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Deep brain stimulation for dystonia (Protocol)

Duarte GS, Rodrigues FB, Prescott D, Ferreira J, Costa J

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[Intervention Protocol]

Deep brain stimulation for dystonia

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To compare the efficacy, safety and tolerability of deep brain stimulation versus placebo, sham intervention, or best medical care, including botulinum neurotoxin and resective/lesional surgery, in people with dystonia.

BACKGROUND

Description of the condition

See Additional Table 1 for glossary of terms.

Dystonia is the third most common movement disorder, after Parkinson's disease and essential tremor, with an estimated overall prevalence of 164 per million (Steeves 2012). Dystonia syndromes are a group of disabling, painful disorders characterised by involuntary sustained or intermittent muscle contractions causing abnormal, often repetitive, movements or postures of the face, neck, trunk or limbs, among other muscles (Albanese 2013). Dystonic movements are typically patterned or twisting, and are often initiated or worsened by voluntary action (Albanese 2013). These neurological disorders are classified according to two different axes. Axis I is based on clinical manifestations of dystonia, and divided into four separate dimensions: age at onset, body distribution, temporal pattern and associated features. Age at onset classifies the dystonia under standard age groups used for other neurological disorders (Jinnah 2014). Body distribution includes focal dystonia, segmental dystonia, multifocal dystonia, hemidystonia and generalised dystonia (Albanese 2013; Tarsy 2006). Temporal pattern classifies dystonia according to its course and type of short-term variation (Jinnah 2014). The absence of other associated features defines isolated dystonia, formerly known as primary dystonia (Albanese 2013). Combined dystonia is defined in the presence of other neurological or systemic features and includes the previous terms of secondary dystonia, dystonia-plus syndromes and heredodegenerative dystonia (Jinnah 2014). Axis II is based on the aetiology of dystonia and divided into three dimensions: heritability, nervous system pathology, and idiopathic. In terms of heritability, dystonia can be defined by association with hereditary neurological conditions (e.g. sex-linked, autosomal or mitochondrial) or by having an acquired cause (Albanese 2013; Jinnah 2014; Tarsy 2006). Among the most common known causes are drug-induced dystonia (caused by agents such as levodopa or antipsychotics) and acquired lesions to the central nervous system (CNS) such as brain injury, infections, toxins, vascular or neoplas-

tic disorders (Calne 1988). Dystonia can also be of psychogenic origin (i.e. functional) (Albanese 2013). The term idiopathic dystonia is used when there is no acquired cause and the dystonia remains genetically unclassified, and it can be further subclassified into sporadic or familial idiopathic dystonia (Jinnah 2014).

The aetiology of most forms of dystonia is still not fully understood, with the exception of early-onset dystonia, for which a hereditary aetiology is common (Balint 2015). In most cases of focal adult-onset dystonia, such as cervical dystonia (the most common form of focal dystonia), the pathophysiology is generally considered to result from impaired inhibition of the CNS at multiple levels resulting in abnormal sensorimotor integration (Hallett 1998).

The generalised increase in cortical and basal ganglia excitability leads to a diminished motor function inhibition, a decrease in spatial and temporal somatosensory discrimination and loss of surround inhibition (incapacity to suppress adjacent regions to activated neural circuits) (Phukan 2011; Tarsy 2006).

Description of the intervention

Deep brain stimulation (DBS) is a method of intracerebral stimulation through the controlled direct application of an electrical current to specific subcortical nuclei. It is important to note that it is not a curative treatment. The most common neurological disease for which DBS is used is Parkinson's disease, and the most common target nucleus in this condition is the subthalamic nucleus (Fasano 2012). In selected Parkinson's disease patients, DBS improves the time without dyskinesia at six months by an average of 4.6 hours a day in participants randomised to DBS versus 0 hours in participants randomised to best medical therapy, while also reporting a higher rate of clinically meaningful motor improvement, at 71% in DBS versus 32% in best medical therapy (Weaver 2009). DBS also appears to have a higher rate of quality of life improvement, at 64% in DBS versus 36% in best medical therapy for Parkinson's disease patients (Weaver 2009).

