bmjmedicine

Check for updates

Deep brain stimulation for Parkinson's disease: systematic review with meta-analysis and trial sequential analysis

Johanne Juul Petersen [1], Caroline Barkholt Kamp [1,2], Pascal Faltermeier,[1] Sophie Juul,[1,3,4] Annemette Løkkegaard,[5] Christian Gluud,[1,2] Janus C Jakobsen[1,2]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjmed-2023-000705).

[1]Centre for Clinical Intervention Research, Copenhagen Trial Unit, Rigshospitalet, Copenhagen, Denmark
[2]Department of Regional Health Research, University of Southern Denmark Faculty of Health Sciences, Odense, Denmark
[3]Stolpegaard Psychotherapy Centre, Mental Health Services in the Capital Region of Denmark, Gentofte, Denmark
[4]University of Copenhagen, Department of Psychology, Copenhagen, Denmark
[5]Department of Neurology, Bispebjerg Hospital, Kobenhavn, Denmark
Correspondence to: Dr Johanne Juul Petersen, Centre for Clinical Intervention Research, Copenhagen Trial Unit, Rigshospitalet, Copenhagen, Denmark; johanne.juul.petersen@ctu.dk

Cite this as: *BMJMED* 2024;3:e000705. doi:10.1136/bmjmed-2023-000705

Received: 10 July 2023
Accepted: 12 July 2024

ABSTRACT

OBJECTIVE To assess the benefits and harms of deep brain stimulation for Parkinson's disease.

DESIGN Systematic review with meta-analysis and trial sequential analysis.

DATA SOURCES Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, Latin American and Caribbean Health Sciences Literature (LILACS), and other sources, from inception to 9 May 2023.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES Randomised clinical trials of deep brain stimulation with antiparkinsonian drug treatment use versus antiparkinsonian drugs only (primary comparison, seven trials) for Parkinson's disease. Other comparisons were deep brain stimulation versus surgery with sham stimulation (three trials) and versus resective surgery (two trials).

RESULTS Primary outcomes were all cause mortality, serious adverse events, and disease specific symptoms. In seven trials, 1125 participants were randomised to receive deep brain stimulation with antiparkinsonian drugs versus antiparkinsonian drugs only. All results had a high risk of bias and the certainty of the evidence was very low for all primary outcomes. Information size was insufficient for assessing all cause mortality (risk ratio 2.69, 95% confidence interval (CI) 0.79 to 9.24; I^2=0.0%; τ^2=0.00; P=0.12; four trials). Meta-analysis showed that deep brain stimulation increased the risk of serious adverse events (risk ratio 2.36, 95% CI 1.37 to 4.09; I^2=73.7%; τ^2=0.24; P<0.01; six trials) mainly because of an increased risk of perioperative complications, such as cerebral haemorrhages and postoperative confusion, and hardware related events, such as infection at the stimulator site, dislocation of the device, or reoperations. Meta-analyses indicated that deep brain stimulation might reduce some symptoms specific to Parkinson's disease, but assessment of disease specific symptoms in these trials had methodological limitations, including not reporting overall symptom scores.

CONCLUSIONS The certainty of evidence was very low for all primary outcomes, and based on the included evidence, the beneficial effects were questionable because of methodological limitations. Compared with only antiparkinsonian drug treatment, deep brain stimulation with antiparkinsonian drugs seemed to increase the risk of serious adverse events, mainly because of perioperative complications and hardware related events. Conducting randomised clinical trials of adequate methodological quality to effectively evaluate the effects of deep brain stimulation is crucial.

SYSTEMATIC REVIEW REGISTRATION PROSPERO CRD42022306556.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Deep brain stimulation has been used for neurological disorders globally since the 1980s
⇒ The benefits and harms associated with deep brain stimulation for Parkinson's disease have not previously been systematically assessed

WHAT THIS STUDY ADDS

⇒ Deep brain stimulation with antiparkinsonian drug treatment seemed to increase the risk of serious adverse events compared with antiparkinsonian drug treatment only
⇒ Preliminary results indicated that deep brain stimulation might reduce symptoms specific to Parkinson's disease, but the beneficial effects are uncertain because of methodological limitations

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Randomised trials assessing patient important outcomes, including adverse effects, are urgently needed
⇒ Observational studies could supplement randomised trials, especially for assessing rare adverse events

Introduction

Parkinson's disease is a neurological disorder with a rising incidence and prevalence, currently affecting more than 1% of the world's population.[1] Parkinson's disease affects different parts of the brain, including the medulla oblongata, midbrain, and neocortex.[2] The pathophysiology includes a reduction in dopaminergic neurons leading to motor symptoms, such as bradykinesia, resting tremor, and rigidity, and non-motor symptoms, such as insomnia, depression, and dementia.[3 4] Currently, no cure for Parkinson's disease exists, and the primary treatment is antiparkinsonian drugs (commonly levodopa) and physical therapy.[5 6] For short term use, levodopa is effective in treating motor symptoms.[5 7 8] For long term use, levodopa can lead to unacceptable adverse effects, such as dyskinesias, and response fluctuations precluding an effective dose.[5 7 8]

Deep brain stimulation has been used for disorders associated with pathophysiological neuronal pathways since the 1980s.[9] Currently, deep brain stimulation is approved globally to treat various

psychiatric and neurological disorders, including Parkinson's disease.[10 11] Deep brain stimulation uses high frequency stimulation through implanted electrodes,[12] theoretically inhibiting pathological beta oscillations caused by loss of dopaminergic neurons.[12] This effect regulates output from the globus pallidus interna to the thalamus and cortex.[12] The main targets when treating Parkinson's disease with deep brain stimulation are the subthalamic nucleus for a reduction in motor symptoms or the internal globus pallidus for a reduction in drug related dyskinesias.[13] After placement of the electrodes in the target area, pulse width, frequency, and amplitude are adjusted to achieve the maximum beneficial effect with minimal adverse effects.[13] Adverse effects of the stimulation include impaired gait and speech, spastic muscle contraction, and autonomic adverse effects, such as nausea.[13] Also, implantation can result in complications associated with surgery, such as intracerebral haemorrhage, infections, or adverse effects related to anaesthesia.[14]

No high quality systematic review has systematically assessed the effects of deep brain stimulation for Parkinson's disease.[15] The objective of this review was to assess the benefits and harms associated with deep brain stimulation for Parkinson's disease in randomised clinical trials.

Methods

We report this systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (online supplemental text 1).[16] The updated methodology used in this systematic review was conducted according to our protocol,[15] which was registered in the PROSPERO database before the start of our literature searches. Differences between the protocol and the review were adding follow-up time and disease duration as post hoc subgroup analyses. We also chose to add beta binomial regression models for our primary outcomes (all cause mortality and serious adverse events) post hoc because of multiple zero event arms.

Search strategy and selection criteria

A full time search specialist searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Medical Literature Analysis and Retrieval System Online (Medline Ovid), Excerpta Medica database (Embase Ovid), Latin American and Caribbean Health Sciences Literature (LILACS; Bireme), CINAHL (EBSCO host), BIOSIS (Web of Science), Science Citation Index Expanded (Web of Science), Chinese Biomedical Literature Database (CBM), Conference Proceedings Citation Index-Science (CPCI-S; Web of Science), China Network Knowledge Information (CNKI), Chinese Science Journal Database (VIP), and Wanfang Database, to identify relevant randomised clinical trials. We searched all databases from their inception to 9 May 2023. Online supplemental text S2 shows details of the search strategies.

