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Botulinum toxin for drooling in Parkinson's disease (Protocol)

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[Intervention Protocol]

Botulinum toxin for drooling in Parkinson's disease

Fiona Hill[1], Nick Miller[2], Richard A Walsh[3], David Mockler[4], Ronald McDowell[5], Margaret Walshe[6]

[1]Department of Speech & Language Therapy, Tallaght Hospital, Dublin 24, Ireland. [2]Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK. [3]Department of Neurology, Tallaght Hospital, Dublin 24, Ireland. [4]John Stearne Library, Trinity Centre for Health Sciences, St. James Hospital, Dublin 8, Ireland. [5]Department of General Practice, Royal College of Surgeons, Dublin 2, Ireland. [6]Clinical Speech and Language Studies, Trinity College Dublin, Dublin, Ireland

Contact address: Fiona Hill, Department of Speech & Language Therapy, Tallaght Hospital, Tallaght, Dublin 24, Ireland. hillfi@tcd.ie.

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ABSTRACT

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

Primary objective: to assess the efficacy of botulinum toxin treatment to reduce or eliminate drooling in adults with Parkinson's disease.

Secondary objective: to assess the adverse effects of botulinum toxin treatment for drooling in adults with Parkinson's disease.

BACKGROUND

Description of the condition

Parkinson's disease (PD) is a progressive degenerative disorder of the nervous system that results from death of dopamine-generating cells in the basal ganglia in the brain (Connolly 2014). Motor symptoms affecting movement are the cardinal features of PD, but are typically accompanied by a range of non-motor symptoms that may include disturbances in speech, cognition, and mood, and may affect swallowing, sleep, and autonomic body functions such as regulation of blood pressure and temperature, and saliva control (Berg 2014; Seppi 2011).

Drooling, which generally refers to an involuntary loss of saliva (Kalf 2009; Lal 2006), is a common problem for people with PD. Drooling in the literature is also frequently termed dribbling, hypersalivation, ptyalism, and sialorrhoea (Bavikatte 2012; Kalf 2011a; Reddihough 2010). Anterior drooling, which describes visible loss of saliva from the mouth, is distinct from posterior drooling where saliva spills into the pharynx (Johnson 2014; Reddihough 2010).

Estimates of prevalence of drooling in people with PD range from 10% to 84% (Nicaretta 2008; Ozdilek 2012, respectively), with the wide variation in the estimates due to the lack of a standard definition of drooling and its diagnostic criteria. There are no standard assessment tools for evaluating the severity of drooling in PD. Available objective tools measure the volume and flow of saliva by means such as suctioning, or measuring the weight of saliva-soaked gauze. Subjective instruments for assessment of drooling in PD include drooling-specific and non-specific rating scales, a limited number of which have been validated (Non-motor Symptoms Questionnaire for PD (Chaudhuri 2006); Non-motor Symptoms Assessment Scale for PD (Chaudhuri 2007); Movement Disorders Society-Unified Parkinson's Disease Rating Scale (Goetz 2008); Rabboud Oral Motor Inventory for PD (Kalf 2011b); Drooling Rating Scale (Marks 2001); Sialorrhea Clinical

Scale for PD (Perez Lloret 2007); Drooling Severity and Frequency Scale (Thomas-Stonell 1988); Scales for Outcomes in PD-Autonomic (Visser 2004)).

At present the exact mechanism responsible for drooling in PD is not fully understood, but it is generally not considered to be due to overproduction of saliva (Srivanitchapoom 2014). Indeed, a number of studies have shown that people with PD who experience drooling actually produce less saliva (Bagheri 1999; Bateson 1973; Proulx 2005), possibly due to dopamine deficiency (Srivanitchapoom 2014). It is suggested that the cause of drooling in PD is multifactorial. Increased speed of salivary flow is considered a potential contributory factor (Nicaretta 2008). Unintentional mouth opening and a flexed head posture may contribute to difficulties in maintaining saliva in the mouth (Kalf 2011a; Kalf 2013). Drooling in PD may also be associated with swallowing difficulties (dysphagia) as there is a reduced ability to clear saliva from the mouth in a timely fashion (Johnson 2014). Dysphagia in PD may stem from the overall slowed movement (bradykinesia) (Srivanitchapoom 2014), delayed or diminished reflexes (Rosenbek 2009), reduced tongue and lip control, as well as difficulty with mastication (chewing) (Umemoto 2011). Severity of dysphagia has been found to correlate with severity of drooling in PD (Johnston 1995; Nobrega 2008a). A positive correlation has also been reported between drooling and severity of PD (Kalf 2011a; Martinez-Martin 2007; Verbaan 2007).