Electrical stimulation of the CNS targets is delivered through electrodes that are surgically implanted and afterwards connected to an implantable pulse generator (IPG), which is most often placed subcutaneously in the pectoral region (Fasano 2012).

Different target nuclei for DBS have been studied in people with dystonia, including the internal globus pallidus (GPi), the thalamus ventrointermediate nucleus (VIM), or the subthalamic nucleus (STN), with the purpose of modulating cortical excitability (Limousin-Dowsey 1999). In routine practice, the GPi is the primary target for people with dystonia (Kupsch 2006; Vidailhet 2005).

Different techniques may be used, among them high or low-frequency stimulation, with these having varying degrees of intensity and effect duration (Fasano 2012; Limousin-Dowsey 1999). The stimulation can be made with constant voltage or, more recently, constant current, which has been suggested to improve the tolerance and effectiveness of DBS (Gross 2013). Adjustments are made to the stimulation parameters (voltage, frequency and others) in ambulatory follow-up examinations, to ensure optimal therapeutic effects (Montuno 2013). IPGs have a limited battery life, at the end of which a battery replacement surgery has to be conducted. Different rechargeable (RC) IPGs have been developed to reduce the number of battery replacement operations (Waln 2014).

How the intervention might work

There are different hypotheses concerning how DBS might work. The inhibitory hypothesis suggests that the therapeutic efficacy of DBS results by reducing the activity of neurons adjacent to the stimulation lead (Filali 2004), most likely due to activation of GABAergic afferent pathways (Chiken 2014). The excitatory hypothesis claims that the excitation of efferent pathways and antidromic excitation of afferent pathways results in suppression of abnormal activity (Hashimoto 2003). Finally, the disruption hypothesis supports the block of aberrant neural stimuli in the cortico-basal ganglia loop, creating a dissociation between neural afferent and efferent signals (Chiken 2015). The most plausible mechanism is probably a combination of different effects.

Why it is important to do this review

Recent studies report the beneficial effects that DBS has in people with certain movement disorders, including selected cases of Parkinson's disease and essential tremor (Flora 2010; Weaver 2009). However, no systematic review has yet examined the available literature on the outcomes of DBS in people with dystonia. There are reports of serious events such as mood changes, cognitive deficit and an increase in suicide among patients treated with DBS for dystonia (Fasano 2012; Foncke 2006) as well as others for patients with Parkinson's disease, among them pulmonary embolism, myocardial infarction, stroke, intracerebral haemorrhage and infection (Fasano 2012; Weaver 2009). Therefore, uncertainty exists regarding the risk-benefit profile of this intervention in dystonia.

OBJECTIVES

To compare the efficacy, safety and tolerability of deep brain stimulation versus placebo, sham intervention, or best medical care, including botulinum neurotoxin and resective/lesional surgery, in people with dystonia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) with a parallel design, of any duration, assessing the efficacy, safety or tolerability of deep brain stimulation (DBS) versus placebo, a sham intervention, or best medical treatment in people with dystonia will be eligible for inclusion in this review. Both open and blinded trials will be considered. We will exclude trials in which participants were their own controls (before/after design and on/off stimulation studies) because of the possibility of selection bias, carry-over effect and the impossibility to isolate the lesional effect of the intervention per se in the outcome estimate.

Types of participants

Adults (i.e. $\geq$ 18 years of age), in any setting, with a clinical diagnosis of any type of dystonia (namely primary or secondary, as well as focal, segmental or generalised). We will adopt a pragmatic approach to the definition of dystonia. Namely, we will consider patients included in randomised trials with the diagnosis of dystonia and in which these were evaluated on a validated and fit-for-purpose dystonia-specific severity scale.

If studies include only a subset of the relevant participants for this review, these will nonetheless be eligible for inclusion.

We will impose no restrictions regarding the number of participants recruited to trials, or the number of recruitment centres.

Types of interventions

We will accept any type of DBS, independent of the target-nucleus, the device used or the stimulation parameters. Depending on the data available, we will compare DBS with either: 1) the best available pharmacological treatment, including botulinum neurotoxin, 2) sham stimulation, or 3) resective/lesional surgery. Sham stimulation will have to be considered fit for purpose in order to be included past the full-text screening stage.