Reference lists of relevant trial publications were checked for unidentified randomised clinical trials. To identify unpublished trials, we searched clinical trial registries in Europe, the US, and China, and websites of pharmaceutical companies, the US Food and Drug Administration, and European Medicines Agency.

We included randomised clinical trials irrespective of publication year, status, and language. We included crossover trials with only data from the first period of the trial. Participants in all age groups with a diagnosis of Parkinson's disease (as defined by trialists) were included. Participants were included irrespective of sex, comorbidities, and risk factors.

We included any type of deep brain stimulation as the intervention (as defined by trialists), independent of the target of the electrodes, stimulation settings, unilateral or bilateral, and device used. As control interventions, we accepted no intervention, usual care, sham stimulation, medical treatment, or resective surgery. We accepted any cointerventions if these were planned to be delivered similarly in the experimental and control groups.

Data extraction and risk of bias assessment

Two authors (JJP and SJ) independently screened relevant trials. Two authors (JJP and PF) independently extracted data with a standardised data extraction sheet and assessed risk of bias based on the Cochrane Risk of Bias tool, version 2 (RoB 2).[17 18] Discrepancies were resolved by discussion or, if required, by discussion with a third author (JCJ). We contacted corresponding authors if relevant data were unclear or missing.

Outcomes and subgroup analyses

Primary outcomes were all cause mortality, serious adverse events (as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH-GCP)),[19] and disease specific symptoms (online supplemental table S1).[15 19] Secondary outcomes were quality of life, depressive symptoms, executive functioning, level of functioning, and non-serious adverse events (online supplemental table S1). We classified non-serious adverse events as any adverse event not assessed as serious, according to the ICH-GCP definition.[19] For all outcomes, we used the trial results reported at maximum follow-up. We also planned subgroup analyses on overall risk of bias, vested interests, target nucleus, subtype of disease, and

severity of disease.[15] We chose to add follow-up time and disease duration as post hoc subgroup analyses.

Assessment of statistical and clinical significance

We performed our aggregate data meta-analyses according to Cochrane,[17] Keus et al,[20] and the eight step assessment by Jakobsen et al[21] for better validation of meta-analytic results in systematic reviews. We used risk ratios for dichotomous outcomes. We assessed three primary outcomes for each comparison, and therefore adjusted our thresholds for significance[21]; we used a P value of ≤0.025 as the threshold for significance.[21] Because we mainly considered the results of the secondary outcomes as hypothesis generating, we did not adjust the P value thresholds for secondary outcomes. We conducted random effects (inverse variance and DerSimonian-Laird) and fixed effect (Mantel-Haenszel) meta-analyses for all analyses and mainly reported the most conservative result (highest P value). Less conservative results were considered in a sensitivity analysis.[17 21 22] Primary outcomes (all cause mortality and serious adverse events) were also analysed with beta binomial regression models because of multiple zero event arms.

We used trial sequential analysis to control random errors.[23–31] Trial sequential analysis estimates the diversity adjusted required information size (DARIS), which is the number of participants needed in a meta-analysis to detect or reject a specific intervention effect. Statistical heterogeneity was quantified by calculating heterogeneity (I^2, τ^2) for traditional meta-analyses, and diversity (D^2) for trial sequential analysis.[28] We used Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to assess the certainty of evidence.[32] We downgraded imprecision in GRADE by two levels if the accrued number of participants was <50% of DARIS and one level if 50-100% of DARIS.[21] We did not downgrade if benefit, harm, futility, or DARIS was reached. We used Fisher's exact test to calculate P values if the results were from only one trial. Stata 17 was used for all statistical analyses.[33]

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting of this research. However, we are committed to a transparent and comprehensive dissemination of our research results. We aim to inform patients, caregivers, clinicians, and other relevant stakeholders through a variety of channels, including conferences and social media platforms. By actively sharing our findings through these channels, we aim to foster an informed community, encourage ongoing dialogue, and enhance the practical application of our research in clinical settings.

Results

Trial characteristics

Our literature searches (up to 9 May 2023) identified 29 269 records after duplicates were removed. We included 12 clinical trials, with 1564 participants randomised to the intervention or control.[34–45] The primary comparison was deep brain stimulation with antiparkinsonian drug treatment versus antiparkinsonian drug treatment only (seven trials).[34–40] Other comparisons were deep brain stimulation with antiparkinsonian drugs versus surgery with sham stimulation and antiparkinsonian drugs (three trials)[43–45] or resective surgery with antiparkinsonian drugs (two trials) (figure 1 and online supplemental table S2).[41 42] We identified two more trials of deep brain stimulation versus surgery with sham stimulation for dementia[46] and balance.[47] In these trials, six participants were randomised but no relevant data were reported and we could not obtain data from the authors; these studies were not included in our analyses.[46 47]

For participants receiving deep brain stimulation, the electrodes were placed bilaterally[34–45] or unilaterally[38 41] in the subthalamic nucleus,[34 36 39 40 42–45] subthalamic nucleus or globus pallidus pars interna,[37 38] caudal zona incerta,[35] or ventral intermediate thalamic nucleus.[41] The stimulation parameters (voltage, frequency, and pulse width) were continuously adjusted after implantation of the electrodes.[34–45] In both the experimental and control groups, antiparkinsonian drug treatment was continuously adjusted for each participant.[34–40]

Online supplemental table S2 shows the characteristics of the included trials. All trials had a high risk of bias (online supplemental table S3). The maximum follow-up time ranged from three months[43–45] to two years after randomisation.[39 40] Figure 2 has a visual overview of all of the results, including the GRADE assessments.

Most trials assessed symptom scores after antiparkinsonian drug treatment was paused in all participants.[34–45] We mainly report assessment of symptom scores when participants received antiparkinsonian drugs because most patients attending everyday clinics will receive drugs continuously. The supplementary material (online supplemental text S3, online supplemental figures S1 and S2) shows the full results of subsections of the Unified Parkinson's Disease Rating Scale (UPDRS) score, when participants received antiparkinsonian drug treatment and when drug treatment was paused, analyses of secondary outcomes, and overall analyses of all cause mortality and serious adverse events, including all comparisons.