Drooling can have a negative impact on the person with PD medically, socially, and psychologically, and can affect quality of life. Negative physical consequences associated with drooling include perioral and oral infections (Bloem 2009; Kalf 2007), halitosis (bad breath) (Reddihough 2010), increased intra-oral occult bacteria, and interference with speech and swallowing (Leibner 2010). There may also be silent saliva aspiration (saliva entering the lungs) (Nobrega 2008b; Rodrigues 2011), which can increase the risk of respiratory tract infections (Nobrega 2008c), especially if oral bacteria are present in the aspirated saliva (Johnson 2014). Reported social and emotional effects include social embarrassment and isolation (Leibner 2010; Politis 2010), increasing emotional distress, and poor quality of life (Kalf 2007). Soiled and damaged clothing and footwear as a result of drooling may necessitate frequent changing of shoes or clothes (Bloem 2009). Carers for people with PD and drooling may experience an increased burden, depression and anxiety, and reduced quality of life (Damian 2012).

Management options for drooling in PD include behavioural, physical, oromotor (relating to movement of lips, tongue and jaw) and oro-sensory (relating to sensation of the face and within the mouth) strategies, radiotherapy, surgical, and pharmacological interventions. The published research on non-pharmacological interventions for drooling in PD is limited, and there are no current recommendations for the use of these treatments in PD. Behavioural modification interventions for drooling in PD have been designed to increase the target behaviour of swallowing, with the aim of managing the amount of saliva in the mouth (Marks 2001; McNaney 2011). Radiotherapy treatment for drooling involves radiotherapy to the parotid glands and superior parts of the submandibular glands to reduce the flow of saliva (Postma 2007). Risks associated with salivary gland radiation include local side effects and an increased risk of malignancy (cancer). Surgical approaches, namely deep brain stimulation, are invasive and have not been studied directly for their effect on drooling in PD; at present there is no evidence to suggest that this approach will influence drooling positively (Srivanitchapoom 2014). Pharmacological treatment options for drooling in PD consist of anticholinergics (Arbouw 2010; Hyson 2002; Lloret 2011; Thomsen 2007), and adrenergic receptor antagonists (Chou 2007), whose side effects preclude their use in the elderly. Another pharmacological agent to treat drooling in PD is botulinum toxin, which is delivered via injection into the salivary glands with the aim of reducing the volume of saliva produced (Chinnapongse 2012; Lagalla 2006; Mancini 2003).

Description of the intervention

Botulinum toxin (BoNT) is a neurotoxin that works by inhibiting the release of acetylcholine from cholinergic nerve endings, which leads to inactivity of muscles or glands (Reddihough 2010). Seven subtypes of BoNT exist, but only two serotypes, botulinum toxin A (BoNT-A) and botulinum toxin B (BoNT-B), are used in clinical practice to manage a variety of cosmetic and medical conditions. Medical conditions include, among others, eye movement disorders, limb and neck dystonias, vocal cord dysfunction, facial movement disorders, spasticity, migraine, overactive bladder, oesophageal conditions, dysphagia, and hypersecretory disorders (Chan 2013; Ney 2007; Persaud 2013).

BoNT-A is the most commonly used neurotoxin for the treatment of drooling. BoNT-A formulations that are currently available include onabotulinum toxin A (BOTOX® (Allergan Inc)), abobotulinum toxin A (Dysport® (Ipsen Ltd)), and incobotulinum toxin A (Xeomin® (Merz Pharmaceuticals)). BoNT-B is available as rimabotulinum toxin B (MyoBloc®/NeuroBloc® (Solstice Neuroscience Inc)). The preparations differ with regard to manufacturing processes, formulation, dose potency and/or equivalency, and employ different methods to establish biological activity (Intiso 2012). While a unit of BOTOX® is roughly equivalent to one unit of Xeomin®, three units of Dysport®, and 40 to 50 units of MyoBloc® a clear conversion factor has not been established between the products (Aoki 2006; Intiso 2012).