Types of outcome measures

Any included study had to explicitly report at least one of the outcomes below.

Critical outcomes

Dystonia-specific symptoms

Measured as the mean change from baseline on any validated dystonia-specific symptomatic rating scale, measured at least one month after DBS surgery.

Adverse events

Measured as the proportion of participants with any adverse event, at any point during study follow-up. We will also study surgery-related adverse events of special interest such as device infection, electrode dislocation, central nervous system haemorrhage, stroke, and death, measured at any point during study follow-up. Additionally, we will look specifically for stimulation-related adverse events of special interest, such as dysarthria, dyskinesia, loss of desired effect, and suicide attempts, measured at any point during study follow-up. Finally, we will aim to study the proportions of participants with specific adverse events, measured at any point during study follow-up.

Important outcomes

Subjective evaluation of clinical status

This outcome may be evaluated by both patients and clinicians, as assessed with validated assessment tools such as Patient Subjective Assessment of Change, Patient Global Assessment of Improvement, Patient Evaluation of Global Response (PEGR), Patient and Physician Global Assessment of Change, Investigator Global Assessment of Efficacy (IGAE), and Physician Global Assessment of Change (PGAC), and Visual analogue scale (VAS) for symptom severity, measured at least one month after DBS surgery. Subjective evaluation of clinical status will be dichotomised into patients that reported improvement or where classified by clinicians as having improved, and patients without improvement.

Quality of life

Changes in quality-of-life assessments, as assessed with validated assessment tools such as Short Form 36 (SF-36) Quality-of-Life questionnaire, measured at any point during study follow-up.

Functional capacity

As assessed using a validated assessment tool, such as the disability domain of Toronto Western Spasmodic Torticollis Rating Scale, measured at any point during study follow-up. We will also seek to study the proportions of participants who are able to perform selected activities of daily living, such as working capabilities and the ability to drive a car, measured at any point during study follow-up.

Emotional state

As assessed by validated scales such as the Beck Depression Inventory, Brief Psychiatric Rating Scale, measured at any point during study follow-up.

Tolerability

As assessed by the proportion of participants that withdraw from the study or alternatively interrupted DBS due to adverse events, measured at any point during study follow-up.

Search methods for identification of studies

Electronic searches

We intent to search the following databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL; latest issue) in the Cochrane Library.
2. MEDLINE Ovid (from 1993 to present).
3. Embase Ovid(from 1993 to present).
4. Web of Science (from 1993 to present).
5. SciELO (Scientific Electronic Library Online; from 1993 to present).
6. LILACS (Latin American and Caribbean Health Science Information database; from 1993 to present).

We will assess non-English language papers equally, translating them as necessary and evaluating them for inclusion.

For the identification of studies considered for inclusion in this review, we developed detailed search strategies for each database searched. Please see Appendix 1 for the CENTRAL search strategy, Appendix 2 for the MEDLINE search strategy, and Appendix 3 for the Embase search strategy.

We intent to run all electronic searches from 1993, the first year DBS was reported in any condition.

Searching other resources

We intent to search the following clinical trial registries.

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov).
2. EU Clinical Trials Register (www.clinicaltrialsregister.eu; from 1995).
3. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).
4. ISRCTN Registry (www.isrctn.com; from 2000).

We intent to search the grey literature via the following databases.

1. OpenSIGLE (from 1993).
2. Database of Abstracts of Reviews of Effects (DARE).
3. British Library Thesis Service.
4. National Technical Information Service (NTIS).

We considered conducting a handsearch of abstracts of the following international congresses of movement disorders:

1. American Academy of Neurology (from 1993);
2. European Academy of Neurology;
3. European Neurological Society (up till 2013);
4. European Federation of Neurological Science (up till 2013);
5. Movement Disorders Society;
6. International Association of Parkinsonism and Related Disorders.

However, owing to the fact that all the conference proceedings are published in indexed journals, at least since 1993, we have opted against conducting a handsearch since we do not expect that further citations will be found.

We will cross-check the reference lists of both selected and potentially eligible studies for additional studies to be included. We will translate non-English reports. Whenever necessary, we will contact study authors and DBS device companies for further access to data.