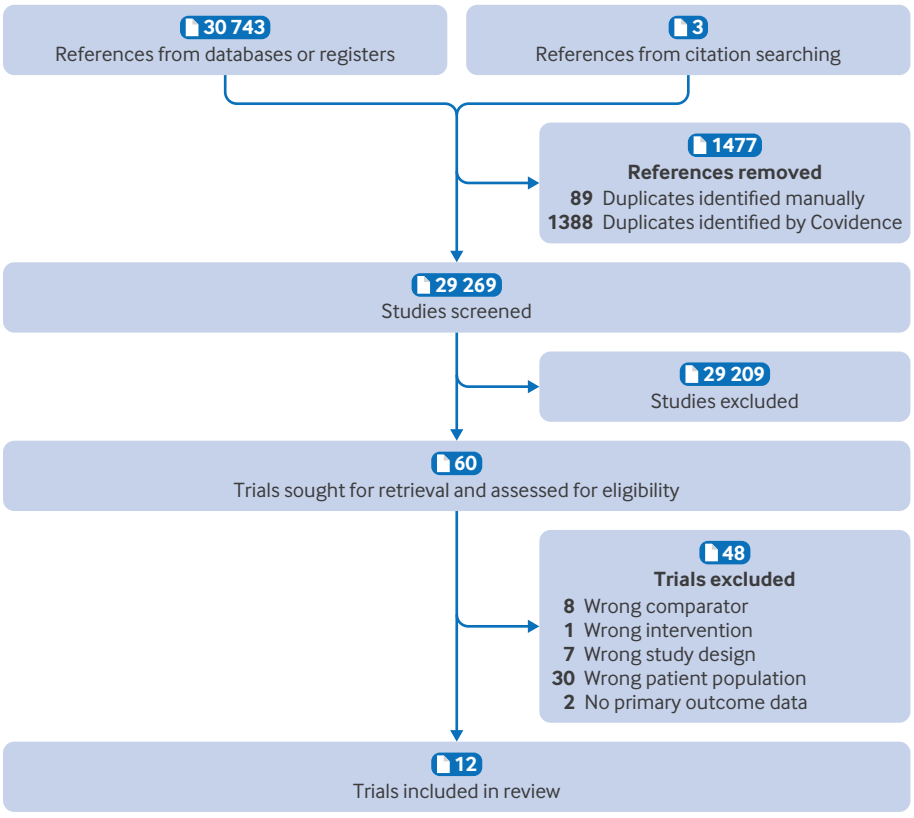

Figure 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of selection of trials

Deep brain stimulation with antiparkinsonian drugs versus antiparkinsonian drugs

We identified seven trials where 1125 participants were randomised to receive deep brain stimulation with antiparkinsonian drug treatment versus antiparkinsonian drug treatment only.[34–40] At follow-up, the difference in levodopa equivalent daily dosage was −190 to −650 mg/day in trials with stimulation in the subthalamic nucleus,[34 36 39 40] −318 to −453 mg/day in trials with stimulation in the subthalamic nucleus or globus pallidus pars interna,[37 38] and −126 mg/day in the trial with stimulation in the caudal zona incerta.[35]

All cause mortality

Seven trials reported all cause mortality at six months,[34 35 37] 12 months,[38] 18 months,[36] and two years[39 40] after randomisation; nine of 539 (1.7%) participants died in the intervention groups versus three of 556 (0.5%) in the control groups. Three trials reported no deaths in either group.[35 36 40] Meta-analysis of the remaining trials indicated no evidence of a difference in all cause mortality (risk ratio 2.69, 95% confidence interval (CI) 0.79 to 9.24; I^2=0.0%; τ^2=0.00; P=0.12; four trials; Bayes factor 1.32) (online supplemental figure S3). Visual inspection of the forest plot and measures to quantify heterogeneity (I^2=0.0%; τ^2=0.00) indicated no heterogeneity. Trial sequential analysis showed that we did not have enough information to confirm or reject a relative risk reduction of 10% between groups (not shown). This outcome result was assessed as having a high risk of bias and the certainty of the evidence was very low (online supplemental table S3 and online supplemental table S4).

Subgroup analyses comparing the effects of different targets of the electrodes (P=0.90), follow-up time (P=0.63), and length of disease (P=0.79) indicated no evidence of a difference in all cause mortality (online supplemental figures S4–S6). The remaining predefined subgroup analyses could not be performed because of lack of relevant data. In a sensitivity analysis, we performed beta binomial regression and the results were similar (risk ratio 3.12, 95% CI 0.84 to 11.62; P=0.09; online supplemental figure S7).

Serious adverse events

Seven trials reported serious adverse events at six months,[34 35 37] 12 months,[38] 18 months,[36] and two years[39 40] after randomisation; 195 of 540 participants (36.1%) had a serious adverse event in the intervention groups versus 100 of 556 (18.0%) in the control groups (table 1). One trial reported no events in either group.[36] Meta-analysis of the remaining trials indicated evidence of a harmful effect of deep brain stimulation with antiparkinsonian drugs (risk ratio 2.36, 95% CI 1.37 to 4.09; I^2=73.7%; τ^2=0.24; P<0.01; six trials; Bayes factor 3.43) (figure 3). Visual

Figure 2 | Visual overview of all results, with Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessments. *Trial sequential analysis showed that required information size had been reached. †Results based on only one trial

inspection of the forest plot and measures to quantify heterogeneity (I^2=73.7%; τ^2=0.24) indicated substantial heterogeneity. This heterogeneity was resolved by conducting the meta-analysis without the study of Schuepbach et a[39] (risk ratio 2.92, 95% CI 2.15 to 3.97; I^2=0.0%; τ^2=0.00; P<0.01; five trials, online supplemental figure 8).

Trial sequential analysis including all trials showed that we did not have enough information to confirm or reject a relative risk reduction of 10% between groups (not shown). The increased risk of serious adverse events with deep brain stimulation was mainly caused by perioperative complications, such as cerebral haemorrhages and postoperative confusion, and events related to the hardware, such as infection at the stimulator site, dislocation of the device, or reoperations. Also, depression was more frequent in participants receiving deep brain stimulation (11/323 *v* 1/339, table 1). This outcome result was assessed as having a high risk of bias and the certainty of the evidence was very low (online supplemental table S3 and online supplemental table S4).

Subgroup analyses comparing the effects of different targets of the electrodes (P=0.43) or follow-up time (P=0.10) indicated no evidence of a difference in serious adverse events (online supplemental figures S9 and S10). Subgroup analysis comparing the effects of different lengths of disease indicated evidence of a difference (P<0.01) in serious adverse events (online supplemental figure S11). The remaining predefined subgroup analyses could not be performed because of lack of relevant data. In a sensitivity analysis, we performed beta binomial regression and the results were similar (risk ratio 2.91, 95% CI 2.07 to 4.08; P<0.01; online supplemental figure S12).

Disease specific symptoms

Symptoms specific to Parkinson's disease were assessed with the UPDRS score in seven trials.[34–40] UPDRS is a tool to measure the severity and progression of Parkinson's disease, with four subsections and a total score ranging from 0 to 199 (lower scores indicate better functioning).[48] No trial used the Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale.[49] In all trials, disease specific symptoms were assessed both when all participants received antiparkinsonian drugs and when drug treatment was paused.[34–40]

One trial reported total UPDRS score when participants received antiparkinsonian drugs, one year after randomisation.[38] Williams et al reported a mean score of 32.7 (standard deviation (SD) 14.6) in 111 participants receiving deep brain stimulation with antiparkinsonian drugs versus 41.6 (16.3) in 107 participants receiving antiparkinsonian drugs only (t test, P<0.01).[38] This outcome result was assessed as having a high risk of bias and the certainty of the

Table 1 | Overview of serious adverse events for deep brain stimulation with antiparkinsonian drug treatment versus antiparkinsonian drug treatment only, occurring in more than one patient

