished by 'off time' per day (0–25%, 26–50%, 51–75%, 76–100%) and death	A: deterministic cohort simulation U: deterministic and probabilistic SA V: external validation of results	*UK* D: efficacy; discount rates P: 87%/73%/72% probability of cost effectiveness for CSAI compared with BMT/DBS/ LCIG at WTP of £20,000 *Germany* P: 12%/50%/72% probability of cost effectiveness for CSAI compared with BMT/DBS/ LCIG at WTP of EUR 20,000	CSAI is a cost-effective therapy
Extended-release CD/LD								
Arnold et al. 2017, USA (F: Impax Laboratories, Inc.) [22]	S: CUA C: extended-release CD/LD vs LCE	A: 60 years G: n.r. DS: mean 'off time' per day 6 hours (at least 2.5 hours were required)	P: payer's perspective MTH: 5 years D: 3%	ICUR (USD/ QALY)	Markov model three health states: <25% 'off time' per day, ≥25% 'off time' per day and death	A: deterministic cohort simulation U: deterministic SA V: external validation of results	D: treatment costs; effects	Extended-release CD/LD was cost effective
LCIG								
Chaudhuri et al. 2022, UK (England) (F: AbbVie Inc.) [24]	S: CUA/CEA C: LCIG vs BMT	A: 64 years G: 59% male DS: 68%, 30%, 2% in HY III–V, severe motor complications (6.75 hours 'off time' per day)	P: payer's perspective MTH: 20 years D: 3.5%	ICUR (£/QALY); ICER (£/LY)	Markov model six health states: HY I–V distinguished by 'off time' per day (0%, 1–25%, 26–50%, 51–75%, 76–100%) and death	A: deterministic cohort simulation U: deterministic and probabilistic SA V: external validation of parameter estimates and results	D: healthcare resource utilization, long-term efficacy of LCIG, discount rate P: 40%/55% probability of cost-effectiveness for LCIG at a WTP £20,00/£30,000	The ICER of LCIG compared to BMT was estimated to be within the WTP thresholds and deemed cost effective

Table 1 (continued)

Study, country (funding (F))	Study type (S) and comparators (C)	Target population: age (A), male gender (G), disease severity (DS)	Perspective (P), modelling time horizon (MTH), discount rate (D)	Outcomes	Analytic approach	Statistical analysis (A), uncertainty (U), model validation (V)	Most sensitive parameters of deterministic SA (D), results of probabilistic SA (P)	Conclusions (by the authors)
Kalabina et al. 2019, UK (Scotland and Wales) (F: AbbVie Ltd.) [33]	S: CUA C: LCIG vs BMT (without apomorphine)	A: 64 years G: 59% male DS: HY III 'off time' 51–75%: 62%, HY III 'off time' 76–100% 3%, HY IV 'off time' 51–75%: 32%, and HY IV 'off time' 76–100%: 3%	P: payer's perspective MTH: 20 years D: 3.5%	ICUR (£/QALY)	Markov model six health states: HY I-V distinguished by 'off time' per day (0%, 1–25%, 26–50%, 51–75%, 76–100%) and death	A: deterministic cohort simulation U: deterministic, scenario-based and probabilistic SA V: n.r.	D: health state costs, long-term efficacy, costs of LCIG, and long-term discontinuations rate P: 22%/44%probability of cost effectiveness for LCIG at a WTP of £30,000/£50,000/QALY	In the setting of a very small population, with considerable unmet need, LCIG represents value for money, as reflected by funding approval across the UK
Lowin et al. 2011, UK (F: Abbott Healthcare Products Ltd.) [35]	S: CUA/CEA C: LCIG vs SoC	A: n.r. G: n.r. DS: 23%, 53%, 23% in HY III–V and 40% 60% with 26–50%/51–75% 'off time' per day	P: payer's perspective MTH: lifetime D: 3.5%	ICUR (£/QALY); ICER (£/LY)	Markov model four health states: HY III–V distinguished by 'off time' per day (0–25%, 26–50%, 51–75%, 76–100%) and death	A: deterministic cohort simulation U: deterministic SA V: n.r.	D: time to treatment, health state on treatment initiation and long-term efficacy	LCIG provides value for money in levodopa-responsive patients with PD with severe motor fluctuations when no other treatment options are effective or suitable. Given LCIG is an orphan drug, it is reasonable to suggest that it may be considered cost effective in the UK setting
Lowin et al. 2017, UK (Ireland) (F: Abbott Healthcare Products Ltd.) [36]	S: CUA/CEA C: LCIG vs BMT	A: 64 years G: n.r. DS: 68%, 30%, 2% in HY III–V, severe motor complications (6.75 hours 'off time' per day)	P: payer's perspective MTH: lifetime (20 years) D: 4%	ICUR (€/QALY); ICER (€/LY)	Markov model six health states: HY I–V distinguished by 'off time' per day (0%, 1–25%, 26–50%, 51–75%, 76–100%) and death	A: deterministic cohort simulation U: deterministic and scenario-based SA V: n.r.	D: healthcare costs, long-term efficacy and discontinuations	LCIG can be considered a cost-effective treatment for advanced PD

Table 1 (continued)

Study, country (funding (F))	Study type (S) and comparators (C)	Target population: age (A), male gender (G), disease severity (DS)	Perspective (P), modelling time horizon (MTH), discount rate (D)	Outcomes	Analytic approach	Statistical analysis (A), uncertainty (U), model validation (V)	Most sensitive parameters of deterministic SA (D), results of probabilistic SA (P)	Conclusions (by the authors)
Opicapone/entacapone								
Hansen et al. 2021, USA (F: Neurocrine Biosciences Inc.) [32]	S: CUA/CEA C: Opicapone vs entacapone (+CD/LD)	A: 64 years G: n.r. DS: 11% in <25% 'off time' per day, 89% in ≥25% 'off time' per day (synthetic cohort $n = 1000$)	P: payer's perspective MTH: 25 years D: 3%	ICUR (USD/QALY); ICER (USD/LY)	Markov model three health states: <25% 'off time' per day, ≥25% 'off time' per day and death	A: deterministic cohort simulation U: deterministic, scenario-based and probabilistic SA V: external validation of results	D: efficacy of treatment P: 60–65% probability of cost effectiveness for opicapone at a WTP of ≥US$5000	Opicapone (+CD/LD) appeared to be cost effective compared with entacapone
Rasagiline/entacapone/LCE								
Farkouh et al. 2012, USA (F: Teva Neuroscience) [29]	S: CUA/CEA C: rasagiline vs ropinirole XL/pramipexole/generic ropinirole/levodopa inhalation powder	A: 61 years G: n.r. DS: HY 1.5 (early PD)	P: managed care perspective MTH: 5 years D: 3%	ICUR (USD/QALY); ICER (USD/LY)	Markov model six health states: treatment with rasagiline, dopamine agonists (with and without dyskinesia) or levodopa (with and without dyskinesia) and death	A: deterministic cohort simulation U: deterministic and probabilistic SA V: external validation of one parameter estimate	D: utility, cost for dyskinesia P: 60.5% probability of cost effectiveness for rasagiline at a WTP of $50,000 per QALY when compared with generic ropinirole	Rasagiline delays treatment with levodopa, delays onset of dyskinesias, and was cost saving or cost effective compared with first-line therapies
Groenendaal et al. 2010, USA (F: Teva Neuroscience) [31]	S: CUA/CEA C: rasagiline/entacapone/LCE vs levodopa	Monte Carlo simulation of a cohort of 100 000 patients of PD patients with at least 1 h 'off time' per day	P: societal/payer's perspective MTH: 2 years D: 3%	ICUR (USD/QALY); ICER (USD/LY)	Markov model three health states: ≤25% 'off time' per day, >25% 'off time' per day and death	A: Monte Carlo simulation U: n.r. V: n.r.	n.r.	From a payer's perspective, rasagiline and LCE were dominant therapies over levodopa, while entacapone was effective at a higher cost