Data collection and analysis

Selection of studies

Two review authors will independently and in duplicate screened all titles and abstracts identified from searches to determine which meet the inclusion criteria. We will retrieve in full text any papers identified as potentially relevant by at least one author or those without an available abstract. Two review authors will independently screen full-text articles, with discrepancies resolved by discussion and by consulting a third author where necessary to reach consensus. We will collate duplicate publications and present these by individual study. The screening and selection process will be outlined in a PRISMA flow chart (Liberati 2009).

Data extraction and management

Two review authors will independently extract study data onto pre-piloted, standardised forms, after which we will cross-check the forms for accuracy. We will use the Covidence platform for this purpose (Covidence 2016). We will resolve disagreements by discussion or, if necessary, arbitration by a third review author. We will extract the following data from each study.

1. Participants: method for referral, inclusion and exclusion criteria, demographics and clinical baseline characteristics, number and reasons for withdrawals, exclusions and loss to follow-up, if any.
2. Interventions: full description of intervention, duration of treatment period and follow-up, providers, and co-interventions, if any.
3. Comparisons: number of randomised participants to each arm, compliance and dropouts, reasons for dropouts, and ability to perform an intention-to-treat analysis.
4. Outcomes: definition of outcomes, use of validated measurement tools, time-point measurements, change from baseline or post-interventional measures, and missing outcomes, if any.
5. Study design: interventional, randomised, controlled, double-blind.

Assessment of risk of bias in included studies

We will assess the risk of bias of included studies according to the domains described in the Cochrane tool for assessing risk of bias (Higgins 2011a), and classify the risk of bias for each domain as high, unclear, or low, and the overall assessment as high or low. We will assess two further domains, which are described below: 'for-profit bias' and 'prospective clinical trial registration'. We will use the following definitions for each domain in the risk of bias assessment.

Random sequence generation

- Low risk of bias: the study performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if an independent person not otherwise involved in the study performed them.
- Unclear risk of bias: the study authors did not report the sequence generation method.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation, sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information to permit judgement of 'low risk' or 'high risk'.
- High risk of bias: participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias.

In addition to these criteria, we will consider the implications of baseline imbalances in prognostic factors affecting the trial outcomes, as these may lead to selection bias (Corbett 2014).

Blinding of participants and personnel

- Low risk of bias: any of the following: no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; or blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinded outcome assessment

We will consider blinding separately for different outcomes, as appropriate.

- Low risk of bias: any of the following: no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; or blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk: the trial reported the following predefined outcomes. If the original trial protocol was available, the outcomes were called for in that protocol. If the trial protocol was obtained from a trial registry, the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, we did not consider those outcomes to be reliable.
- Unclear risk: the study authors do not report all predefined outcomes fully, or it is unclear whether the study authors recorded data on these outcomes or not.
- High risk: the study authors do not report one or more predefined outcomes.

For-profit bias

In order to assess the study source of funding, this domain was added in place of the 'other bias' domain.

- Low risk of bias: the trial appears to be free of industry sponsorship or other type of for-profit support that may manipulate the trial design, conductance, or trial results.
- Unclear risk of bias: the trial may or may not be free of for-profit bias as the trial does not provide any information on clinical trial support or sponsorship.
- High risk of bias: the trial is sponsored by industry or received other type of for-profit support.

Prospective clinical trial registration

- Low risk of bias: a trial protocol is available, and was published before the start of the trial.
- Unclear risk of bias: insufficient information to permit judgement of 'low risk' or 'high risk'.
- High risk of bias: no trial protocol is available or the trial was registered after it had already begun.

Measures of treatment effect

Whenever possible, we will extract continuous outcomes. These data will then be pooled from the studies, where adequate, and used for comparison.

Dichotomous data

We will analyse these data based on the number of events and the number of people assessed in the intervention and comparison groups. We will use these to calculate the risk ratio (RR) and 95% confidence interval (CI).

