Pharmacological interventions for sialorrhoea in people with Parkinson's Disease: a Systematic Review and Meta-analysis

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Abstract

Background/objectives: Sialorrhoea is a common non motor complication experienced by people with Parkinson's disease (PD). Despite its prevalence there is conflicting evidence on how to effectively treat it. Our aim was to establish the efficacy and safety outcomes of pharmacological interventions used to treat sialorrhoea in people with idiopathic PD.

Methods: We registered and conducted a systematic review and meta-analysis (PROSPERO: CRD42016042470). We searched 7 electronic databases from inception until July 2022. Quantitative synthesis was performed where data allowed using random effects models.

Results: From 1374 records we included 13 studies (n=405 participants). Studies were conducted in Europe, North America and China. There was marked heterogeneity in the interventions used, follow up times and outcome measures investigated. The main source of risk of bias identified was reporting bias. 5 studies were included in the quantitative synthesis. Summary estimates showed administration of botulinum toxin significantly reduced saliva production, improved patient reported functional outcomes and was associated with an increase in adverse events.

Conclusion: Sialorrhoea in PD is an important condition, but current data does not allow for strong recommendations on optimal pharmacological treatments. There is significant heterogeneity in outcomes measures used to evaluate the burden of sialorrhoea with lack of consensus on what constitutes clinically meaningful change. More research is required to better understand the underlying mechanism and potential treatments of sialorrhoea in idiopathic PD

Introduction

Sialorrhoea is defined as the inability to control oral secretions resulting in excessive saliva accumulating within the oropharynx (1). This may result in drooling, which refers to the unintentional flow of saliva outside the oral cavity. Drooling can be a problematic symptom in many neurological disorders such as Parkinson's disease (PD), cerebral palsy, amyotrophic lateral sclerosis and stroke (2).

Sialorrhoea in PD is thought to be multifactorial. Contributory factors include swallowing dysfunction, flexed head posture and hypomimia rather than overproduction of saliva (3). In fact, studies have demonstrated reduced rates of saliva production in people with PD (4). Sialorrhoea is a common non-motor complication of PD and prevalence is estimated to be as high as 80% in some studies (2). It can lead to social embarrassment and negatively impact upon quality of life (5) as well as result in life threatening consequences such as aspiration and subsequent pneumonia (6).

Treatments for sialorrhoea include non-pharmacological therapies such as speech therapy, leading to behavioural modifications to encourage swallowing saliva (7). However, such physical therapies may not suit all people living with PD and longer-term effects of therapies are debated (8). Surgical interventions can be used for severe or intractable cases but are invasive and carry a risk of serious complications (9). Pharmacological treatments that aim to

63 decrease saliva production are available but efficacy is debated and their use may be limited
64 due to adverse effects (10).

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66 Despite the burden of sialorrhoea in people with PD there are few licensed treatments. The
67 U.S Food and Drug Administration (FDA) has approved two Botulinum toxin formulations,
68 Incobotulinum Toxin A (Xeomin®) and Rimabotulinum Toxin B (Myobloc®), to treat adults with
69 chronic sialorrhea (7). Incobotulinum Toxin A is also approved by the European Medicines
70 Agency (EMA) and along with glycopyrrolate forms the two treatments recommended by
71 National Institute for Health and Care Excellence (NICE) in the UK (11).

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73 Our aim was to perform a systematic review of pharmacological interventions used to reduce
74 volume or burden of sialorrhoea in people with idiopathic Parkinson's disease, describing
75 efficacy and safety outcomes.

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Methods

Protocol and registration

This review was reported in accordance with the Preferred Reporting of Items in Systematic Reviews and Meta-Analyses (PRISMA) guidance (12). The protocol was registered on the PROSPERO database: (CRD42016042470; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42016042470).

Eligibility Criteria

Studies were eligible if they were trials and included participants with a diagnosis of idiopathic PD of any age and at any stage of their disease.

The intervention of interest was any pharmacological therapy aimed at reducing sialorrhoea.

Studies were excluded if participants did not have a diagnosis of idiopathic PD, for example, drug induced or Parkinson's plus syndromes. Trials in mixed populations that included participants with idiopathic PD as well as participants with other diagnoses such as stroke or cerebral palsy were also excluded

Non-English language studies and research involving non-pharmacological or surgical interventions were also excluded.