Table 1 (continued)

Study, country (funding (F))	Study type (S) and comparators (C)	Target population: age (A), male gender (G), disease severity (DS)	Perspective (P), modelling time horizon (MTH), discount rate (D)	Outcomes	Analytic approach	Statistical analysis (A), uncertainty (U), model validation (V)	Most sensitive parameters of deterministic SA (D), results of probabilistic SA (P)	Conclusions (by the authors)
Ropinirole								
van Boven et al. 2014, the Netherlands (F: GlaxoSmithKline) [40]	S: CUA C: ropinirole prolonged vs immediate release	A: 65 years G: n.r. DS: 60%, 33%, 6% in HY II–IV (95% >25% 'off time' per day)	P: healthcare providers' perspective MTH: 5 years D: 4% for costs and 1.5% for effects	ICUR (€/QALY)	Markov model six health states: HY I–V distinguished by 'off time' per day (>25% and ≤25%) and death	A: deterministic cohort simulation U: deterministic and probabilistic SA V: external validation of one parameter estimate	D: utility, dyskinesia, adherence P: 97.8% probability of cost effectiveness for ropinirole prolonged release at WTP of €20,000 per QALY	The results indicate a high likelihood of ropinirole prolonged release being cost saving or at least cost effective
Surgical treatment								
DBS								
Dams et al. 2013, Germany (F: German Ministry of Education and Research) [26]	S: CUA/CEA C: DBS vs BMT	A: 60 years G: 52.6% male DS: 50%, 30%, 20% in HY III–V with motor complications	P: payer's perspective MTH: lifetime D: 3%	ICUR (€/QALY) ICER (€/UPDRS point)	Markov model six health states: HY I–V (without treatment) and death HY I–V (with treatment) were assigned to HY states without treatment	A: deterministic cohort simulation U: deterministic and scenario-based SA V: external validation on parameter estimates and model structure	D: efficacy, duration to battery exchange, discount rate	DBS can be considered cost effective
Dams et al. 2016, Germany (no funding) [25]	S: CUA/CEA C: DBS vs BMT	A: 52 years G: 52.6% male DS: 5%, 65%, 20%, 10% in HY I–IV with early motor complications	P: payer's perspective MTH: lifetime D: 3%	ICUR (€/QALY) ICER (€/PDQ-39 point)	Markov model six health states: HY I–V (without treatment) and death HY I–V (with treatment) were assigned to HY states without treatment	A: deterministic cohort simulation U: deterministic SA V: external and internal validation on parameter estimates	D: duration to battery exchange, cost for battery exchange, surgery, drugs, efficacy	DBS is considered cost effective

Table 1 (continued)

Study, country (funding (F))	Study type (S) and comparators (C)	Target population: age (A), male gender (G), disease severity (DS)	Perspective (P), modelling time horizon (MTH), discount rate (D)	Outcomes	Analytic approach	Statistical analysis (A), uncertainty (U), model validation (V)	Most sensitive parameters of deterministic SA (D), results of probabilistic SA (P)	Conclusions (by the authors)
Eggington et al. 2014, UK (F: Medtronic International) [27]	S: CUA C: DBS vs BMT	A: 60.5 years G: n.r. DS: 15%, 20%, 50% and 10% in HY I–IV (0–25% 'off time' per day: 30%; 26–50% 'off time' per day: 48%; 51–75% 'off time' per day: 20%, 76–100% 'off time' per day: 2%)	P: payer's perspective MTH: 5 years D: 3.5%	ICUR (£/QALY)	Markov model six health states: HY I–V distinguished by 'off time' per day (0–25%, 26–50%, 51–75%, 76–100%) and death	A: deterministic cohort simulation U: deterministic and scenario-based SA V: external validation on parameter estimates	D: utilities, drug costs, surgery costs	Results suggest that DBS is cost effective
Fann et al. 2020, Taiwan (F: Medtronic) [28]	S: CUA/CEA C: DBS vs BMT	hypothetical cohort of 10,000 patients with late PD A: 65.2 years G: 57.3% male DS: 15%, 52%, 28%, 27% and 16% in HY I–V	P: societal perspective MTH: 10 years D: 3.5%	ICUR (USD/QALY) ICER (USD/LY)	Markov model five health states: HY I–IV and death	A: Markov chain Monte Carlo simulation U: probabilistic SA V: external validation on parameter estimates	P: DBS is an optimal strategy when the willingness to pay is over $41,000/QALY	DBS was more cost effective in terms of LY and QALY gained
Fundament et al. 2016, UK (F: Medtronic) [30]	S: CUA C: DBS vs BMT	A: 52.6 years G: 71.3% male DS: 1.06, 4.85 12.29 and 5.54 UPDRS I–IV points (early motor complications)	P: payer's perspective MTH: 15 years D: 3.5%	ICUR (£/QALY)	Markov model three health states: DBS, BMT and death (patients could withdrawal from DBS to BMT, continue with DBS or BMT, or die)	A: deterministic cohort simulation U: deterministic and probabilistic SA V: external validation on parameter estimates	D: time horizon, costs of surgery, effect duration P: 99% probability of DBS being cost effective at a WTP of £30,000/QALY	Results indicate that DBS is cost effective

Table 1 (continued)