Continuous data

We will analyse these data based on the mean, standard deviation (SD) and number of people assessed for both the intervention and comparison groups to calculate mean difference (MD) and 95% CI. Where the MD is reported without individual group data, we will use this to report the study results. If more than one study measures the same outcome using different validated tools, we will calculate a standardised mean difference (SMD), namely Hedges' (adjusted) *g* (Hedges 1985), and 95% CI. For interpretation of effect sizes with SMDs, we will use a rule of thumb to define a small effect (SMD = 0.2), a moderate effect (SMD = 0.5), or a large effect (SMD = 0.8) (Cohen 1988). If necessary for comparison, we will dichotomised rating scales using each study author's own criteria for improvement or no improvement. If these criteria are not described, we will define 'improvement' as any beneficial change from baseline, and 'no improvement' as lack of improvement or any deterioration from baseline.

Unit of analysis issues

The primary data of analysis in the included studies should be individual trial participants.

We will examine data from parallel-group RCTs and will preferentially use data from intention-to-treat analyses.

If data are presented at different periods of follow-up, we will report the same outcome separately each time it is presented, based on the different periods of follow-up being reported. If the number of studies cannot adequately populate such subgroups, we will opt to select the longest period of follow-up for each study.

In case studies included multiple active DBS arms, we will combine all arms into a single pair-wise comparison, using the Review Manager (RevMan) 5.3 calculator (RevMan 2014), using the methods suggested by Cochrane (Higgins 2011c).

Given that individual participants are liable to experience an adverse event more than once, and adverse events may be reported as such, we will preferentially request data from study authors concerning the number of participants with adverse events. If this approach is not successful we will treat adverse events not as categorical data (did or did not experience the event), but rather, as count data. Thus, we will consider not only if the data were reported, but how many times they were reported. In such cases we will treat the adverse events as Poisson data, and will preferentially summarise the data as rate ratios, standardised to a given time period, to be defined post-hoc.

Dealing with missing data

For missing outcome or summary data we will use imputation methods to derive the missing data (where possible) and report any assumptions in the review. All cases will be investigated, through sensitivity analyses, regarding the effects of any imputed data on pooled effect estimates.

As a first option we will choose to use the available information (e.g. standard error (SE), 95% CI or exact P value) to algebraically recover the missing data (Higgins 2011b; Higgins 2011c; Wiebe 2006). When change from baseline SD are not reported or not possible to extract we will attempt to create a correlation coefficient based on another study in this review, and then use this correlation coefficient to impute a change from baseline SD (Abrams 2005; Follmann 1992; Higgins 2011c).

If this is to fail, and if at least one sufficiently large and similar study were to exist, we will use a method of single imputation (Furukawa 2006; Higgins 2011c).

Lastly, if a sufficient number of included studies with complete information is to exist, we will use multiple imputation methods to derive missing data (Carpenter 2013; Rubin 1991).

If none of these methods are successful we will conduct a narrative synthesis for the data in question.

In case relevant data are only reported through figures or graphs, two authors will independently extract the relevant information. We will only use the data if the two extractions give the same result.

Assessment of heterogeneity

Where data are pooled using meta-analysis, we will assess the degree of heterogeneity by visual inspection of forest plots and by examining the Chi^2 test for heterogeneity. We will quantify heterogeneity using the I^2 statistic. We will consider an I^2 value of 50% or more to represent substantial levels of heterogeneity, but interpret this value in light of the size and direction of effects and the strength of the evidence for heterogeneity, based on the P value from the Chi^2 test (Higgins 2003). Where heterogeneity is found in pooled effect estimates, we will explore possible reasons for variability by conducting subgroup and sensitivity analyses.

Assessment of reporting biases

We intend to assess publication bias through visual inspection of funnel plot asymmetry (Sterne 2001) and Peters' regression tests (Peters 2006), provided that 10 or more studies per outcome are available (Sterne 2011).

Data synthesis

We will perform statistical analysis using Review Manager (RevMan) version 5.3 (RevMan 2014), Stata version 14 (Stata 2015) and Trial Sequential Analysis (TSA) (Thorlund 2011; TSA 2011) software.