Despite an increasing body of evidence reporting improvements in drooling in PD with use of BoNT, the effects of the BoNT are temporary, lasting from three to five months after which reinjection is often required (Srivanitchapoom 2014). Adverse side effects include dry mouth or thickening of saliva (Chinnapongse 2012; Contarino 2007; Dogu 2004; Guidubaldi 2011; Nobrega 2007; Ondo 2004; Pal 2000; Racette 2003; Su 2006; Tintner 2005), swallowing difficulties (Lagalla 2006; Lagalla 2009), re-

duced mastication ability (Lagalla 2009), diarrhoea, gait disturbance and neck pain (Ondo 2004).

How the intervention might work

The three paired major salivary glands, the parotids, submandibular and sublinguals, as well as several hundred minor salivary glands, are responsible for saliva production and secretion. The salivary glands are innervated by the parasympathetic and sympathetic nervous systems (Bavikatte 2012). The mechanism of action of BoNT is inhibition of acetylcholine release (Intiso 2012). When injected locally into salivary glands BoNT reduces the secretion of saliva by inhibiting cholinergic parasympathetic and postganglionic sympathetic activity (Chou 2007; Srivanitchapoom 2014). Therapeutic effects are usually seen within one week of the injection, and are reported to last from three to five months (Srivanitchapoom 2014). Peripheral neuronal sprouting (formation of new nerve tissue) prevents the effects of BoNT from being permanent (Ney 2007).

Why it is important to do this review

The prevalence and incidence of PD increases with age (Pringsheim 2014; von Campenhausen 2005). It affects 428 per 100,000 people between the ages of 60 to 69 years, rising to 1903 per 100,000 in people over 80 years of age (Pringsheim 2014). The ageing global population means that in future larger numbers of people worldwide will reach the age where the incidence of PD is highest (Dorsey 2007). Drooling, a pervasive problem in PD, particularly with advancing disease (Rana 2012), will be a significant issue in the future management of PD.

A Cochrane Review, Walshe 2012, found insufficient evidence to provide firm support for the use of BoNT to treat drooling in children with cerebral palsy. However, a Cochrane Review on the use of BoNT for drooling in motor neurone disease supported this intervention in this population (Young 2011). Early clinical research on the use of BoNT as an intervention for drooling in PD reported a marked objective reduction in saliva secretion (Jost 1999), and a subjective improvement in the degree of drooling (Jost 1999; Pal 2000). Open label trials, retrospective studies, case series, and controlled clinical trials performed since these early studies have documented varying efficacy of BoNT in the treatment of drooling in PD (Chinnapongse 2012; Contarino 2007; Dogu 2004; Friedman 2001; Guidubaldi 2011; Lagalla 2006; Lagalla 2009; Lipp 2003; Mancini 2003; Narayanaswami 2015; Nobrega 2007; Ondo 2004; Pal 2000; Racette 2003; Santamato 2008; Su 2006). The American Academy of Neurology recommends that BoNT should be considered for treatment of drooling in PD (Naumann 2008), and the Movement Disorder Society have concluded that BoNT is an efficacious and 'clinically useful' intervention for drooling in PD (Seppi 2011), with "an acceptable risk with specialized monitoring" (S71). Despite the support for this intervention there exists a lack of clear consensus on the safest and most effective method of treatment, and clinical guidelines or recommendations specific to the use of BoNT for drooling in PD have not been established. As a result, healthcare professionals working with people with PD have difficulty determining the candidacy, efficacy, and safety of BoNT to treat drooling, which is a concern when the growing use of this intervention in clinical practice is considered. It is vital to collate evidence on the benefits and risks of this intervention, as well as directions for future research, in order to optimise the care of people with PD and drooling. In the absence of a comprehensive Cochrane systematic review of the evidence in this area, BoNT interventions may be delivered with little attention to, or consideration of, adverse effects and long-term safety of the person with PD, as these are not yet well established. Evidence is required in order to inform decision making by healthcare professionals, multidisciplinary teams, individuals with PD, their caregivers, and other key stakeholders.

OBJECTIVES

Primary objective: to assess the efficacy of botulinum toxin treatment to reduce or eliminate drooling in adults with Parkinson's disease.