Study, country (funding (F))	Study type (S) and comparators (C)	Target population: age (A), male gender (G), disease severity (DS)	Perspective (P), modelling time horizon (MTH), discount rate (D)	Outcomes	Analytic approach	Statistical analysis (A), uncertainty (U), model validation (V)	Most sensitive parameters of deterministic SA (D), results of probabilistic SA (P)	Conclusions (by the authors)
Kawamoto et al. 2016, Japan (no funding) [34]	S: CUA C: DBS vs BMT	A: 60 years G: 100% male DS: early (HY III), intermediate (HY IV), later stages PD (HY V) with motor complication	P: payer's perspective MTH: 10 years D: n.r.	ICUR (Yen and USD/QALY)	Markov model six health states: HY I–V distinguished by 'off time' per day (0–25%, 26–100%) and death	A: deterministic cohort simulation U: deterministic and probabilistic SA V: external validation on parameter estimates	D: costs of surgery, drug costs, utilities P: 93% probability of cost effectiveness for DBS at WTP of 5 million Yen/QALY	Results suggests that DBS is cost effective
Pietzsch et al. 2016, USA (no funding) [38]	S: CUA C: DBS vs BMT	A: 60.5 years G: 64% male DS: advanced PD	P: payer's perspective MTH: 10 years D: 3%	ICUR (USD/QALY)	Markov model six health states: HY I–V distinguished by 'off time' per day (0–25%, 26–50%, 51–75%, 76–100%) and death	A: deterministic cohort simulation U: deterministic SA V: external validation on parameter estimates	D: costs of surgery, utilities, time to battery exchange, time horizon	DBS is a cost-effective treatment strategy
MRgFUS								
Meng et al. 2020, Canada (Medtronic, Canadian Institute of Health Research Clinician Scientist Award; Focused Ultrasound Foundation, InSightec) [37]	S: CUA C: MRgFUS vs DBS or BMT	Tremor-dominant patients with PD	P: societal perspective MTH: lifetime D: 1.5%	ICUR (CAN$/QALY)	Decision tree three health states: no, minor and major complications for DBS and MRgFUS; distinguished whether reoperation is needed or not in the case of DBS	A: deterministic cohort simulation U: deterministic SA V: n.r.	D: efficacy, costs of DBS and MRgFUS, time horizon	MRgFUS is a cost-effective treatment for patients with tremor-dominant PD, particularly over BMT. While MRgFUS remains competitive with DBS, the cost-effectiveness advantage is less substantial

BMT best medical treatment, *CD/LD* carbidopa/levodopa, *CEA* cost-effectiveness analysis, *CSAI* continuous subcutaneous apomorphine infusion, *CUA* cost-utility analysis, *DBS* deep brain stimulation, *HY* Hoehn & Yahr, *ICER* incremental cost-effectiveness ratio, *ICUR* incremental cost-utility ratio, *LCE* levodopa/carbidopa/entacapone, *LCIG* levodopa carbidopa gastrointestinal gel, *LY* life-years, *MRgFUS* magnetic resonance-guided focused ultrasound, *MDS-UPDRS* Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale, *n.r.* not reported, *'off time'* times with treatment indicated motor complications, *PD* Parkinson's disease, *PDQ-39* Parkinson's disease questionnaire, *QALY* quality-adjusted life-year, *SA* sensitivity analysis, *SoC* standard of care, *UPDRS* Unified Parkinson's Disease Rating Scale, *WTP* willingness to pay

Table 2 Summary of input parameters of published cost-effectiveness models

Study, publication year, country	Transition probabilities	Efficacy	Utilities	Costs
Medical treatment				
Apomorphine				
CADTH 2018, Canada [23]	'Off time'-specific progression [35] Life tables + PD-specific mortality [48]	29–46% reduction in 'off time' per day for the first years with apomorphine	QALYs based on the EQ-5D (Swedish data) [35] Disutility for 2 months because of adverse events for apomorphine injection [41]	Direct cost for hospitalization, specialist visits, general practitioner visits, magnetic resonance tomography, computer tomography + intervention-specific costs for drugs and adverse events
Thach et al. 2021, USA [39]	HY/'off time'-specific progression [38] 'Off time' per day was calculated as the product of self-reported number of daily 'off time' and the typical duration of an 'off time' [58] Life tables + PD-specific mortality risk [48]	Changes in 'off time' per day by each treatment on demand Discontinuation because of adverse events for the first 12 weeks	QALYs based on the EQ-5D (Swedish data) [35] + utility gain for each 'off time' reduced + disutilities for adverse events (US data) [55]	Direct costs for hospital stays, emergency room visits, informal care, specialists + intervention-specific costs for drugs and adverse events
Walter et al. 2015, UK and Germany [41]	HY/'off time'-specific progression [43, 54, 55] PD-specific mortality [43]	Intervention-specific reduction in 'off time' per day of 35% (CSAI), 40% (LCIG) and 37% (DBS) compared with BMT Improvement in HY of 44% (CSAI), 47% (LCIG) and 46% (DBS) for 6 months	QALYs based on the EQ-5D (Swedish data) [35] Disutilities for adverse events	Costs for specialists visits, general practitioner visits, community nurse, hospital visits, magnetic resonance tomography, computer tomography, single photon emission computed tomography + intervention-specific costs for drugs and adverse events + supplies for apomorphine, LCIG or surgery, battery exchange and complications for DBS
Extended-release CD/LD				
Arnold et al. 2017, USA [22]	'Off time'-specific progression [55]	Intervention-specific changes in 'off time' for the first 6 months	QALYs based on the valuation of 'off time' per day (US trial data) [53]	Direct medical costs + intervention-specific drug costs

Table 2 (continued)

Study, publication year, country	Transition probabilities	Efficacy	Utilities	Costs
LCIG				
Chaudhuri et al. 2022, UK (England) [24]	HY/'off time'-specific progression [54, 55, 59] Life tables + PD-specific mortality [47, 59]	Improvement in 'off time' per day and HY + delayed progression for 12 months under LCIG ½ of persons treated with LCIG improved in 'off time' for 5 years	HY/'off time'-specific QALYs based on the EQ-5D (UK data) + caregiver' disutilities (UK data)	NHS data on healthcare utilization for each health state Intervention-specific costs for drugs + LCIG equipment, follow-up visits and adverse events
Kalabina et al. 2019, UK (Scotland and Wales) [33]	HY/'off time'-specific progression [55, 59] Life tables + PD-specific mortality	Improvement in 'off time' per day and HY + delayed progression for 12 months under LCIG ½ of persons treated with LCIG improved in 'off time' after 12 months	HY/'off time'-specific QALYs based on the EQ-5D (UK data) + caregiver' disutilities (UK data)	NHS data on healthcare utilization for each health state Intervention-specific costs for drugs + LCIG equipment, follow-up visits and adverse events
Lowin et al. 2011, UK [35]	HY/'off time'-specific progression [43, 54, 55] PD-specific mortality [43]	Improvement in 'off time' per day and HY + delayed progression for 6 months under LCIG ½ of persons treated with LCIG improved in 'off time' after 6 months	HY/'off time'-specific QALYs based on the EQ-5D (Swedish data)	NHS data on healthcare utilization for each health state Intervention-specific costs for drugs + LCIG equipment, follow-up visits and adverse events
Lowin et al. 2017, UK (Ireland) [36]	HY/'off time'-specific progression [54, 55, 59] Life tables + PD-specific mortality [59]	Improvement in 'off time' per day and HY + delayed progression for 6 months under LCIG + discontinuation of treatment ½ of persons treated with LCIG improved in 'off time' after 6 months	HY/'off time'-specific QALYs based on the EQ-5D (UK data)	NHS data on healthcare utilization for each health state Intervention-specific costs for drugs + LCIG equipment, follow-up visits and adverse events
Opicapone/entacapone				
Hansen et al. 2021, USA [32]	'Off time'-specific progression [53] Life tables + PD-specific mortality [50]	Intervention-specific improvement of 35% (entacapone) and 37% (opicapone) in 'off time' per day Intervention-specific discontinuation probabilities between 15% (opicapone) and 20% (entacapone) for 1 year	QALYs based on the valuations on 'off time' per day (US data) [54] Utility decrements of 0.026 per 'off time' per day	Costs for adverse events, specialist visits, general practitioner, nurse visit, hospital + intervention-specific drug costs