Meta-analysis

We intent to pool effect measures by applying the Mantel-Haenszel method for dichotomous outcomes, the inverse-variance method for continuous, rate ratio and count data syntheses, if required. We will conduct data synthesis using a random-effects model by default independently of the presence or not of considerable statistical heterogeneity owing to the variety of disease subtypes that we intent to analyse. We will present all results with 95% CI.

We intend to calculate the number of participants needed to treat for an additional beneficial outcome (NNTB) and for an additional harmful outcome (NNTH) from meta-analysis estimates, rather than treating data as if they came from a single trial, as the latter approach is more prone to bias, especially when there are significant imbalances between groups within one or more trials in the meta-analysis (Altman 2002). However, caution is needed in interpreting these findings since they may be misleading because of variation in the event rates in each trial, differences in the outcomes considered, effects of secular trends on disease risk, and differences in clinical setting (Smeeth 1999).

Where data from the study reports could not be combined into a meta-analysis, we will present a qualitative summary of the study results in the review text.

Trial sequential analysis

In order to explore whether the cumulative data were adequately powered to evaluate the critical outcomes of this review, we intend to perform a trial sequential analysis (Wetterslev 2008), and calculate a required information size (also known as the 'heterogeneity-adjusted required information size') (Wetterslev 2009). Trial sequential analysis aims to evaluate whether statistically significant results of meta-analysis are reliable by accounting for the required information size (i.e. the number of participants in the meta-analysis required to accept or reject an intervention effect). The technique is analogous to sequential monitoring boundaries in single trials. Trial sequential analysis adjusts the threshold of statistical significance and has been shown to reduce the risk of random errors due to repetitive testing of accumulating data (Imberger 2016).

We intend to calculate the required information size and compute the trial sequential monitoring boundaries using the O'Brien-Fleming approach (O'Brien 1979). The required information size will be based on the event proportion or standard deviation in the control group; assumption of a plausible relative risk reduction (RRR) of 20%; a 5% risk of type I error; a 20% risk of type II error (power = 80%); and the observed heterogeneity of the meta-analysis (Jakobsen 2014; Wetterslev 2009).

Assessment of confidence in cumulative evidence

As recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group methodology (Atkins 2004), two review authors will independently assess all of the outcomes in the following domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. In case of disagreement the authors will meet to reach consensus, consulting an independent third review author if necessary. For this purpose, we will use GRADEproGDT software (GRADEproGDT 2014), which we will then extract into the form of a 'Summary of findings' table for inclusion into the review manuscript.

To ensure the consistency and reproducibility of GRADE judgements, we will apply the following criteria to each domain for all key comparisons of the critical outcomes.

- Study limitations: downgrade once if more than 30% of participants were from studies classified as being at a high risk of bias across any domain.
- Inconsistency: downgrade once if heterogeneity is statistically significant or if the I^2 value is more than 40%. When a meta-analysis was not performed we will downgrade once if trials did not show effects in the same direction.
- Indirectness: downgrade once if more than 50% of the participants were outside the target group.
- Imprecision: downgrade once if the optimal information size criterion is not met or, alternatively, if it is met but the 95%

CI fails to exclude important benefit or important harm (Guyatt 2011).

- Publication bias: downgrade once where there is direct evidence of publication bias or if estimates of effect are based on small scale, industry-sponsored studies raising a high index of suspicion of publication bias.

We will apply the following definitions of the quality of evidence (Balshem 2011)

- .High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

The list of outcomes we intend to include in the GRADE analysis are the following.

- Dystonia-specific symptoms.
- Proportion of participants with adverse events.
- Subjective evaluation of clinical status.
- Quality-of-life assessment.
- Functional capacity.
- Emotional state.
- Tolerability.

'Summary of findings' table

As has become standard practice in Cochrane reviews, we will include a 'Summary of findings' table to present the main findings of this review in a simple tabular format. In particular, we will include key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the available outcomes.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses have been planned for the following areas.

1. Disease subtypes (i.e. generalised and non-generalised dystonia; primary and secondary dystonia).
2. Target-nucleus (i.e. internal globus pallidus (GPi), thalamus ventrointermediate nucleus (VIM) and subthalamic nucleus (STN).
3. Stimulation parameters (i.e. constant current and constant voltage).
4. Risk of bias (i.e low, high and unclear).
5. Control intervention used (i.e. botulinum treatment and lesional surgery; placebo and sham intervention).