	Deep brain stimulation with antiparkinsonian drugs		Antiparkinsonian drugs	
Trial	No and type of serious adverse events	Proportion with serious adverse event	No and type of serious adverse events	Proportion with serious adverse event
Blomstedt 2018[35]	—	1/9	—	0/10
Deuschl 2006[34]	3 deaths, 3 worsening of mobility, 2 infections	10/78	—	3/78
Schuepbach 2013[39]	39 events related to Parkinson's disease, 12 life threatening events, 10 other events related to surgery or device, 6 depression, 5 worsening of mobility, 4 other related to drugs or stimulation, 4 dislocation of device, 4 impaired wound healing, 3 injuries, 2 reoperation to repair device, 2 intracerebral abscess or oedema, 2 suicide attempts, 2 suicides	68/124	31 events related to Parkinson's disease, 11 worsening of mobility, 9 life threatening events, 6 psychosis or hallucinations, 7 motor fluctuations, 5 other related to drugs or stimulation, 5 impulse control disorders, 2 dyskinesia, 2 anxiety, 2 suicide attempts, 2 cardiac disorders	56/127
Schüpbach 2007[36]	—	0/10	—	0/10
Williams 2010[38]	19 other events, 16 infections, 11 worsening of symptoms of Parkinson's disease or uncontrolled symptoms of Parkinson's disease, 5 postoperative confusion, 4 urinary retention, 4 haemorrhage, 3 neuropsychiatric disturbances (including hallucinations or paranoia), 3 constipation, 3 falls, 2 neck pain, 2 seizure, 2 pulmonary embolism, 2 Parkinson's disease related and drug related, 2 deaths	65/183	18 other events, 7 falls, 2 worsening of symptoms of Parkinson's disease or uncontrolled symptoms of Parkinson's disease, 2 constipation, 2 Parkinson's disease related and drug related	26/183
Weaver 2009[37]	15 nervous system disorders, 12 infection at the stimulation site, 6 falls, 4 glioma, lung neoplasm malignant, or prostate cancer, 3 confusional state, 2 mental status change, 2 anaemia, 2 medical device complication, 2 procedural complications, 2 cerebrovascular accident, 2 angioplasty, bone graft, or transurethral prostatectomy, 2 dyskinesia, 2 deaths	49/121	3 nervous system disorders, 2 falls	15/134
Charles 2014[40]	—	2/15	—	0/14

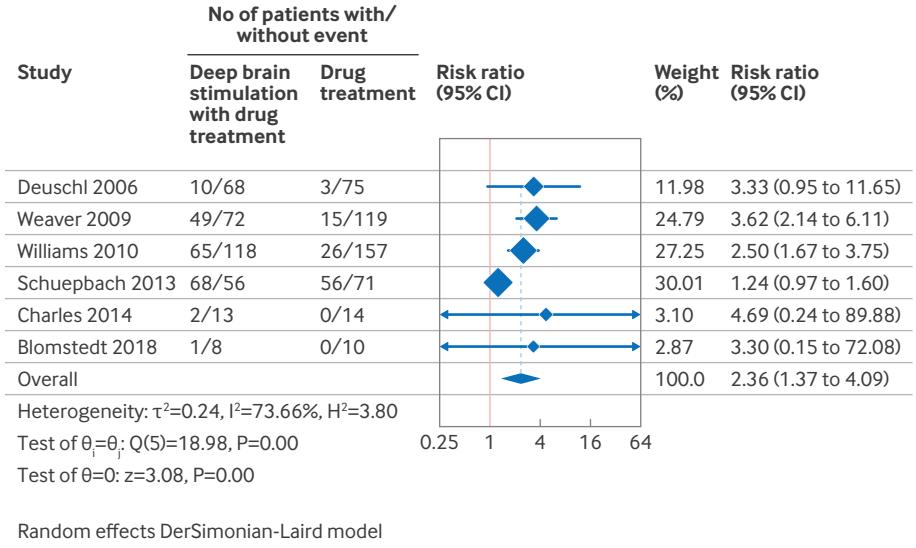

Figure 3 | Meta-analysis (risk ratio with 95% confidence interval (CI)) of deep brain stimulation with antiparkinsonian drug treatment versus antiparkinsonian drug treatment only, on serious adverse events[34 35 37–40]

evidence was very low (online supplemental table S3 and online supplemental table S4). Charles et al reported total UPDRS score when participants received antiparkinsonian drugs but excluding the domain rigidity, two years after randomisation.[40] A t test indicated no evidence of a difference in disease specific symptoms (P=0.99).[40]

Several trials reported subsections of the UPDRS (parts I, II, III, and IV)[34–40] at six months,[34 35 37] 12 months,[38] 18 months,[36] and two years[39 40] after randomisation. UPDRS I measures mentation, behaviour, and mood, with a score of 0-16; UPDRS II measures activities of daily living, with a score of 0-52; UPDRS III measures motor function, with a score of 0-108; and UPDRS IV measures complications of treatment, with a score of 0-23.[48] Meta-analyses indicated no evidence of a difference in UPDRS I score (mean difference −0.23, 95% CI −0.49 to 0.03; I^2=0.0%; τ^2=0.00; P=0.08; five trials) or UPDRS II score (mean difference −1.53, 95% CI −3.17 to 0.11, I^2=82.3%; τ^2=3.16; P=0.07; six trials) (online supplemental figures S13–S16). Meta-analyses indicated evidence of a beneficial effect of deep brain stimulation with antiparkinsonian drugs on UPDRS III score (mean difference −3.34, 95% CI −4.21 to −2.48, I^2=0.0%; τ^2=0.00; P<0.01; six trials) and UPDRS IV score (mean difference −2.58, 95% CI −4.10 to −1.06; I^2=91.7%; τ^2=2.71; P<0.01; five trials) (online supplemental figures S17–S19). All of these outcome results were assessed as having a high risk of bias (online supplemental table S3). Analyses of total UPDRS scores, UPDRS II scores, and UPDRS III scores when antiparkinsonian drug treatment was paused generally showed lower scores in the deep brain stimulation groups (online supplemental table S3 and online supplemental figures S20–S23).

Secondary outcomes

Meta-analysis indicated evidence of a beneficial effect of deep brain stimulation with antiparkinsonian drugs on quality of life (mean difference −6.97, 95% CI −8.71 to −5.22; I^2=0.0%; P<0.01; seven trials) (online supplemental figures S24 and S25). Analyses indicated no evidence of a difference in depressive symptoms, executive functioning, level of functioning, or non-serious adverse events (online supplemental figures S26–S31). All secondary outcome results were assessed as having a high risk of bias and the certainty of the evidence was low or very low (online supplemental text S3).

Deep brain stimulation versus surgery with sham stimulation

We identified three trials where 360 participants were randomised to receive deep brain stimulation with antiparkinsonian drugs versus surgery with sham stimulation and antiparkinsonian drugs.[43–45] All participants in the control group underwent surgery and had electrodes implanted, but the stimulation was not turned on until three months after surgery.[43–45] At follow-up, the difference in levodopa equivalent daily dosage was −307 to −408 mg/day in the two trials reporting these data.[43 44]

All cause mortality

One trial reported all cause mortality at three months after randomisation[45] but no deaths in either group. This outcome result was assessed as having a high risk of bias and the certainty of the evidence was very low (online supplemental table S3 and online supplemental table S5).