No restrictions were made on date of publication. To be eligible, papers had to be published in peer review journals. If abstracts were identified, we searched for subsequent full-text publications, and contacted the authors if full texts were not available

The outcomes of interest were any benefits and/or adverse effects of pharmacotherapy for sialorrhoea in people with idiopathic PD. Symptom burden of sialorrhoea was quantified through use of sialorrhoea rating scales. There are multiple measurement tools for sialorrhoea. These include clinical rating scales that are generic such as the drooling severity and frequency scale (DFSS), drooling rating scale (DRS), and scales that are designed for people living with PD such as the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) item number 6 and the Sialorrhoea Clinical Scale for Parkinson's Disease (SCS-PD) (2). All of these were considered eligible.

Search strategy

We searched multidisciplinary, electronic databases: MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCO), PyschINFO (EBSCO), LILACS (Bireme), CENTRAL (Cochrane) and clinicaltrials.gov from inception with last search July 2022. We hand searched references of relevant reviews and potentially eligible studies and searched abstracts from the International Movement Disorder Conference, Movement Disorder Society International Congress and World Parkinson's Congress from April 2013 to April 2019. We further performed hand searching of published journals from the Movement Disorder Journal (Movement Disorder Society) and Neurology (American Academy of Neurology) from 2013 to 2019. We did not search the grey literature.

The search syntax was developed with the help of a subject specialist librarian. The full strategy is included in Supplementary Text.

Study selection and data collection

All aspects of title searching, data extraction and quality assessment were performed by paired, trained reviewers, working independently. For the title searching we used Covidence systematic review software (13). A third author (TQ) resolved conflicts. Data extraction was performed using a predesigned data extraction form.

We extracted data on sample size, age, sex, country, study design, data collection period, setting, duration and/or severity of PD, intervention, change in symptom burden of sialorrhoea including significant or adverse effects.

Risk of bias within studies

We assessed risk of bias using the Cochrane Risk of Bias Tool (14) which considers 6 standard domains (selection, performance, detection, attrition, reporting and other bias). We graded studies as low/high or indeterminate risk based on overall assessment, rather than a pre-specified score. We presented data using a traffic light system at individual study and aggregate level (15). We did not exclude studies on the basis of bias but included the risk of bias in our evidence synthesis.

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143 **Data synthesis**

144 Studies were included in the quantitative synthesis if they reported relevant data as
145 differences between groups with comparative significance testing; or if these data could be
146 derived from the available results. There was a threshold of 3 studies for considering meta-
147 analysis. Studies involving Botulinum Toxin A or B were combined and analysed together
148 regardless of heterogeneity in doses used and glands injected. Studies which investigated
149 other interventions were not included in the meta-analysis due to the heterogeneity in
150 administration and therapeutics of the interventions.

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152 Quantitative analysis was performed using Comprehensive Meta-Analysis software (16). We
153 estimated summary effect size as mean difference or standardised mean difference where
154 appropriate. Anticipating clinical heterogeneity, we made an a-priori decision to assess
155 effects using random effects models. We quantitatively assessed heterogeneity using the I^2
156 test and complemented this with an assessment of clinical heterogeneity.

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158 The review data were evaluated using the Grading of Recommendations Assessment,
159 Development and Evaluation (GRADE) approach to describe the overall quality of the
160 evidence (17). This system rates evidence as being of high, moderate, low or very low quality
161 depending on parameters that can downgrade the quality of evidence such as risk of bias,
162 heterogeneity and imprecision.

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Results

Study selection

Database searches identified 1374 records after initial de-duplication. Following title and abstract screening 149 records underwent full text review and 13 articles were chosen to be included in the systematic review (18–30). See Figure 1 (PRISMA flow diagram).

Included study characteristics

The total review population included 405 participants from studies based in Europe, North America and China. The sample size varied from 7 to 96 participants (median sample size 26; interquartile range [IQR] 19). The study duration ranged from 4 weeks to 32 weeks (median study duration 6 weeks; IQR 8 weeks) although was not reported in 3 studies.

The mean age of participants in studies ranged from 67 years to 72 years. In all studies the majority of participants were male. The mean duration of Parkinson's disease for participants varied from 4 years to 13.4 years across 11 studies (not reported in two studies). The severity of Parkinson's disease for participants was reported in 10 out of 13 studies. 6 studies reported severity using the Hoehn and Yahr scale and 4 studies reported severity using the MDS-UPDRS, either total score or score in a relevant sub section (31,32).