Secondary objective: to assess the adverse effects of botulinum toxin treatment for drooling in adults with Parkinson's disease.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all published and unpublished randomized controlled trials (RCTs) and quasi-RCTs. Relevant trials for this review will be those with at least one group receiving BoNT with the aim of reducing or eliminating drooling, and one group receiving a placebo or no treatment, with concurrent enrolment and follow-up of the BoNT and control-treated groups. We will exclude cross-over trials as the period of washout of BoNT is not established. Cross-over trials are defined as trials in which each participant is randomized to a sequence of interventions (Higgins 2011a). We will consider quasi-RCTs as eligible for inclusion due to the potentially small number of RCTs in this area. As described in the *Cochrane Handbook for Systematic Reviews of Interventions,* quasi-RCTs will be defined as trials where the method of allocation is not considered to be strictly random, for example allocation by

alternation or date of birth (Lefebvre 2011). We will not apply any language limits or date restrictions to our searches for trials.

Types of participants

We will include trials that enrol adults over 18 years of age of either gender with a clinical diagnosis of PD according to the UK Parkinson's Disease Society Brain Bank diagnostic criteria (Hughes 1992), or other similar published clinical diagnostic criteria. We will include people at all stages of the disease, at all disease severity levels, and presenting with all severities of drooling. We will include trials that include participants with medical conditions other than PD, if subgroup data on the participants who present with drooling as a consequence of PD can be extracted separately, or the data can be provided by the trial authors. We will exclude trials that include participants with PD who also have independent or co-morbid causes of drooling (e.g. atypical parkinsonian syndromes, motor neuron disease, stroke, cerebral palsy, intellectual disability, head and neck cancer).

Types of interventions

We will consider all trials that involve delivery of BoNT injections into one or more of the major salivary glands (parotid, submandibular, sublingual). This intervention can be delivered with or without ultrasound guidance. It must be administered by a trained medical professional. We will include trials that involve all BoNT serotypes, commercial brands, dosages, injection sites, and all administration schedules. We will make the following comparisons:

1. BoNT versus no BoNT;
2. BoNT versus placebo intervention.

Types of outcome measures

Primary outcomes

1. Changes in:
   i) volume;
   ii) frequency; and
   iii) severity of drooling, as assessed by quantitative measures (e.g. weight of oral swabs, saliva collection, number of swallows), frequency measures (e.g. number of clothes changes, amount of handkerchiefs, wiping saliva, frequency of suctioning used pre- and postintervention), or as measured by a relevant clinical scale (e.g. Sialorrhea Clinical Scale for PD (SCS-PD) (Perez Lloret 2007)).
2. Quality of life as measured by a validated quality of life scales (e.g. Parkinson's Disease Questionnaire 39 (Peto 1995)), by participant/carer report, or both.

Secondary outcomes

1. Adverse effects attributable to the intervention.
2. Participant or carer satisfaction (or both) with the intervention evaluated through questionnaire or interview.
3. Number of withdrawals from treatment.

We will consider short-term (less than three months), medium-term (three to six months), and long-term (more than six months) changes in primary and secondary outcomes.

Summary of findings table

A 'Summary of findings' table will provide key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes for a given comparison. We will conduct quality assessment of the results using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which specifies four levels of quality (high, moderate, low and very low), where the highest quality rating is for a body of evidence based on randomized trials (Schünemann 2011). Quality will be assessed separately for each outcome. We aim to select the following main outcomes for inclusion in the 'Summary of findings' table:

1. volume of saliva;
2. frequency of drooling;
3. severity of drooling;
4. quality of life;
5. adverse effects.

We will use GRADEpro software to import data from Review Manager 5.3 and prepare the tables (GRADEpro 2014; Revman 2014).

Search methods for identification of studies

Electronic searches

We will search for articles with combinations of subject headings and key words and synonyms relating to drooling; PD; and BoNT, using the controlled vocabulary used for indexing specific to each database searched. We will use the Cochrane Highly Sensitive Search Strategy for identifying randomized controlled trials (Lefebvre 2011).

We will search the following databases from inception to the present for published trials in any language.

1. Elsevier EMBASE (1974 to present) (Appendix 1);
2. PubMed (1946 to present) (Appendix 2);
3. EBSCO CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1937 to present) (Appendix 3);
4. The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library) (Appendix 4);
5. EBSCO AMED (Allied and Complementary Medicine) (1941 to present) (Appendix 5);

6. Thomson Scientific Web of Science (1864 to present);
7. Elsevier Scopus.

We will also search major clinical trials registers:

1. World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch);
2. European Union Clinical Trials Register (www.clinicaltrialsregister.eu);
3. Clinical Trials (www.clinicaltrials.gov);
4. ISRCTN Registry (www.isrctn.com).