Serious adverse events

Two trials reported serious adverse events at three months after randomisation[43 45]; 28 of 222 participants (12.6%) had a serious adverse event in the intervention groups versus eight of 74 (10.8%) in the control groups (online supplemental table S6). Meta-analysis indicated no evidence of a difference in serious adverse events (risk ratio 1.17, 95% CI 0.56 to 2.45; I^2=0.0%; τ^2=0.00; P=0.68; two trials; Bayes factor 1.17) (figure 4). Visual inspection of the forest plot and measures to quantify heterogeneity (I^2=0.0%, τ^2=0.00) indicated no heterogeneity. Trial

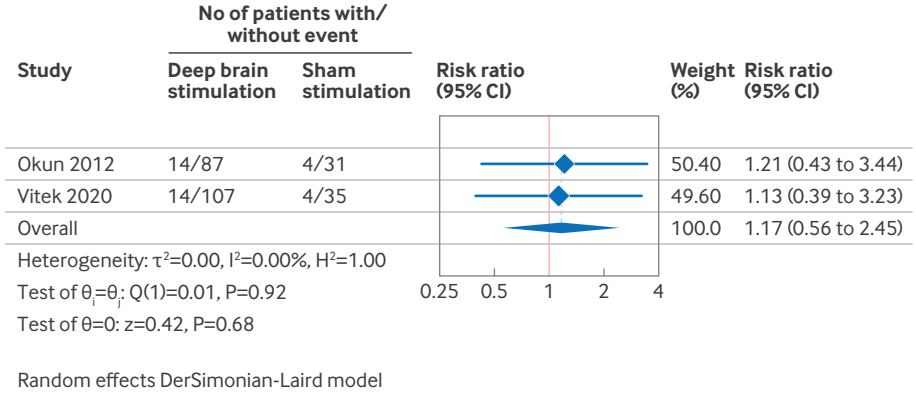

Figure 4 | Meta-analysis (risk ratio with 95% confidence interval (CI)) of deep brain stimulation with antiparkinsonian drug treatment versus surgery with sham stimulation and antiparkinsonian drug treatment, on serious adverse events[43 45]

sequential analysis showed that we did not have enough information to confirm or reject a relative risk reduction of 10% between groups (not shown). This outcome result was assessed as having a high risk of bias and the certainty of the evidence was very low (online supplemental table S3 and online supplemental table S5).

Disease specific symptoms

Symptoms specific to Parkinson's disease were assessed with the UPDRS score in three trials.[43–45] In all trials, disease specific symptoms were assessed both when all participants received antiparkinsonian drugs and when drug treatment was paused.[43–45] One trial reported the total UPDRS score when participants received antiparkinsonian drugs, three months after randomisation.[43] Okun et al reported a mean score of 32.7 (SD 14.8) in 75 participants receiving deep brain stimulation with antiparkinsonian drugs versus 44.6 (13.6) in 33 participants receiving surgery with sham stimulation and antiparkinsonian drugs (t test, P<0.01).[43] This outcome result was assessed as having a high risk of bias and the certainty of the evidence was very low (online supplemental table S3 and online supplemental table S5).

Three trials reported subsections of UPDRS (parts I, III, and IV), three months after randomisation.[43–45] Meta-analyses indicated no evidence of a difference on UPDRS I score (mean difference −0.08, 95% CI −0.70 to 0.54; I^2=0.0%; τ^2=0.00; P=0.80; two trials) (online supplemental figure S32). Meta-analyses indicated evidence of a beneficial effect of deep brain stimulation with antiparkinsonian drugs on UPDRS II score (mean difference −1.64, 95% CI −3.11 to −0.17; I^2=0.0%; τ^2=0.00; P=0.03; three trials), UPDRS III score (mean difference −5.12, 95% CI −8.33 to −1.91; I^2=55.2%; τ^2=4.41; P<0.01; three trials), and UPDRS IV score (mean difference −3.25, 95% CI −4.25 to −2.25; I^2=0.0%; τ^2=0.00; P<0.01; two trials) (online supplemental figures S32–S38). All of these outcome results were assessed as having a high risk of bias (online supplemental table S3). Analyses of UPDRS III scores when antiparkinsonian drug treatment was paused showed lower scores in the deep brain stimulation groups (online supplemental text S3 and online supplemental figures S39 and S40).

Secondary outcomes

Analyses indicated evidence of a beneficial effect of deep brain stimulation with antiparkinsonian drugs on quality of life (t test, P<0.01) and level of functioning (mean difference 5.97, 95% CI 0.18 to 11.76; I^2=72.6%; P=0.04; two trials) (online supplemental figures S41 and S42). Analyses indicated no evidence of a difference on executive functioning or non-serious adverse events (online supplemental figures S43 and S44). All secondary outcome results were assessed as having a high risk of bias and the certainty of the evidence was very low (online supplemental text S3).

Deep brain stimulation versus resective surgery

We identified two trials where 79 participants were randomised to receive deep brain stimulation with antiparkinsonian drugs versus resective surgery with antiparkinsonian drugs.[41 42] Participants receiving resective surgery underwent pallidotomy[42] or thalamotomy of the ventral intermediate thalamic nucleus.[41] At follow-up, the difference in levodopa equivalent daily dosage was −485 mg/day in the trial reporting these data.[42–44]

All cause mortality

Two trials reported all cause mortality six months after randomisation[41 42]; two of 42 participants (4.8%) died in the intervention groups versus one of 37 (2.7%) in the control groups. Meta-analysis indicated no evidence of a difference in all cause mortality (risk ratio 1.16, 95% CI 0.06 to 23.84; I^2=48.9%; τ^2=2.33; P=0.92; two trials; Bayes factor 1.01) (online supplemental figure S45). Visual inspection of the forest plot and measures to quantify heterogeneity (I^2=48.9%, τ^2=2.33) indicated moderate heterogeneity. Trial sequential analysis showed that we did not have enough information to confirm or reject a relative risk reduction of 10% between groups (not shown). This outcome result was assessed as having a high risk of bias and the certainty of the evidence was very low (online supplemental table S3 and online supplemental table S7).

Subgroup analysis comparing the effects of different targets of the electrodes indicated no evidence of a difference in all cause mortality (P=0.16) (online supplemental figure S46). The remaining predefined subgroup analyses could not be performed because of lack of relevant data. In a sensitivity analysis, we performed beta binomial regression and the results were similar (risk ratio 1.89, 95% CI 0.16 to 21.96; P=0.61; online supplemental figure S47).