6 studies investigated the use of Botulinum toxin (Botox A or B) in participants. 4 studies assessed anticholinergic medication. 1 study looked at a dopamine agonist, 1 assessed an alpha-adrenergic medication and 1 study researched a Traditional Chinese Medication formulation.

There was significant heterogeneity in the outcome measures used to assess the impact of these interventions on symptom burden of sialorrhoea. Objective measurements aimed at quantifying saliva volume were used in 8 studies. Eleven studies reported outcomes which relied on subjective change as reported by participants or caregivers and were quantified via various symptom scales.

Risk of Bias within Studies

The risk of bias assessment is summarised in Figure 2. No study was assessed as being at low risk of bias within all the domains. The main risk of bias was reporting bias due to lack of published study protocols. Two studies were open label trials with no randomisation or blinding and one study reported a computer drive malfunction resulting in the loss of participant data (25,27,30). Three studies involved selection bias with either unclear methods of sequence generation or substantial differences in baseline characteristics between groups (21,22,25).

Quantitative results

The 13 included studies involved a range of interventions and used different approaches to describe and assess the volume and burden of sialorrhoea. Baseline characteristics are displayed in Figure 3 and results are summarised in Supplementary Table S1 with additional results data available in Supplementary Table S2.

3 studies looked at administration of Botulinum toxin type A (22,24,30).

Lagalla e*t al.* recruited 32 participants and injected 50 units of Botulinum toxin type A (BoNTX) into each parotid gland using anatomical landmarks. At 1 month follow up they found a significant improvement in both objective and subjective measures of salivation after treatment with BoNTX compared to participants that received placebo. 1 participant from the intervention group complained of swallowing difficulties that resolved after 10 days. No other serious adverse events were reported.

Narayanaswami *et al.* used a purified Botulinum toxin type (Incobotulinum Toxin A (Xeomin®)) in 10 participants. They injected 20 units into each parotid gland and 30 units into each submandibular gland using anatomical landmarks. This was a crossover trial with a 3 month evaluation then a washout period before crossing over to the other intervention. Objective evaluation of saliva weight at 1 month post injection found no significant change after Incobotulinum Toxin A injection compared to placebo. Subjective outcomes also showed no significant differences between groups. In terms of adverse events 1 participant experienced

difficulty in chewing and another had viscous saliva after the Incobotulinum Toxin A injections, both of which resolved after 6 weeks.

Tiigimäe-Saar *et al.* used Botulinum toxin type A (BNT-A) and injected a total of 250 units in the submandibular and parotid glands of 12 participants with PD using ultrasound guidance. Of note these participants had tried non-pharmacological treatments to decrease salivation but had not found them to be effective. This group was compared with 13 participants with PD but no sialorrhoea and a third group of 13 age-matched and healthy controls. 1 month after BNT-A injection in the first group there was a significant reduction in the amount of 5-minute saliva collected. No adverse events were reported.

Three studies investigated Botulinum toxin type B (20,21,25).

Ondo *et al.* studied the use of Botulinum toxin B (BTX-B). 2,500 units were injected using anatomical landmarks into the parotid and submandibular glands of 8 participants in the intervention group and compared with 8 participants in the placebo group. At 1 month follow up the BTX-B group reported a significant improvement in subjective scores of sialorrhoea. Adverse events reported in the BTX-B group included dry mouth (3 participants), worsened gait (1 participant), diarrhoea (1 participant) and neck pain (1 participant).

Lagalla *et al.* (2009) investigated the use of BTX-B in 18 participants. 4000 units were injected into each parotid gland using anatomical landmarks and compared to placebo injections. At

1 month follow up the BTX-B group showed a significant improvement in objective and subjective measures of salivation compared to the placebo group. In terms of adverse events, 3 participants in the BTX-B group complained of mild, transient swallowing difficulties.

Chinnapongse *et al.* recruited 54 participants and divided them into 4 groups. 3 groups received Botulinum toxin B (BoNT-B) injected into parotid and submandibular glands using anatomical landmarks at varying doses (1,500, 2,500 or 3,500 units) and 1 group received a matched placebo injection. Groups were followed up for 3 months. Treatment with any dose of BoNT-B resulted in a significant decrease in salivary flow rate as well as improvements in subjective measures of salivation scored by the investigators and participants. Adverse events were reported by at least half of the participants in each group of mild or moderate intensity.