Table 2 (continued)

Study, publication year, country	Transition probabilities	Efficacy	Utilities	Costs
Rasagiline/entacapone/LCE				
Farkouh et al. 2012, USA [29]	Time-dependent trial based transition probabilities between different treatments [60, 61] and for the occurrence of dyskinesia [61, 62] time-dependent trial based mortality [42]	Transition probabilities were based on treatment options and included treatment efficacy	QALYs based on the valuations on 'off time' per day (US data) [54]	Costs for inpatient and outpatient treatment, long-term care, medical equipment + intervention-specific drug costs
Groenendaal et al. 2010, USA [31]	'Off time'-specific progression [63, 64] mortality [65]	Intervention-specific changes in 'off time' for the first year	QALYs based on the valuations on 'off time' per day (US data) [54]	Costs for inpatient and outpatient treatment, long-term care and indirect medical costs + intervention-specific drug costs
Ropinirole				
van Boven et al. 2014, Netherlands [40]	HY/'off time'-specific progression [66, 67] Life tables + PD-specific mortality [45]	Improvement in 'off time' per day and adherence to treatment	QALYs based on the valuations on HY and 'off time' per day	direct medical costs + intervention-specific drug costs
Surgical treatment				
DBS				
Dams et al. 2013, Germany [26]	Natural progression [68] + progression under treatment Life tables + PD-specific mortality [51] + DBS-specific mortality [69-72]	49% improvement in motor complications for 4 years 16.1% improvement in UPDRS II score for the first year; 18.2% and 14.8% in UPDRS III score for the first 2 years	QALYs (EQ-5D) had been estimated by PDQ-39 data (German data) [57] + improvements due to DBS for 4 years + perioperative utility reduction for 3 months	Direct medical costs + cost for surgery, battery exchange, adverse events and changes in drug costs due to DBS
Dams et al. 2016, Germany [25]	Natural progression [68] + progression under treatment Life tables + PD-specific mortality [51] + DBS-specific mortality [69-72]	41% and 32% improvement in motor complications for the first year and afterwards	QALYs (EQ-5D) had been estimated by PDQ-39 data (German data) [57] + improvements due to DBS + perioperative utility reduction for 3 months	Direct medical costs + cost for surgery, battery exchange, adverse events and changes in drug costs due to DBS
Eggington et al. 2014, UK [27]	HY/'off-time'-specific progression [54, 55, 73] Life tables + PD-specific mortality [48]	For each treatment arm, transition probabilities were modified using time-to-event curves	HY/'off time'-specific QALYs based on the EQ-5D (US and Swedish data) [35, 54]	Costs for drugs, falls/hospitalisation, outpatient specialist visits, PD-nurse visits + DBS-specific costs for surgery, battery exchange and adverse events

Table 2 (continued)

Study, publication year, country	Transition probabilities	Efficacy	Utilities	Costs
Fann et al. 2020, Taiwan [28]	Multinomial logistic regression model to derive HY-specific progression based on UPDRS III and PD-specific mortality	Improvements in UPDRS III due to DBS	HY-specific QALYs based on the EQ-5D (US and Swedish data) [35, 54]	Costs for drugs, outpatient neurology appointment, home care, terminal care, productivity loss due to death + DBS-specific costs for surgery and battery exchange
Fundament et al. 2016, UK [30]	Expert opinion on probability for withdrawal Life tables + UPDRS-specific mortality [49]	Efficacy was modelled by different disease courses in UPDRS I, II, III and IV for each treatment arm over 2 years afterwards different courses in UPDRS IV (motor complications) were assumed	QALYs (EQ-5D) had been estimated by PDQ-39 data [74] + improvements due to DBS for the first 2 years	Costs for drugs, hospitalisation, adverse events, falls, PD nurse visits + DBS-specific costs for surgery and battery exchange
Kawamoto et al. 2016, Japan [34]	HY/'off time'-specific progression [44, 54, 55, 73] PD-specific mortality [44]	Efficacy was modelled by different disease courses in HY and 'off time' per day for the first 6 months	HY/'off time'-specific QALYs based on the EQ-5D (US and Swedish data [35, 54])	Intervention-specific drug costs + DBS-specific costs for surgery, battery exchange, and adverse events
Pietzsch et al. 2016, USA [38]	HY/'off time'-specific progression [55, 73] Life tables + PD-specific mortality [48]	Efficacy was modelled by different disease severities for the initial population	HY/'off time'-specific QALYs based on the EQ-5D (US and Swedish data) [35, 54]	Intervention-specific costs for drugs, withdrawal treatment, falls/hospitalisation, specialist visits + DBS-specific costs for surgery, battery exchange and adverse events
MRgFUS				
Meng et al. 2020, Canada [37]	Occurrence of complications and reoperation based on several clinical trials	Efficacy was realised by different transition probabilities for the occurrence of complications and reoperation	QALYs has been estimated by PDQ-39 data [75]	drug costs + MRgFUS-specific costs for surgery and complications or DBS-specific costs for surgery, reoperation and complications

BMT best medical therapy, *CD/LD* carbidopa/levodopa, *DBS* deep brain stimulation, *EQ-5D* EuroQoL-5 Dimensions, *HY* Hoehn & Yahr, *LCE* levodopa/carbidopa/entacapone, *LCIG* levodopa carbidopa gastrointestinal gel, *MRgFUS* magnetic resonance-guided focused ultrasound, *NHS* National Health Service, *n.r.* not reported, *'off time'* times with treatment indicated motor complications, *PD* Parkinson's disease, *PDQ-39* Parkinson's disease questionnaire, *QALY* quality-adjusted life-year, *UPDRS* Unified Parkinson's Disease Rating Scale