Sensitivity analysis

We will conduct sensitivity analyses by excluding studies in which imputation methods were applied as well as studies assessed as being at high risk of bias in order to evaluate the robustness of our results.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Glossary of terms

Term	Definition
Deep brain stimulation	Neurosurgical procedure whereby an electric current delivered by electrodes placed in the deep brain stimulate target nuclei
Target nucleus/nuclei	Groups of neuronal cell bodies, located in the deep areas of the brain, aimed to be stimulated by deep brain stimulation
Dystonia	Common movement disorder in which people have abnormal torsion movements or postures of one or more body segments, such as the neck or a limb, that they cannot control. It is frequently accompanied by social embarrassment and pain
Primary dystonia	Dystonic disorder caused by an intrinsic basal ganglia problem unrelated to any other disease. It is sometimes caused by mutation and dystonia is the main clinical manifestation in the majority of primary dystonias
Secondary dystonia	Dystonic disorder caused by another disease (i.e. caused by stroke)
Generalised dystonia	Dystonia affecting all body segments (i.e. trunk, upper and lower limbs)
Cervical dystonia	Dystonia affecting the neck
Blepharospasm	Dystonia affecting the eye lids

APPENDICES

Appendix 1. CENTRAL search strategy

1. MeSH descriptor: [Dystonia] explode all trees
2. dystonia
3. MeSH descriptor: [Dystonic Disorders] explode all trees
4. dystonic disorder
5. MeSH descriptor: [Blepharospasm] explode all trees
6. blepharospasm
7. MeSH descriptor: [Meige Syndrome] explode all trees
8. Meige syndrome
9. MeSH descriptor: [Torticollis] explode all trees
10. torticollis
11. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12. MeSH descriptor: [Deep Brain Stimulation] explode all trees
13. deep brain stimulation
14. MeSH descriptor: [Electric Stimulation] explode all trees
15. electric stimulation
16. #12 or #13 or #14 or #15
17. #11 and #16 in Trial

Appendix 2. MEDLINE search strategy

1. "randomized controlled trial".pt.
2. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
3. (retraction of publication or retracted publication).pt.
4. or/1-3
5. (animals not humans).sh.
6. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
7. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.
8. or/5-7
9. 4 not 8 (728284)10 exp Deep Brain Stimulation/
10. (stimulat* or stimuli* or stimulu*).ab,ti.
11. DBS.ab,ti.
12. exp Dystonic Disorders/
13. dyston*.ab,ti.
14. exp dystonia/
15. or/10-12
16. or/13-15
17. and/9,16-17
18. remove duplicates from 18

Appendix 3. Embase search strategy

1. exp Deep Brain Stimulation/
2. (stimulat* or stimuli* or stimulu*).ab,ti.
3. DBS.ab,ti.
4. exp Dystonic Disorders/
5. dyston*.ab,ti.
6. exp dystonia/
7. or/1-3
8. or/4-6
9. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
10. RETRACTED ARTICLE/
11. or/9-10
12. (animal$ not human$).sh,hw.
13. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
14. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
15. or/12-14
16. 11 not 15
17. and/7-8,16
18. limit 17 to embase

CONTRIBUTIONS OF AUTHORS

All authors contributed to the conception and design of the protocol. All authors approved the protocol: Gonçalo S Duarte (GSD), Filipe B Rodrigues (FBR), David Prescott (DP), Joaquim Ferreira (JF), João Costa (JC).

Conceiving the review: FBR, GSD, JC, JF.

Designing the review: FBR, GSD, JC.

Co-ordinating the review: JC.

Designing search strategies: FBR, GSD, JC.

Providing general advice on the review: JC, JF.

DECLARATIONS OF INTEREST

Gonçalo S Duarte: none known.

Filipe B Rodrigues: none known.

David Prescott: none known.

Joaquim Ferreira: he has held consultancy functions with GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, BIAL, Merck-Serono, Merz, Ipsen and has received grants from GlaxoSmithKline, Grunenthal, Fundação MSD (Portugal) and TEVA.

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