Serious adverse events

Two trials reported serious adverse events six months after randomisation[41 42]; three of 42 participants (7.1%) had a serious adverse event in the intervention groups versus one of 37 (2.7%) in the control groups (online supplemental table S8). Meta-analysis indicated no evidence of a difference in serious adverse events (risk ratio 1.72, 95% CI 0.23 to 12.67; I^2=0.0%; τ^2=0.00; P=0.59; two trials; Bayes factor 1.06) (figure 5). Visual inspection of the forest plot and measures to quantify heterogeneity (I^2=0.0%, τ^2=0.00) indicated no heterogeneity. Trial sequential analysis showed that we did not have enough information to confirm or reject a relative risk reduction of 10% between groups (not shown). This outcome result was assessed as having a high risk of

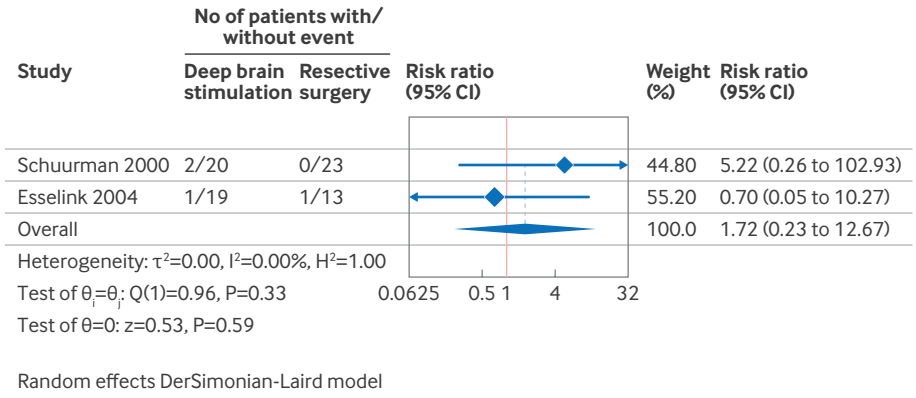

Figure 5 | Meta-analysis (risk ratio with 95% confidence interval (CI)) of deep brain stimulation with antiparkinsonian drug treatment versus resective surgery with antiparkinsonian drug treatment, on serious adverse events[41 42]

bias and the certainty of the evidence was very low (online supplemental table S3 and online supplemental table S7).

Subgroup analysis comparing the effects of different targets of the electrodes indicated no evidence of a difference in serious adverse events (P=0.33) (online supplemental figure S48). The remaining predefined subgroup analyses could not be performed because of lack of relevant data. In a sensitivity analysis, we performed beta binomial regression and the results were similar (risk ratio 2.71, 95% CI 0.27 to 27.52; P=0.40; online supplemental figure S49).

Disease specific symptoms

Symptoms specific to Parkinson's disease were assessed with the UPDRS score in one trial.[42] In this trial, disease specific symptoms were assessed both when all participants received antiparkinsonian drugs and when drug treatment was paused.[42] No trials reported total UPDRS score when participants received antiparkinsonian drugs.[41 42] One trial reported UPDRS III with and without drug treatment, three months after randomisation.[42] Esselink et al reported a lower median UPDRS III score of 13 (interquartile range 7-21) in 13 participants receiving deep brain stimulation with antiparkinsonian drugs versus a median score of 19 (8-26) in 14 participants receiving pallidotomy and antiparkinsonian drugs.[42] This trial also reported lower scores in the brain stimulation groups for UPDRS III scores when antiparkinsonian drug treatment was paused.[42] Both outcome results were assessed as having a high risk of bias (online supplemental table S3).

Secondary outcomes

Analyses indicated evidence of a beneficial effect of deep brain stimulation with antiparkinsonian drugs on level of functioning (t test, P<0.01). Analysis indicated no evidence of a difference in non-serious adverse events (online supplemental figures S50 and S51). All secondary outcome results were assessed as having a high risk of bias and the certainty of the evidence was very low (online supplemental text S3).

Discussion

Principal findings

In this systematic review assessing the benefits and harms of deep brain stimulation for Parkinson's disease, we identified seven trials where 1125 participants were randomised to receive deep brain stimulation with antiparkinsonian drugs versus antiparkinsonian drugs only (primary comparison). All results had a high risk of bias and the certainty of the evidence was very low for all primary outcomes. The information size was insufficient when assessing all cause mortality. Meta-analysis showed that deep brain stimulation increased the risk of serious adverse events, mainly because of an increased risk of perioperative complications, such as cerebral haemorrhages and postoperative confusion, and events related to hardware, such as infection at the stimulator site, dislocation of the device, or reoperations. Meta-analyses indicated that deep brain stimulation might reduce symptoms specific to Parkinson's disease, but the assessments of disease specific symptoms had several methodological limitations.

Strengths and limitations of this study

Our systematic review had several strengths. We used up-to-date methods to assess the methodological quality of the included trials.[21 50 51] Our methodology was predefined and described in detail before starting the literature searches,[15] and was based on the eight step assessment, suggested by Jakobsen et al,[21] and trial sequential analysis.[23] Risk of bias was assessed with the Cochrane RoB 2[50] and overall certainty of the evidence with GRADE.[51] Therefore, both risks of random errors (play of chance) and systematic errors (bias) were taken into account in our review.

Our systematic review had several limitations. Firstly, the maximum follow-up period in most trials was less than a year, and therefore long term beneficial and harmful effects could not be assessed. Secondly, all of the included trials were assessed as having a high risk of bias, mainly because of missing

data, lack of blinding, and poor reporting without prespecified protocols, clinical trial registrations, or statistical analysis plans. Hence our results presumably overestimated the beneficial effects of deep brain stimulation.[52–54] Thirdly, the overall risk of type I errors was increased because of the large number of outcomes, comparisons, and subgroup analyses. We adjusted our thresholds for significance only according to the total number of primary outcomes. Fourthly, the included trials differed in participant characteristics (eg, age, sex, and length of disease) and trial design (eg, follow-up time and placement of electrodes), increasing the risk of statistical heterogeneity. We investigated these concerns by performing subgroup analyses, when possible, but lack of relevant data limited the power of these analyses. Only the subgroup analysis comparing different lengths of disease when assessing serious adverse events (online supplemental figure S11) indicated evidence of a difference. This finding was mainly influenced by the study of Schuepbach et al enrolling participants with early motor complications.[39] Although the relatively reduced risk of serious adverse events with deep brain stimulation seen in this trial could be attributed to the shorter length of disease, two smaller trials included in the same subgroup did not indicate any evidence of this trend.[35 40] Therefore, whether a longer length of disease increases the risk of serious adverse events is not known.

Measurement of symptoms specific to Parkinson's disease in the included trials also had methodological challenges. Only one trial reported total UPDRS score when participants received antiparkinsonian drugs. Many studies focused on UPDRS III scores, which only evaluated motor scores, and only a few trials[39 40 45] had predefined disease specific symptoms as their focus. Also, most trials assessed symptoms when antiparkinsonian drug treatment was paused. This situation is challenging to apply to the clinic where most participants are expected to receive antiparkinsonian drugs, although the efficacy of deep brain stimulation is perhaps more precisely assessed when drug treatment is paused.

Our results showed that participants receiving deep brain stimulation were likely to reduce their dose of antiparkinsonian drugs. This finding could be a result of more frequent hospital visits for stimulation, and adjustments to drug treatment, in the intervention groups receiving deep brain stimulation, or an effect of deep brain stimulation itself. Because antiparkinsonian drugs are known to have adverse effects, some of the beneficial effects in subsections of the UPDRS might be linked to the decrease in drug dose because of deep brain stimulation (eg, reducing fluctuations and adverse effects of drugs, as seen in UPDRS IV). This finding could also explain the beneficial effects seen in some subsections of the UPDRS of deep brain stimulation with antiparkinsonian drugs versus antiparkinsonian drugs only, when drug treatment was paused, as seen in UPDRS II and UPDRS III. These results from the meta-analyses are difficult to interpret, however, as the assessment scales used by the trialists were not related to predefined and evidence based minimal important differences.[55–58] These methodological limitations need to be considered when interpreting the analysis results based on disease specific symptoms.