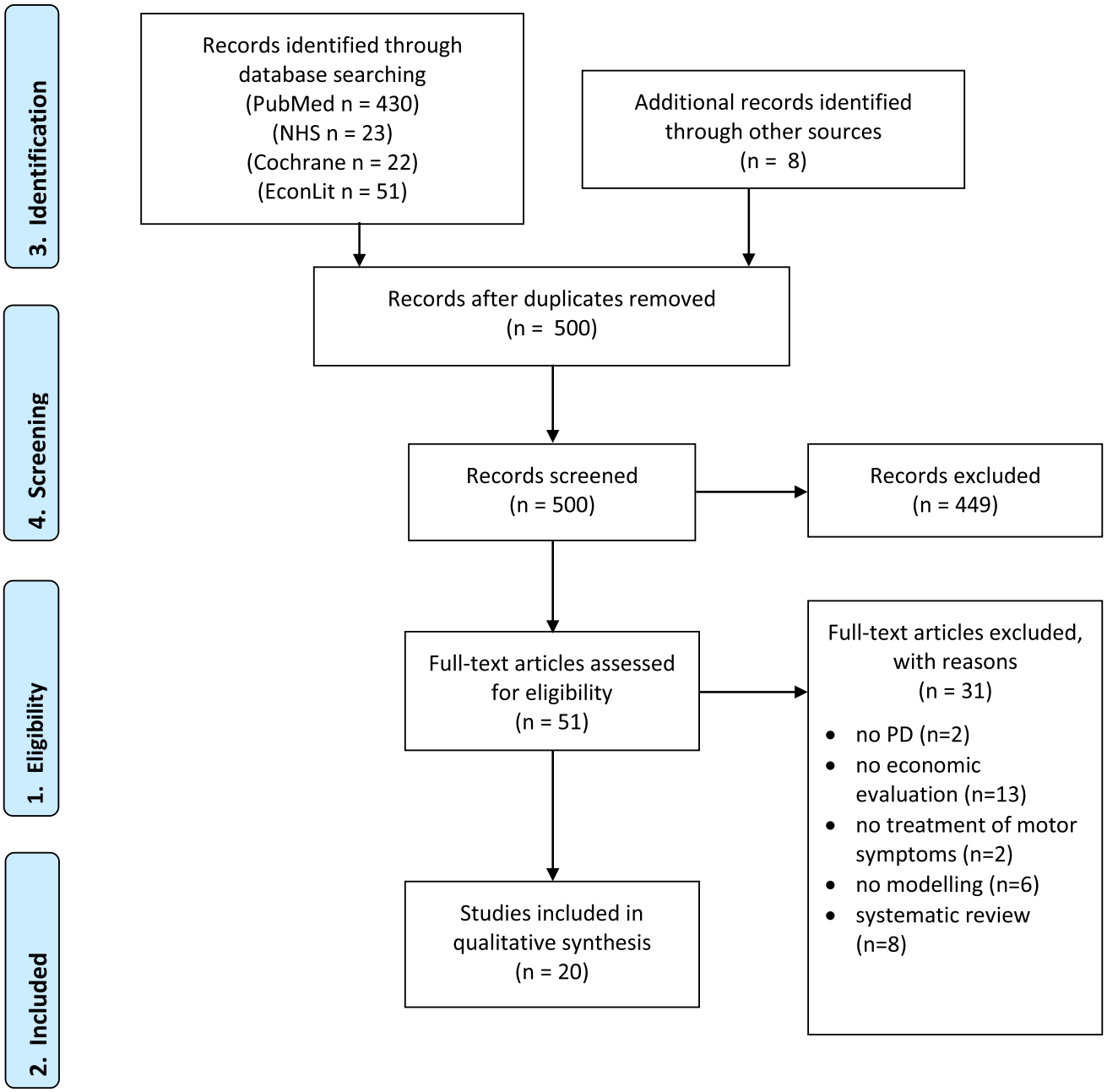

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. *NHS* National Health Service, *PD* Parkinson's disease

motor complications caused by treatment measured using the UPDRS IV question no. 32 [22–27, 31–36, 38–41] (Table 1). Thereby, the majority of models chose a combination of HY levels and 'off times' per day [23, 24, 27, 33–36, 38, 40, 41]. In addition to HY levels and 'off times' per day, two studies integrated the natural progression that occurs because of the lack of disease-modifying treatments in PD, despite adequate symptom reduction with medication [25, 26]. Other models were based on surgical complications [37]. In addition, two publications modelled changes in treatment caused by discontinuation of treatment during the course of PD [29, 30]. Furthermore, one microsimulation modelled 'off times' per day by estimating parameter distributions [39].

The transition probabilities for disease progression and treatment efficacy were taken from clinical trials (Table 2). Progression reported in the trials differed by target population. Treatment efficacy was either realised through improvements in 'off times' per day [22, 23, 25, 26, 31, 32, 39, 40], through a combination of improvements in HY stages

and 'off times' per day [24, 27, 33–36, 38, 41], or through improvements in UPDRS scores [28, 30]. In addition to disease progression, effects on treatment adherence [40], treatment discontinuation [32, 36, 39] and the incidence of surgical complications [37] were also considered. Efficacy (if stated) was assumed to last between 3 months and 5 years [22–26, 29–36, 38, 39, 41].

To reflect increased mortality due to PD, either PD-specific data from clinical trials [28, 29, 34, 35, 41] or country-, age- and/or sex-specific data from mortality tables were weighted with appropriate risk rates [23–27, 30, 32, 33, 36, 38–40]. The probability to die within 1 year based on PD-specific data ranged from 0.004 to 0.225 [42–44], with severity-specific values reported once [43]. The relative risk of death compared to the general population ranged from 1.18 to 4.99 [45–52], again considering disease severity [47, 48]. One study did not include a PD-specific mortality risk [31]. Two other studies did not report transition probabilities for mortality [22, 37].

3.3 Utilities

All studies were cost-utility studies and thus included QALYs as the outcome (Table 2). Three US studies [53–55] were used to determine utilities (standard gamble) for different 'off times' per day [22, 27–29, 31, 32, 34, 38, 39]. In addition, Swedish data (EQ-5D index) [35] were integrated into models based on HY stages and 'off times' per day [23, 27, 28, 34, 35, 38, 39, 41]. The data quality was significantly reduced by the older publication date of the studies [53–55] and small sample sizes [35, 54, 55], with data for later stages of the disease not reported on in any study. One study failed to elaborate on the methodology used to determine QALYs [53]. Several authors calculated the EQ-5D index based on HY stages and 'off-times' per day using UK tariffs [24, 33, 36]. In four studies, PD questionnaire (PDQ-39) data were used to predict the EQ-5D index because data on country-specific utilities were missing [25, 26, 30, 37]. Treatment-related improvements in QALYs [25, 26, 30, 39], reductions in QALYs because of adverse events [23, 25, 26, 32, 37, 39, 41] as well as caregiver disutilities [24, 33] were also considered.

A total of eight studies reported QALYs without referring to the country of the health system under study [23, 27, 28, 34, 35, 38, 39, 41]. In two studies, the country for which QALYs were calculated could not be determined [37, 40]. Clinical effectiveness were integrated as life-years gained [24, 28, 29, 31, 32, 35, 36, 39], UPDRS [26] and PDQ-39 [25] points gained, as well as avoided 'off time' [39] (Table 1).