Four studies investigated the use of anti-cholinergic medications (18,23,26,29).

Arbouw *et al.* studied the efficacy of glycopyrrolate, an anti-cholinergic that does not cross the blood-brain barrier in considerable amounts (33). 23 participants took part in a crossover trial that compared 1mg of glycopyrrolate taken 3 times daily against placebo. A sialorrhoea scoring scale was used to assess efficacy and significant improvements were found in the group treated with glycopyrrolate. The most common adverse event was dry mouth reported by 52.2% of participants taking glycopyrrolate.

Mestre *et al.* investigated the longer terms effects of glycopyrrolate in 28 participants. The intervention group received oral glycopyrrolate capsules at an initial dose of 0.5mg 3 times daily, increased by 0.5mg 3 times daily every 4 days for2 weeks followed by a 10 week maintenance phase. At 3 months there were significant improvements in subjective measures of salivation in the intervention group. The most common adverse events were dry mouth (42.9%) and constipation (28.6%).

Thomsen *et al.* investigated the use of ipratropium bromide spray in 17 participants in a crossover trial. Participants were instructed to use 1 to 2 metered doses of ipratropium bromide spray sublingually up to a maximum of 4 times a day. There was no significant difference between groups in terms of salivation as assessed by objective and subjective measures. 1 participant reported a nosebleed that may have been related to the study drug. There were no other adverse events recorded.

Perez-Lloret *et al.* recruited 19 participants into a crossover trial to investigate the effects of intra-oral films of tropicamide. 0.3mg, 1mg, 3mg of tropicamide or placebo were administered to participants over 4 visits with a 7 day washout period. Measurements were taken up to 120 min after treatment administration. The difference in objective measurement of saliva volume and subjective scores of sialorrhoea between baseline and up to 120 minutes were not significant. No adverse events were detected.

The remaining three studies are summarised below (19,27,28).

Schirinzi *et al.* studied a dopamine agonist in the form of a rotigotine patch. They recruited 7 participants to an open label pilot trial of rotigotine patch that was titrated up to 4mg/24hours. This dose was maintained for 4 weeks before reassessment. They found an improvement in all clinical scores when comparing baseline and end of treatment results. No adverse events were reported.

Sun *et al.* evaluated Lian-Se Formula, a Traditional Chinese Medication herbal formulation in 96 participants over the course of 6 weeks. 48 participants received the intervention and 48 received placebo. After 6 weeks there was a significant decrease in the total daily quantity of saliva in the intervention group compared to placebo. No adverse events were reported.

Cheng *et al.* investigated the use of dihydroergotoxine mesylate, a selective alpha-adrenergic blocker. 20 participants participated in a randomised controlled crossover trial. A significant response was found in the intervention group with improvement in subjective scores of sialorrhoea. Adverse events were mild and transient such as dry mouth and orthostatic hypotension and did not significantly differ between groups.

Other evidence

Zheng *et al.* are conducting an ongoing prospective randomised controlled trial investigating combined treatment with entacapone and pramipexole and its effects on autonomic symptoms in PD (34). The trial is not yet completed but open label single arm pilot data from 100 participants has indicated no effects on salivation after 3 weeks of combined treatment.

A further 4 studies were identified as being potentially relevant but excluded at full text review stage due to being published as abstracts only with no corresponding full text paper yet. Velzen *et al.* investigated the use of glycopyrrolate but as an inhaled formulation in 10 participants with PD(35). They report an improvement in subjective sialorrhoea scores however the drop out rate due to side effects was 30%. Ekmekci *et al.* studied the use of levodopa-carbidopa intestinal gel in 22 participants with PD and found treatment resulted in an improvement in non-motor symptoms including sialorrhoea(36). Pan et *al.* looked at Lian-Se Formula and noted beneficial effects on sialorrhoea in participants treated with the herbal formulation(37). Bergmans *et al.* evaluated the efficacy and safety of Incobotulinum Toxin A injections in 16 PD patients. 69% of the participants had already received botulinum toxin injections previously for sialorrhoea. They concluded there was an improvement in subjective scores of drooling. REF

335 M**eta-analyses**

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337 Data was analysed from 5 studies involving Botulinum toxin type A or B to calculate summary
338 estimates for 3 outcomes: saliva production, adverse events and functional outcomes. Results
339 are displayed in Figure 4. There was a 6th study involving Botulinum toxin type A but the data
340 from this study was not included as there was no comparative group that received a placebo.
341 [ref 30].