Comparison with other studies

Previous reviews have assessed deep brain stimulation for Parkinson's disease.[59–62] Generally, these reviews showed a beneficial effect of deep brain stimulation on UPDRS score, troublesome dyskinesias, and quality of life.[59–62] As well as methodological limitations, these reviews[15] mainly focused on the effects of deep brain stimulation on motor symptoms, dyskinesias, and quality of life, whereas little or no information on adverse effects was reported. Furthermore, previous reviews have not considered the implications of using scales without predefined and validated minimal important differences to assess motor symptoms.

Study implications

The use of deep brain stimulation for Parkinson's disease is increasing and will likely become part of standard care.[63] When an intervention has already been approved and integrated as part of standard care, setting up randomised clinical trials is often difficult because clinicians might question whether patients should be randomised to a treatment that does not include the intervention in question. Hence the results of our review highlight the urgent need for well conducted, long term randomised trials with patient important outcomes, including assessing adverse effects, before deep brain stimulation has been even further integrated as part of the standard care. Observational studies could supplement randomised trials, especially for investigating rare adverse events.

Conclusions

In this review, we found that the certainty of evidence was very low for all primary outcomes, and based on the included evidence, the beneficial effects of deep brain stimulation were questionable because of methodological limitations. Compared with only antiparkinsonian drug treatment, deep brain stimulation with antiparkinsonian drugs seemed to increase the risk of serious adverse events, mainly because of perioperative complications and hardware related events. Conducting randomised clinical trials of adequate methodological quality to effectively evaluate the effects of deep brain stimulation is crucial.

Acknowledgements We thank Sarah Louise Klingenberg, information specialist, Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital-Rigshospitalet, Denmark, for help with developing the search strategy and conducting the searches.

Contributors JJP, CBK, SJ, AL, CG, and JCJ contributed to the conceptualisation and design of the study. JJP and SJ screened studies for inclusion. JJP and PF extracted the data. JJP analysed the data. JJP and JCJ wrote the original draft. All authors commented and approved the final manuscript. JJP and JCJ are the guarantors. The guarantors had full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of the data analyses, and had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead authors (the guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All results are based on aggregate data available from the individual trial reports, which are all cited accordingly. All results of our meta-analyses can be found in the forest plots in the supplementary materials, risk of bias can be found in table S3, and our GRADE assessments can be found in the summary of findings in table S4, table S5, and table S7 in the online supplemental material.

ORCID iDs

Johanne Juul Petersen http://orcid.org/0000-0001-9837-1958
Caroline Barkholt Kamp http://orcid.org/0000-0002-7756-4694

REFERENCES

1 GBD Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol* 2019;18:459–80.
2 Braak H, Del Tredici K, Rüb U, *et al*. Staging of brain pathology related to sporadic parkinson's disease. Neurobiol Aging 2003;24:197–211. 10.1016/s0197-4580(02)00065-9
3 Reichmann H. Clinical criteria for the diagnosis of parkinson's disease. Neurodegener Dis 2010;7:284–90. 10.1159/000314478
4 DeMaagd G, Philip A. Parkinson's disease and its management: part 1: disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis. P T 2015;40:504–32.
5 Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet 2021;397:2284–303. 10.1016/S0140-6736(21)00218-X
6 Armstrong MJ, Okun MS. Diagnosis and treatment of parkinson disease: a review. JAMA 2020;323:548–60. 10.1001/jama.2019.22360
7 Thanvi BR, Lo TCN. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. Postgrad Med J 2004;80:452–8. 10.1136/pgmj.2003.013912
8 Hansen CA, Miller DR, Annarumma S, *et al*. Levodopa-induced dyskinesia: a historical review of parkinson's disease, dopamine, and modern advancements in research and treatment. J Neurol 2022;269:2892–909. 10.1007/s00415-022-10963-w
9 Perlmutter JS, Mink JW. Deep brain stimulation. Annu Rev Neurosci 2006;29:229–57. 10.1146/annurev.neuro.29.051605.112824
10 Tierney TS. Deep brain stimulation: foundations and future trends. Front Biosci 2018;23:162–82. 10.2741/4586
11 Zhang C, Ramirez-Zamora A, Meng F, *et al*. An international survey of deep brain stimulation utilization in Asia and oceania: the DBS think tank east. Front Hum Neurosci 2020;14:162. 10.3389/fnhum.2020.00162
12 Kühn AA, Kempf F, Brücke C, *et al*. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with parkinson's disease in parallel with improvement in motor performance. J Neurosci 2008;28:6165–73. 10.1523/JNEUROSCI.0282-08.2008
13 Koeglsperger T, Palleis C, Hell F, *et al*. Deep brain stimulation programming for movement disorders: current concepts and evidence-based strategies. Front Neurol 2019;10:410. 10.3389/fneur.2019.00410
14 Buhmann C, Huckhagel T, Engel K, *et al*. Adverse events in deep brain stimulation: a retrospective long-term analysis of neurological, psychiatric and other occurrences. PLoS One 2017;12:e0178984. 10.1371/journal.pone.0178984
15 Petersen JJ, Juul S, Jørgensen CK, *et al*. Deep brain stimulation for neurological disorders: a protocol for a systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. Syst Rev 2022;11:218. 10.1186/s13643-022-02095-z
16 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:71. 10.1136/bmj.n71
17 Higgins J, Thomas J, Chandler J. Cochrane handbook for systematic reviews of interventions. Cochrane, 2019. Available: https://onlinelibrary.wiley.com/doi/book/10.1002/9781119536604
18 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. 10.1136/bmj.l4898
19 ICH Harmonised Guideline. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. 2015. Available: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf]
20 Keus F, Wetterslev J, Gluud C, *et al*. Evidence at a glance: error matrix approach for overviewing available evidence. BMC Med Res Methodol 2010;10:90. 10.1186/1471-2288-10-90
21 Jakobsen JC, Wetterslev J, Winkel P, *et al*. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol 2014;14:120. 10.1186/1471-2288-14-120
22 Higgins JPT, Spiegelhalter DJ. Being sceptical about meta-analyses: a bayesian perspective on magnesium trials in myocardial infarction. Int J Epidemiol 2002;31:96–104. 10.1093/ije/31.1.96
23 Copenhagen Trial Unit. TSA - trial sequential analysis. 2021 Available: http://www.ctu.dk/tsa
24 Wetterslev J, Thorlund K, Brok J, *et al*. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 2008;61:64–75. 10.1016/j.jclinepi.2007.03.013
25 Brok J, Thorlund K, Gluud C, *et al*. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. J Clin Epidemiol 2008;61:763–9. 10.1016/j.jclinepi.2007.10.007
26 Brok J, Thorlund K, Wetterslev J, *et al*. Apparently conclusive meta-analyses may be inconclusive--trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. Int J Epidemiol 2009;38:287–98. 10.1093/ije/dyn188
27 Thorlund K, Devereaux PJ, Wetterslev J, *et al*. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? Int J Epidemiol 2009;38:276–86. 10.1093/ije/dyn179
28 Wetterslev J, Thorlund K, Brok J, *et al*. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC Med Res Methodol 2009;9:86. 10.1186/1471-2288-9-86
29 ThorlundK, EngstrømJ, Brok J, *et al*. User manual for trial sequential analysis (TSA). 2011. Available: http://wwwctudk/tsa/files/tsa_manualpdf