3.4 Costs

The majority of studies were based on average health states costs to which intervention costs were added [22–26, 29, 31–33, 35–37, 39, 40] (Table 2). Only six studies did not rely on health states but included cost categories expected to be influenced by treatment [27, 28, 30, 34, 38, 41].

Intervention costs included drug costs [22–41] and costs related to adverse events [23–27, 33–39, 41]. In the case of LCIG and apomorphine, costs of equipment and supplies were added [24, 33, 35, 36, 41], while in the case of surgical interventions, cost of surgery and battery replacement, if appropriate, was considered [25–28, 30, 34, 37, 38, 41]. If not included in the average health state costs, costs of follow-up visits [24, 27, 28, 30, 33, 35, 36, 38], nursing/care [27, 28, 30, 38] and falls [27, 30, 38] were integrated separately. Indirect costs due to productivity losses were considered by two studies [28, 31].

Reimbursement data were used in all studies to determine costs, especially intervention costs [22–41]. In addition, data from randomised controlled trials for drug costs [22, 25–27, 30] and adverse event costs [23, 25–27, 34, 38, 39] were used. Occasionally, medical costs were based on hospital reimbursement data [28], survey data [22] and results of meta-analyses [38]. Average costs of health states were taken from cost-of-illness studies [25, 26, 29, 31], reimbursement data [23, 24, 33, 35, 36] and a Dutch guideline for PD [40]. Three authors stated that they relied partially on expert opinion to calculate costs [22, 24, 33].

Most studies measured costs from a payer's [22–27, 30–36, 38, 39] or healthcare provider's perspective [29, 40, 41] (Table 1). Three studies indicated that they were conducted from a societal perspective [28, 31, 37].

3.5 Assumptions

Assumptions about model structure were reported in five studies [22, 23, 27, 30, 40], with two studies providing only very limited information [22, 40]. In more than half of the studies, assumptions about parameter estimates were reported [23, 24, 27, 30, 33–36, 38–41], and again with some studies reporting them only briefly [22, 34, 40, 41]. Overall, justifications for assumptions were often missing [22, 27, 33, 35, 41] or only partially reported [23, 24, 30, 38]. In addition, only two studies presented assumptions made in an aggregated form [23, 39]. Seven studies did not elaborate on assumptions [25, 26, 28, 29, 31, 32, 37].

3.6 Uncertainty and Validation

Uncertainties of parameter estimates were assessed using one-way sensitivity analyses [22–27, 29, 30, 32–38,

40, 41], scenario analyses [26, 27, 32, 33, 36, 39] and probabilistic sensitivity analyses [23, 24, 28–30, 32–34, 40, 41] (Table 1). For this purpose, parameter ranges reported in the literature were primarily used [25–27, 29, 30, 36] or variations between 10% and 50% were assumed. These were supplemented by scenarios that considered the research question and the intervention under study [26, 27, 32, 33, 36, 39]. In probabilistic sensitivity analyses, the underlying distributions were often not explicitly named [23, 32, 33, 41]. When specified, costs were assumed to be gamma distributed [24, 29, 30, 40], transition probabilities were assumed to be beta distributed [24, 29, 30, 34, 40] and utilities were assumed to be normally [30] or beta distributed [24, 29, 40]. The distribution parameters were not specified.

The majority of the results depended on the parameter estimates based on treatment efficacy and effects [22–26, 30, 32, 33, 35–37, 40, 41], intervention cost [22, 25, 27, 30, 33, 34, 37, 38], healthcare utilisation costs [24, 33, 36] and utility values used to assess health status [27, 29, 34, 38, 40] (Table 1). Furthermore, model assumptions in the discount rate [24, 26, 33, 41] and the time horizon [30, 37, 38] led to major variations in the results. For validation parameters, estimates [24–30, 34, 38, 40] and results [22, 24, 26, 32, 39, 41] were discussed in relation to the published literature (Table 1).

3.7 Quality Assessment

Overall, a mean score of 42.1 points (out of 56 points; 75%) on the checklist of the German Scientific Working Group (range between 32 and 52 points; Table 3) was achieved in the quality assessment of the included studies. The introduction was often described in detail. However, some studies only briefly presented the comparative interventions and target population [23, 25–28, 34, 37, 38, 41]. In addition, some studies failed to consider a sufficiently long time horizon (>3 years) [31, 37]. The methodology used was mainly adequately selected and applied. Some studies showed deficiencies in the transparent presentation of parameter estimates [23, 25, 26, 28, 29, 34, 36, 37] and model assumptions [22, 24–26, 28, 29, 31–37, 40]. Furthermore, parameter estimates for utilities were often not country specific [23, 27, 28, 34, 35, 39, 41] and cost categories were not always presented [23, 25, 26, 28]. In addition, costs were not justified by the perspective used [23, 31, 37]. In some cases, currency adjustments [23, 28, 32, 35, 36] were not reported. All included studies presented results as (incremental) costs, effects and incremental cost-effectiveness ratios. However, information on the effectiveness was missing for some studies [37] or results were presented superficially [28, 29, 31–33, 36, 37, 39–41]. Uncertainty was addressed by deterministic, scenario-based and probabilistic sensitivity analyses, although results were not always used for interpretation [23, 24, 29, 32, 35, 36, 39]. Likewise, the majority of studies failed to interpret results practically and give implications for the respective health system [22, 23, 25–34, 36, 40] as well as to validate the model structure [22, 23, 27–41] and assumptions [22, 23, 28, 31–33, 35, 37, 39–41].

3.8 Funding

Fifteen studies were funded by manufacturing companies providing the treatment assessed [22, 24, 27–33, 35–37, 39–41]. Two studies received public funding [23, 26] and three studies were not funded [25, 34, 38].

4 Discussion

The literature on model-based economic evaluations of interventions for PD since 2010 [22–41] comprised 20 articles. Most target populations comprised patients with advanced PD, with a mean age of ≥60 years, and mainly intermediate disease stages (HY II–IV) [22–24, 26–28, 32–40]. All but three studies [23, 31, 33] considered the evaluated interventions to (might) be cost effective. None of the studies clearly rejected the intervention under evaluation. Sensitivity analyses showed that in particular the estimates of the treatment efficacy [22–26, 30, 32, 33, 35–37, 40, 41], cost [22, 24, 25, 27, 30, 33, 34, 36–38] and effectiveness/utility parameters [27, 29, 34, 38, 40], as well as model assumptions on the time horizon [30, 37, 38] and discount rate [24, 26, 33, 41] had a major impact on the cost-effectiveness results.