Searching other resources

We will search within previous reviews on the same topic and review reference lists from all included studies to identify further relevant trials. We will handsearch published abstracts of conference proceedings from the Dysphagia Research Society and the European Society of Swallowing Disorders (both published in *Dysphagia*) and the International Parkinsons and Movement Disorder Society (published in *Movement Disorders*). We will also search ProQuest Dissertations & Theses for relevant dissertation abstracts. We will contact primary authors for data or clarification on trials as relevant. We will contact pharmaceutical companies identified from clinical trials registers to identify further published, unpublished, and ongoing trials.

Data collection and analysis

Selection of studies

We will merge search results using reference management software, remove duplicate records of the same report, and import the results into Covidence, a web-based systematic review software platform (Covidence 2013). In Covidence two review authors (FH and NM) will independently examine titles, abstracts and key words identified from the literature search. The results of this search will be categorised as either 'yes', 'no', or 'maybe' relevant. If it is unclear from titles and abstracts whether a study should be included, we will obtain full texts of these trial reports for further examination. We will resolve disagreement about selection of studies by consensus discussion. We will list those studies excluded in the 'Characteristics of excluded studies' table. FH will retrieve full texts of relevant and potentially relevant reports and link multiple reports of the same study. Two authors (FH and MW) will independently examine the full texts for compliance with eligibility criteria. We will contact study authors for further information, where appropriate, to clarify study eligibility. The review team will not be blinded to information about study authors, institutions, journal of publication, or results. We will resolve any disagreements through discussion.

Data extraction and management

Two review authors (FH and MW) will independently extract data from all eligible studies using a standardised, piloted data extraction form. This form will be used to collate information on participants, interventions, outcomes, and study design, as well as details of funding sources and declarations of interest for the primary investigators for each included study. When any of the data are incomplete or unclear we will attempt to contact the study authors for clarification. Studies in a language other than English will be translated into English and then data will be extracted, according to the extraction process outlined above, from both the translated and the original article. To check accuracy of data extraction, a third review author (RW), blinded to the other authors' data extraction, will extract data from a random sample of 20% of included studies. We will resolve all disagreements through discussion. We will complete transformations of reported data where possible, if required statistics are not published in the study paper, according to the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). FH will enter the data in Review Manager 5.3 (Revman 2014), and they will be checked for accuracy by a second author (NM).

Assessment of risk of bias in included studies

Three review authors (FH, MW, RW) will independently assess all included studies for risk of bias. We will use the Cochrane 'Risk of bias' tool to assess domains of bias including sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other potential threats to validity, and other biases such as differences in baseline characteristics between the experimental groups, sources of funding, e.g. from the pharmaceutical industry, and conflict of interest (Higgins 2011c).

We will answer prespecified questions about the adequacy of a study in relation to the above seven domains. We will make our judgements about risk of bias for each domain according to the specified criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). We will make judgements of 'low risk' of bias, 'high risk' of bias, and 'unclear risk' of bias. A judgment of unclear risk of bias will be made where insufficient detail is reported, where the risk of bias is unknown, or if an entry is not relevant to a study. Justification for judgements will be presented in a 'Risk of bias' table.

Where participants or personnel, or both, have not been blinded to the nature of the intervention, or where blinding is not complete, the blinding will be considered to be at low risk of bias if the review authors judge that the outcome is not likely to be influenced by lack of blinding; at high risk of bias if the outcome is likely to be influenced by lack of blinding; and at unclear risk of bias if there is insufficient information to permit a judgment of low or high risk (Higgins 2011c). We will assess the use of appropriate analysis

methods for quasi-RCTs (e.g. propensity score methods) under the risk domain of 'other potential threats to validity'. A study will be classified as being at low overall risk of bias if there is a low risk of bias across all domains including sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting. A study will be classified as being at high overall risk of bias if there is a high risk of bias in at least one of these domains. All studies neither at high risk nor low risk will be considered at unclear risk of bias. We will resolve any disagreements by discussion or by consulting review author NM.