30 Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. an example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. Clin Epidemiol 2010;2:57–66. 10.2147/clep.s9242
31 Imberger G, Thorlund K, Gluud C, *et al*. False-positive findings in cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. BMJ Open 2016;6:e011890. 10.1136/bmjopen-2016-011890
32 McMaster University and Evidence Prime. GRADEpro GDT: gradepro guideline development tool. 2022. Available: https://www.gradepro.org/
33 StataCorp. Stata statistical software: release 16. College Station, TX: StataCorp LLC, 2019.
34 Deuschl G, Schade-Brittinger C, Krack P, *et al*. A randomized trial of deep-brain stimulation for parkinson's disease. N Engl J Med 2006;355:896–908. 10.1056/NEJMoa060281
35 Blomstedt P, Stenmark Persson R, Hariz G-M, *et al*. Deep brain stimulation in the caudal zona incerta versus best medical treatment in patients with parkinson's disease: a randomised blinded evaluation. J Neurol Neurosurg Psychiatry 2018;89:710–6. 10.1136/jnnp-2017-317219
36 Schüpbach WMM, Maltête D, Houeto JL. Neurosurgery at an earlier stage of parkinson disease: a randomized, controlled trial. Neurol (ECronicon) 2007;68:267–71. 10.1212/01.wnl.0000250253.03919.fb
37 Weaver FM, Follett K, Stern M, *et al*. Bilateral deep brain stimulation vs best medical therapy for patients with advanced parkinson disease: a randomized controlled trial. JAMA 2009;301:63–73. 10.1001/jama.2008.929
38 Williams A, Gill S, Varma T, *et al*. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced parkinson's disease (PD SURG trial): a randomised, open-label trial. Lancet Neurol 2010;9:581–91. 10.1016/S1474-4422(10)70093-4
39 Schuepbach WMM, Rau J, Knudsen K, *et al*. Neurostimulation for parkinson's disease with early motor complications. N Engl J Med 2013;368:610–22. 10.1056/NEJMoa1205158
40 Charles D, Konrad PE, Neimat JS, *et al*. Subthalamic nucleus deep brain stimulation in early stage parkinson's disease. Parkinsonism Relat Disord 2014;20:731–7. 10.1016/j.parkreldis.2014.03.019
41 Schuurman PR, Bosch DA, Bossuyt PM, *et al*. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med 2000;342:461–8. 10.1056/NEJM200002173420703
42 Esselink RAJ, de Bie RMA, de Haan RJ, *et al*. Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD. Neurol (ECronicon) 2004;62:201–7. 10.1212/01.WNL.0000103235.12621.C3
43 Okun MS, Gallo BV, Mandybur G, *et al*. Subthalamic deep brain stimulation with a constant-current device in parkinson's disease: an open-label randomised controlled trial. Lancet Neurol 2012;11:140–9. 10.1016/S1474-4422(11)70308-8
44 Li D, Zhang C, Gault J, *et al*. Remotely programmed deep brain stimulation of the bilateral subthalamic nucleus for the treatment of primary parkinson disease: a randomized controlled trial investigating the safety and efficacy of a novel deep brain stimulation system. Stereotact Funct Neurosurg 2017;95:174–82. 10.1159/000475765
45 Vitek JL, Jain R, Chen L, *et al*. Subthalamic nucleus deep brain stimulation with a multiple independent constant current-controlled device in parkinson's disease (INTREPID): a multicentre, double-blind, randomised, sham-controlled study. Lancet Neurol 2020;19:491–501. 10.1016/S1474-4422(20)30108-3
46 Gratwicke J, Zrinzo L, Kahan J, *et al*. Bilateral deep brain stimulation of the nucleus basalis of meynert for parkinson disease dementia: a randomized clinical trial. JAMA Neurol 2018;75:169–78. 10.1001/jamaneurol.2017.3762
47 Bourilhon J, Olivier C, You H, *et al*. Pedunculopontine and cuneiform nuclei deep brain stimulation for severe gait and balance disorders in parkinson's disease: interim results from a randomized double-blind clinical trial. J Parkinsons Dis 2022;12:639–53. 10.3233/JPD-212793
48 FahnS, EltonRL, *et al*. Unified parkinson's disease rating scale. In: FahnS, MarsdenCD, CalneD, eds. Recent developments in parkinson's disease. 1987: 153–63.
49 Goetz CG, Tilley BC, Shaftman SR, *et al*. Movement disorder society-sponsored revision of the unified parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23:2129–70. 10.1002/mds.22340
50 Higgins J, Thomas J, Chandler J, *et al*. Cochrane handbook for systematic reviews of interventions version 6.2. 2022.
51 Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6. 10.1136/bmj.39489.470347.AD
52 Gluud LL. Bias in clinical intervention research. Am J Epidemiol 2006;163:493–501. 10.1093/aje/kwj069
53 Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001;135:982–9. 10.7326/0003-4819-135-11-200112040-00010
54 Moher D, Pham B, Jones A, *et al*. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998;352:609–13. 10.1016/S0140-6736(98)01085-X
55 Shulman LM, Gruber-Baldini AL, Anderson KE, *et al*. The clinically important difference on the unified parkinson's disease rating scale. Arch Neurol 2010;67:64–70. 10.1001/archneurol.2009.295
56 Sánchez-Ferro Á, Matarazzo M, Martínez-Martín P, *et al*. Minimal clinically important difference for UPDRS-III in daily practice. Mov Disord Clin Pract 2018;5:448–50. 10.1002/mdc3.12632
57 Horváth K, Aschermann Z, Ács P, *et al*. Minimal clinically important difference on the motor examination part of MDS-UPDRS. Parkinsonism Relat Disord 2015;21:1421–6. 10.1016/j.parkreldis.2015.10.006
58 Schrag A, Sampaio C, Counsell N, *et al*. Minimal clinically important change on the unified parkinson's disease rating scale. Mov Disord 2006;21:1200–7. 10.1002/mds.20914
59 Perestelo-Pérez L, Rivero-Santana A, Pérez-Ramos J, *et al*. Deep brain stimulation in parkinson's disease: meta-analysis of randomized controlled trials. J Neurol 2014;261:2051–60. 10.1007/s00415-014-7254-6
60 Lachenmayer ML, Mürset M, Antih N, *et al*. Subthalamic and pallidal deep brain stimulation for parkinson's disease-meta-analysis of outcomes. NPJ Parkinsons Dis 2021;7:77. 10.1038/s41531-021-00223-5
61 Wong JK, Cauraugh JH, Ho KWD, *et al*. STN vs. GPI deep brain stimulation for tremor suppression in parkinson disease: a systematic review and meta-analysis. Parkinsonism Relat Disord 2019;58:56–62. 10.1016/j.parkreldis.2018.08.017
62 Bratsos S, Karponis D, Saleh SN. Efficacy and safety of deep brain stimulation in the treatment of parkinson's disease: a systematic review and meta-analysis of randomized controlled trials. Cureus 2018;10:e3474. 10.7759/cureus.3474
63 Sarica C, Conner CR, Yamamoto K, *et al*. Trends and disparities in deep brain stimulation utilization in the united states: a nationwide inpatient sample analysis from 1993 to 2017. Lancet Reg Health Am 2023;26:100599. 10.1016/j.lana.2023.100599

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjmed-2023-000705).