Numerous reviews have addressed the evidence on economic evaluations of PD treatment to inform decision makers about the economic efficiency of PD interventions [1–10]. However, the methodological aspects of modelling approaches were only addressed by three systematic reviews, including $n = 19$ studies published before 2010 [17–19]. Compared with the earlier literature, the quality of the model design had improved so that models were capable of comparing more than two treatment options [29, 31, 39, 41] or were able to simulate treatment changes [29, 30]. Furthermore, improvements had been made in modelling PD symptoms and motor complications by adequately combining these two factors to model treatment efficacy [23–27, 29, 33–41], as well as in using a PD-specific mortality [23–30, 32–36, 38–41]. In addition, the natural progression of the disease had been considered in two studies [25, 26]. Thus, the efficacy of interventions had been assessed by improvements or delayed worsening of PD severity [23, 24, 27, 28, 30, 33–36, 38, 41] and motor complications [22–27, 30–36, 38–41]. Furthermore, some models included adverse events [23–27, 30, 32–35, 37–39, 41] or treatment discontinuation/

Table 3 Quality assessment using the checklist of the German Scientific Working Group

	Evaluations of medical treatment												Evaluations of surgical treatment							
	Apomorphine			Extended-release carbidopa-levodopa	LCIG				Opicapone	Rasagiline		Ropinirole	DBS							MRgFUS
	CADTH 2018, Canada [23]	Thach et al. 2021, USA[40]	Walter et al. 2015, UK/Germany [41]	Arnold et al. 2017, USA [22]	Chaudhuri et al. 2022, UK [24]	Kalabina et al. 2019, UK [33]	Lowin et al. 2011, UK [35]	Lowin et al. 2017, UK [36]	Hansen et al. 2021, USA [32]	Farkouh et al. 2012, USA [29]	Groenendaal et al. 2010, USA [31]	van Boven et al. 2014, the Netherlands [40]	Dams et al. 2013, Germany [26]	Dams et al. 2016, Germany [25]	Eggington et al. 2014, UK [27]	Fann et al. 2020, Taiwan [28]	Fundament et al. 2016, UK [30]	Kawamoto et al. 2016, Japan [34]	Pietzsch et al. 2016, USA [38]	Meng et al. 2020, Canada [37]
Context (2)	1.5	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Evaluation frame (8)	7	7	7.5	8	8	8	8	8	8	8	7.5	8	6.5	6.5	5	5	8	7	6	4.5
Analytical methods and modelling (4)	2	4	4	3	3	3.5	3	3	2.5	2.5	2.5	3.5	1.5	1.5	4	1.5	4	2.5	4	2
Health outcomes (7)	4.5	6.5	5.5	5.5	7	6.5	6.5	6.5	6	5	5.5	3	6.5	6.5	5.5	5.5	6.5	5	6	4.5
Costs (9)	4	7	6.5	8	8	7.5	4.5	4.5	4	8	8	7	6.5	6.5	7	4	6	6	7	6
Discounting (4)	2.5	3.5	4	4	4	3.5	2.5	2	3	4	4	4	4	4	4	2	4	1	4	3.5
Presentation of results (7)	5	5.5	6	5.5	6	4	5	4	6	5	5	4	7	7	5.5	5	5.5	5.5	5.5	2
Uncertainty (6)	2	3	5	4	5	5	3.5	4.5	6	5	0	5	5	4	5	2.5	5	5	4	3
Discussion (7)	2	4.5	4.5	3.5	6.5	1.5	5	4	2	3	1.5	3	4	4	5	1.5	4	3.5	5.5	4
Conclusion (2)	1.5	2	1.5	2	2	1.5	1.5	1.5	1.5	1.5	2	2	2	2	2	2	2	2	2	1.5
Sum (56)	32	45	47	45.5	52	43	42	40	41	44	38	42	45	44	45	31	47	40	46	33

Table 4 Recommendations for future models

Model design
The course of Parkinson's disease should be modelled by clinical symptom scales including (non-)motor complications.
For long-term analyses, treatment discontinuations and changes should be considered.
For upcoming disease-modifying therapies, natural progression (not to be confounded with 'off time' per day or motor complications) needs to be modelled.
Parameter estimates
All parameter estimates should be presented transparently.
The efficacy of interventions should be reflected by altered transition probabilities and/or delayed disease progression. Long-term efficacy should decline over time and not be assumed far beyond the time horizon of empirical data. The assumptions made must be justified.
Effectiveness parameters should include utility values and clinical measures. Utilities should be country specific, and if country-specific data are missing, authors should critically present and discuss uncertainties and limitations.
Cost categories and their data basis should be explicitly stated and justified by the chosen perspective. If possible, a societal perspective should be chosen.
Results
The results on (incremental) costs, effects and incremental cost-effectiveness ratio should be presented transparently in tabular and textual form.
Sensitivity analysis and validation
The sensitivity analyses should include deterministic, scenario-based and probabilistic sensitivity analyses.
The parameter estimates, model design and assumptions should be externally and internally validated and critically discussed. Assumptions should be explicit stated (e.g. as a bulleting list or table).
Discussion and conclusions
Interpretation of the results should consider results of sensitivity analyses and the respective healthcare system to derive recommendations for decision making.
Reviewing manuscripts
Innovative new modelling approaches should be more frequently used to overcome current limitations (e.g. integration of treatment discontinuation and changes, natural progression, late-stage disease).
The quality of future economic models should be reviewed by authors and reviewers against published checklists prior to publication, focusing on methodological weaknesses identified in this review.

adherence [32, 36, 38–40]. However, the consequences of motor symptoms (such as falls) [27, 30, 38] or caregivers' and patients' disutilities due to PD/adverse events [23–26, 33, 39, 41] were only occasionally considered. As most of the modelling mapped the course of PD on the HY scale, courses based on more differentiated scales, such as the UPDRS, remain unconsidered. However, the integration of more differentiated symptom scales (compared to the HY scale) into Markov models is often challenging because the health states must be independent of each other, which is more difficult to achieve with more complex scales. Nevertheless, a more differentiated view of the course of disease would be desirable. Limitations also remain in the estimation of parameter values and in the lack of sensitivity analyses and validations conducted, which will be discussed in the following sections. Recommendations for future modelling can be found in Table 4.

4.1 Parameter Estimates

Sensitivity analyses revealed a large impact of efficacy, cost and effectiveness parameters on the results, making it necessary to account for uncertainties and assumptions around these parameter estimates. Efficacies of interventions were estimated using empirical data with follow-up periods that ranged from 3 months to 5 years, so that influences on PD symptoms and motor complications could be adequately addressed. However, effects were often assumed to be maintained over the entire time horizon (10–25 years), although the literature has reported reduced efficacy of treatments over the course of PD, which in turn lead to treatment changes [11]. Thus, it may be unrealistic to assume efficacy far beyond the time horizon of empirical data, and at least a decline in efficacy should be modelled when considering long time horizons.