Measures of treatment effect

Data will be analyzed using Review Manager 5.3 (Revman 2014). If sufficient trials are available and their populations are clinically similar, we will carry out meta-analyses of primary and secondary end points. For dichotomous data we will derive risk ratios (RRs) and 95% confidence intervals (CI) and for continuous data we will calculate mean difference (MD) or standardised mean differences (SMD), standard deviation (SD), and 95% CI for each outcome. We will use final scores in preference to change scores for continuous outcome measures. For rates, and rate ratios we will report 95% confidence intervals (CI). Ordinal data may be analyzed using proportional odds methods. Alternatively, we may treat longer ordinal scales as continuous measures, and convert shorter ordinal scales into a binary variable by combining adjacent categories together using a cutpoint appropriate to that scale and as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Unit of analysis issues

The unit of analysis will be the person with PD. We will examine whether the number of measurements in the analysis matches the number of individuals with PD who were randomized to the intervention. For parallel groups where there are multiple observations of an outcome at different time points, we will analyse repeated observations of participants separately (i.e. short-term, medium-term and long-term follow-up outcome measures).

Dealing with missing data

In the event of missing data within published studies we will contact the original trial investigators, where reasonable, to obtain missing data or seek clarification about the data. If there are any missing data we will state this explicitly. We will undertake sensitivity analyses, according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions,* to assess how sensitive results are to reasonable changes in the assumptions that are made (Higgins 2011d). We will comment on the potential impact of missing data on the review findings in the 'Discussion' section.

Assessment of heterogeneity

We will perform a test of statistical heterogeneity using a standard Chi² test (significance at $P < 0.1$). We will quantify heterogeneity using the I^2 statistic following the guide for interpretation provided in the *Cochrane Handbook for Systematic Reviews of Interventions (*Deeks 2011).

1. 0% to 40%: might not be important.
2. 30% to 60%: may represent moderate heterogeneity.
3. 50% to 90%: may represent substantial heterogeneity.
4. 75% to 100%: represents considerable heterogeneity.

If statistical heterogeneity is identified, we will use a number of strategies to address this. We will recheck data to ensure they are correct and we will explore heterogeneity, possibly by subgroup analysis or meta-regression, or both, if there are sufficient studies to permit this. We may decide not to pool data in a meta-analysis if I^2 exceeds 75%. .

Assessment of reporting biases

We will minimise reporting biases (publication bias, time lag bias, duplicate publication bias, location bias, citation bias, language bias or outcome reporting bias) through a comprehensive search for studies, inclusion of unpublished studies and use of trial registries. We will compare outcomes published in trial reports with those listed in trial protocols, where these are available, and we will examine studies to see whether they reported outcomes routinely measured in this area. Where there are concerns about selective reporting, we will ask study authors for additional information.
If there are sufficient studies available, we will create funnel plots for the primary outcomes. We will conduct formal statistical tests for funnel plot asymmetry (Egger 1998). We will not use funnel plots for outcomes where there are 10 or fewer studies, or where all studies are of similar size. Given that asymmetry could be caused by publication bias, or by a relationship between effect size and sample size, we will examine any observed effect for clinical heterogeneity and may carry out additional sensitivity tests.

Data synthesis

If a sufficient number of comparable studies are available, we will conduct a meta-analysis using Review Manager 5.3 to synthesise the available data (Revman 2014). For all outcomes, as far as possible, we will undertake analyses on an intention-to-treat basis. Given that we expect there to be clinical heterogeneity between studies, and that the real efficacy of BoNT will vary between studies (e.g. due to different comparators) we will apply random-effects analysis to all meta-analyses, regardless of the value of I^2. If it is inappropriate to combine the numerical results of the studies, we will provide a descriptive summary of the results and a narrative review. Results will be stratified by design type in order to distinguish between RCTs and quasi-RCTs.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, we will conduct subgroup analyses. The following intervention characteristics will be considered for subgroup analysis:

1. type of botulinum toxin formulation;
2. dosage of botulinum toxin;
3. site of injection of botulinum toxin;
4. method of delivery of botulinum toxin;
5. needle used.

It may also be possible to examine subgroups based on severity of drooling, stages and severity of PD, and age. We will follow Cochrane guidance and keep the number of subgroup analyses to a minimum. Priority will be given to those that are particularly relevant to the implementation of any future intervention.