Effectiveness measures included utilities (QALYs) [22–41] and life-years [24, 28, 29, 31, 32, 35, 36, 39], complemented by clinical effect measures (UPDRS [26] and PDQ-39 [25] points gained, as well as avoided 'off hours' [39]). As a QALY is a generic measure and results could be compared in different disease areas, all authors draw conclusions based on QALYs as an effect measure. Unfortunately, only limited data exist on health-related quality of life of patients with PD to calculate QALYs. Currently, only five studies were used as the basis for utility values in all included studies [35, 53, 54, 56, 57], four of which were published before 2005 [53, 54, 56, 57]. Data on severe PD were completely lacking.

Thus, country-specific utilities could only be used in nine studies [22, 24–26, 29–33] and results are likely to be influenced by the lack of data on country-specific utility values. Country-specific utility data are therefore highly desirable for future studies. However, until data on health-related quality of life are available, authors should describe in detail the methods used to calculate effectiveness parameters, and uncertainties in parameter estimates should be adequately addressed in sensitivity analyses and validations. Moreover, results should be critically discussed.

In contrast, cost parameters were based on country-specific data. However, not all of the studies described the methods for calculating costs in sufficient detail (e.g. the cost categories included and their monetary valuation [23, 25, 26, 28, 32, 35, 36] and some failed to justify the cost categories based on the cost perspective chosen [23, 31, 37]). In particular, only adverse events related to the administration of LCIG, apomorphine, or DBS [23–27, 33–39, 41] and falls [27, 30, 38] were considered as cost categories, and the models did not consider other consequences of motor symptoms or non-motor complications (e.g. depression or sleep disorders). Moreover, indirect costs from a societal perspective were only considered by two studies [28, 31]. A detailed methodological description of parameter estimation and a more frequently applied societal perspective for cost parameters is therefore strongly recommended for the future.

4.2 Sensitivity Analyses and Validations

Compared with previous systematic reviews [17–19], the current evidence included more comprehensive sensitivity analyses. The previous literature included deterministic sensitivity analyses, but only a few studies carried out scenario-based or probabilistic sensitivity analyses. In contrast, more recent studies supplemented deterministic sensitivity analyses with scenario analyses [26, 27, 32, 33, 36, 39] and probabilistic sensitivity analyses [23, 24, 28–30, 32–34, 40, 41] to account for uncertainty around point parameter estimates. The parameter ranges used were based on the literature [25–27, 29, 30, 36] or on percentage variations around the estimated values [22, 24–26, 32–38, 40, 41]. In particular, the values varied widely, between 10 and 50%, without justification, for example by considering the distribution of parameter estimates or external validated values from the literature [22, 24–26, 32–38, 40, 41]. It would therefore be useful to describe the methods of sensitivity analyses transparently and justify chosen parameter ranges, as well as specify distributions and distribution parameters determined for probabilistic sensitivity analyses.

Unfortunately, the results of sensitivity analyses were rarely used to interpret results, thus for eight studies (all manufacturer funded), conclusions on cost effectiveness should be considered with caution [23, 29, 32, 33, 35–37, 41]. In general, the interpretation of probabilistic sensitivity is less frequently incorporated into conclusions and misinterpreted. For example, a probability for the cost effectiveness of 70% is often misinterpreted as cost effective for the intervention under study. Thereby, the authors neglect that the counter probability indicates that on average 30% of the cases in the comparison group are expected to be cost effective. In such a case, the results can only be interpreted as a tendency towards the cost effectiveness of the studied intervention, and this therefore requires precise description within conclusions. The cost effectiveness of the evaluated intervention is therefore only (mathematically) certain if the probability of cost effectiveness exceeds a high threshold (e.g. 95% assuming a commonly used α-level of 0.05).

In addition to internal validation of parameter estimates through sensitivity analyses, parameter estimates [24–30, 34, 38, 40] and results [22, 24, 26, 32, 39, 41] were also externally validated against values reported in the literature, although not all parameter estimates were always explicitly reported [23, 25, 26, 28, 29, 34, 36, 37]. However, internal and external validations of model structures [24–26] and assumptions [23, 27, 30, 38, 39, 41] were rarely reported. It would therefore be desirable to validate the model structure and assumptions like parameter estimates in future research.

4.3 Conflicts of Interest

Because of the methodological weaknesses described, compliance with the recommendations on good modelling practice is extremely important [16, 20]. Only if the development of the model is independent of conflicts of interest, and methods and results are presented transparently and discussed critically, can correct and meaningful interpretation of results and conclusions be achieved. Most of the included studies were funded by the manufacturing companies, so that a financial conflict of interest and possible influence on results cannot be excluded [22, 24, 27–33, 35–37, 39–41]. A Canadian study was part of a health technology assessment and independently reviewed by the Canadian Agency for Drugs and Technologies in Health Common Drug Reviews, where the results of the review did not confirm those of the authors [23]. Only three studies were conducted financially independently [25, 34, 38]. We therefore recommend that authors and reviewers check the (methodological) quality of the economic evaluations using published checklists [16, 20, 21] prior to publication.

4.4 Strengths and Limitations

This study examines the methodological quality of the modelling approaches used in economic evaluations of interventions for PD published between 2010 and 2022. Unlike previous reviews that assessed economic evaluations based on empirical data and focused on cost-effectiveness results and their socioeconomic consequences [1–10], the current study provided methodological recommendations to improve future modelling by systematically assessing the quality of the published literature. For this purpose, a German checklist of the German Scientific Working Group from 1999 was used [21]. Unfortunately, international checklists to assess the quality of economic evaluations, such as CHEERS [16] or the checklist by Drummond et al. [20], do not explicitly focus on aspects on modelling quality and therefore could not be used in the current study. Accordingly, an international checklist focusing on modelling for health economic evaluations is needed. Furthermore, the current review mainly focused on Markov models, which were used by most of the included studies. Thus, other modelling approaches, such as microsimulation or discrete event simulation, were not addressed in this study. However, innovative new methodological approaches might overcome some limitations of Markov models (e.g. the consideration of discrete time intervals, the Markov assumption of independence in health states over time or the integration of treatment changes) and should therefore be used more frequently to model cost effectiveness in the future. Finally, it should be noted that two of the included studies were published by the first author of this review [25, 26]. Although the evaluation was independently cross-checked by the other co-authors, this may have led to unintended bias.

5 Conclusions

Overall, compared with the previous literature up to 2010 [17–19], the quality of models for economic evaluations of interventions in PD and the transparency of their presentation has improved over the last decade. Caution was taken in cost and transition parameter estimation, as well as in consideration of uncertainty via probabilistic sensitivity analyses. However, most of the limitations mentioned by previous systematic reviews are still not adequately addressed. Future research should therefore strive to integrate the consequences of motor symptoms (e.g. comorbidities/falls, discontinuation of or changes in treatment) and non-motor complications (e.g. depression, sleep disorders, dementia). Furthermore, parameter estimates should be presented transparently and, if possible, adopted to the societal perspective. The uncertainty of parameter estimates should be assessed by sensitivity analyses and be considered in the interpretation of results. Moreover, validations of the model design and assumptions are recommended.

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