Sensitivity analysis

We will conduct sensitivity analyses to examine the robustness of the results by repeating the analysis with the following adjustments:

1. excluding studies with unclear random sequence generation or concealment of allocation, or both;
2. excluding studies in which outcome evaluation was not blinded;
3. excluding studies in which loss to follow-up was greater than 10%;
4. excluding studies with missing data;
5. excluding studies assessed as having a higher risk of bias.

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None

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. EMBASE search strategy

1. 'hypersalivation'/exp
2. 'salivation'/exp
3. 'salivary gland'/exp
4. 'saliva'/exp
5. (drool* OR dribbl* OR Hypersalivation OR sialorrhea OR sialorrhoea OR 'oral secretions'):ab,ti
6. (Saliva* Near/3 (excess* OR manage* OR volume OR reduction OR reduce)):ab,ti
7. (Salivary OR parotid OR submandibular):ab,ti
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. 'botulinum toxin'/exp
10. 'Clostridium botulinum'/exp
11. 'botulinum toxin A'/exp
12. 'botulinum toxin B'/exp
13. (Botox OR botulin* OR dysport* OR abobotulin* OR incobotulin* OR onabotulin* OR rimabotulin OR BoNT OR xeomin OR myobloc OR neurobloc):ab,ti
14. 9 OR 10 OR 11 OR 12 OR 13
15. 'Parkinson disease'/exp
16. parkinson*:ab,ti
17. 15 OR 16
18. 8 AND 9 AND 17
19. 'randomized controlled trial'/de
20. 'clinical trial'/de
21. 'controlled clinical trial'/de

22. 'randomization'/de
23. 'single blind procedure'/de
24. 'double blind procedure'/de
25. 'crossover procedure'/de
26. 'placebo'/de
27. 'prospective study'/de
28. ((clinical OR controlled OR comparative OR placebo OR prospective* OR randomi*ed) NEAR/3 (trial OR stud*)):ti:ab
29. ((random*) NEAR/7 (allocate* OR allot* OR assign* OR basis* OR divid* OR order*)):ti:ab
30. ((singl* OR doubl* OR trebl* OR tripl*) NEAR/7 (blind* OR mask*)):ti:ab
31. (cross*over*):ti:ab OR (cross NEAR/1 over*):ti:ab
32. ((allocate* OR allot* OR assign* OR divid*) NEAR/3 (condition* OR experiment* OR intervention* OR treatment* OR therap* OR control* OR group*)):ti:ab
33. RCT:ti:ab
34. 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 Or 29 OR 30 OR 31 OR 32 OR 33
35. 'case study'/de OR 'abstract report'/de OR 'letter'/de
36. 34 NOT 35
37. 18 AND 36

Appendix 2. MEDLINE search strategy

1. "Salivation"[Mesh]
2. "Sialorrhea"[Mesh]
3. "Salivary Glands"[Mesh]
4. "Saliva"[Mesh]
5. drool*[tiab] OR hypersalivation[tiab] OR sialorrhea[tiab] OR sialorrhoea[tiab] OR oral secret*[tiab] OR saliva*[tiab] OR dribbl*[tiab] OR parotid[tiab] OR salivary[tiab] OR submandibular[tiab]
6. 1 OR 2 OR 3 OR 4 OR 5
7. "Botulinum Toxins"[Mesh]
8. "Clostridium botulinum"[Mesh]
9. Botox[tiab] OR botulin*[tiab] OR dysport*[tiab] OR abobotulin*[tiab] OR incobotulin*[tiab] OR onabotulin*[tiab] OR BoNT[tiab] OR xeomin[tiab] OR myobloc[tiab] OR neurobloc[tiab]
10. 7 OR 8 OR 9
11. "Parkinsonian Disorders"[Mesh]
12. Parkinson*[tiab]
13. 11 OR 12
14. 6 AND 10 AND 13
15. "Randomized Controlled Trial" [pt]
16. "Controlled Clinical Trial" [pt]
17. randomized[tiab] OR randomised[tiab]
18. placebo[tiab]
19. "Placebos"[Mesh]
20. drug therapy[sh]
21. randomly[tiab]
22. trial[tiab]
23. groups[tiab]
24. 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
25. 14 AND 24

Appendix 3. CINAHL search strategy

1. (MH "Sialorrhea")
2. (MH "Salivation")
3. (MH "Salivary Glands+")
4. (MH "Saliva")
5. TI (Saliva* N3 (excess* OR manage* OR volume OR reduction OR reduce)) OR AB (Saliva* N3 (excess* OR manage* OR volume OR reduction OR reduce))
6. TI (drool* OR dribbl* OR Hypersalivation OR sialorrhea OR sialorrhoea OR 'oral secretions' OR salivary OR parotid OR submandibular) OR AB (drool* OR dribbl* OR Hypersalivation OR sialorrhea OR sialorrhoea OR 'oral secretions' OR OR salivary OR parotid OR submandibular)
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. (MH "Botulinum Toxins")
9. (MH "Clostridium+")
10. TI ((Botox OR botulin* OR dysport* OR abobotulin* OR incobotulin* OR onabotulin* OR rimabotulin OR BoNT OR xeomin OR myobloc OR neurobloc)) OR AB ((Botox OR botulin* OR dysport* OR abobotulin* OR incobotulin* OR onabotulin* OR rimabotulin OR BoNT OR xeomin OR myobloc OR neurobloc))
11. 8 OR 9 OR 10
12. (MH "Parkinsonian Disorders+")
13. TI parkinson* OR AB parkinson*
14. 12 OR 13
15. 7 AND 11 AND 14
16. PT clinical trial
17. (MH "Clinical Trials+")
18. TI clinical trial* OR AB clinical trial*
19. TI (single blind* or double blind*) OR AB (single blind* or double blind*)
20. TI random* OR AB random*
21. 16 OR 17 OR 18 OR 19 OR 20
22. 15 AND 21

Appendix 4. CENTRAL search strategy

1. [mh "Salivation"]
2. [mh "Sialorrhea"]
3. [mh "Salivary Glands"]
4. [mh "Saliva"]
5. (drool* OR dribbl* OR Hypersalivation OR sialorrhea OR sialorrhoea OR 'oral secretions'):ti,ab,kw
6. (Saliva* near/3 (excess* OR manage* OR volume OR reduction OR reduce)):ti,ab,kw
7. (Salivary OR parotid OR submandibular):ti,ab,kw
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. [mh "Botulinum Toxins"]
10. [mh "Clostridium botulinum"]
11. (Botox OR botulin* OR dysport* OR abobotulin* OR incobotulin* OR onabotulin* OR rimabotulin OR BoNT OR xeomin OR myobloc OR neurobloc):ti,ab,kw
12. #9 OR #10 OR #11
13. [mh "Parkinsonian Disorders"]
14. parkinson*:ti,ab,kw
15. #13 OR #14
16. #8 AND #12 AND #15

Appendix 5. AMED search strategy

1. (DE “SIALORRHEA”)
2. (DE “SALIVA”)
3. (DE “SALIVARY GLAND DIS”)
4. TI (Saliva* N3 (excess* OR manage* OR volume OR reduction OR reduce)) OR AB (Saliva* N3 (excess* OR manage* OR volume OR reduction OR reduce))
5. TI (drool* OR dribbl* OR Hypersalivation OR sialorrhea OR sialorrhoea OR ‘oral secretions’ OR salivary OR parotid OR submandibular) OR AB (drool* OR dribbl* OR Hypersalivation OR sialorrhea OR sialorrhoea OR ‘oral secretions’ OR OR salivary OR parotid OR submandibular)
6. 1 OR 2 OR 3 OR 4 OR 5
7. (DE “BOTULINUM TOXINS”)
8. TI (Botox OR botulin* OR dysport* OR abobotulin* OR incobotulin* OR onabotulin* OR rimabotulin OR BoNT OR xeomin OR myobloc OR neurobloc) OR AB (Botox OR botulin* OR dysport* OR abobotulin* OR incobotulin* OR onabotulin* OR rimabotulin OR BoNT OR xeomin OR myobloc OR neurobloc)
9. 7 OR 8
10. (DE “PARKINSON DIS”)
11. TI parkinson* OR AB parkinson*
12. 10 OR 11
13. 6 AND 9 AND 12

CONTRIBUTIONS OF AUTHORS

F Hill drafted the protocol with support from M Walshe. N Miller and R Walsh reviewed the protocol. D Mockler developed the search strategy. R McDowell provided methods and statistical support.

DECLARATIONS OF INTEREST

F Hill: none known

N Miller: none known

RA Walsh: none known

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R McDowell: none known

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