342

343 Saliva production was significantly reduced by the administration of botulinum toxin (-1.35
344 95% CI: -2.64 to -0.06) [Figure 4-Panel A]. Botulinum toxin treatment improved participant
345 reported functional outcomes (-1.23 95% CI -1.75 to -0.70) [Figure 4-Panel B]. Treatment with
346 botulinum toxin was also associated with increased adverse events (Pooled odds ratio [OR]
347 4.97, 95% CI: 0.94 to 26.28) [Figure 4-Panel C]. Certainty of the evidence was assessed as per
348 GRADE and found to be very low or low for each outcome (Table 1).

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Discussion

This review included 13 studies, representing 405 participants with idiopathic PD from 6 countries. Despite the focussed review question, there was marked heterogeneity in the interventions used, follow up times and outcome measures investigated.

The most commonly assessed therapy was botulinum toxin. There was a positive association between administration of Botulinum toxin and most outcomes of efficacy including, improvement in objective measures of salivation as well as an improvement in perceived severity of drooling, impact on daily activities and participant satisfaction. Two of the studies had a prolonged follow up highlighting that the beneficial effects of treatment could last for a few months after injection (20,24). These findings are consistent with the results of other systematic reviews that have investigated the use of botulinum toxin in managing sialorrhoea across a range of neurological conditions including ALS and cerebral palsy. They have generally found botulinum toxin treatment to be safe, well tolerated and efficacious compared to placebo (38–40). The benefits of toxin need to be weighed against the potential for harm, with participants receiving this treatment five times more likely to have adverse events. We did not consider factors such as cost or the practicalities of having a skilled practitioner to administer the injections. We note the lack of consensus as to the approach to administration. 1 study used ultrasound guidance with the remainder relying on

anatomical landmarks to guide administration of injections. 4 studies injected both the parotid and submandibular glands whereas 2 studies focused on the parotid glands only.

An alternative licensed treatment in certain countries is glycopyrronium bromide. Two studies assessed this anti-cholinergic agent and reported significant improvements in patient-rated outcomes in favour of the intervention. Again, use is limited by adverse effects. Unlike botulinum toxin, adverse effects can be systemic including exacerbating cognitive dysfunction, psychosis and other non-motor complications.

Non-pharmacological management of sialorrhoea involving referral to a speech and language therapist is still first line management (11). Attention-to-effort therapies work by encouraging participants to pay attention to their outputs such as swallowing. Most studies have focussed on swallowing output in the context of reducing aspiration risk rather than sialorrhoea (41). One systematic review assessed non-invasive management of sialorrhoea across a range of aetiologies including PD and concluded that studies consistently showed positive results relating to a decrease in sialorrhoea but with insufficient long term effects (42). The likelihood of adverse events is low but there is little to suggest long lasting improvements can be made with these strategies. In the included studies it was often not clear what, if any, non-pharmacological treatments were used. This limits interpretation of the data and is a reminder of the need for detailed descriptions of usual care in PD intervention trials.

Quality of evidence

The main source of risk of bias identified was reporting bias. Lack of published study protocols meant reporting bias could not be adequately assessed. Registering study protocols is accepted as best practice for randomised controlled trials to ensure all findings are reported. Increased governance in this area should remove this bias in future. Results of the quantitative analysis were affected by reporting bias and imprecision. This resulted in the quality of the evidence being downgraded to low to very-low quality.

Strengths and limitations of the review

We offer a comprehensive review of the international literature following best practice in conduct and reporting. The data allowed for quantitative synthesis and results were framed using the GRADE method. We were limited by the modest number of eligible studies and the small sample size in each.

There was substantial heterogeneity, particularly in the outcomes used to assess efficacy. Most studies attempted to evaluate the burden of sialorrhoea using both objective and subjective measures. Objective measures such as estimating salivary outflow result in quantifiable and comparative data. However, these can be practically difficult to measure and may suffer from inter-observer variability (25). Of the subjective measures, some attempt to quantify the severity and frequency of drooling and others try to describe the functional impact of sialorrhoea, while other describe quality of life. For many of the scales used there is a lack of validation in a PD population, and limited understanding of the minimal clinically important difference.

Conclusions

Implications for practice

The current data do not allow us to make strong recommendations on the optimal pharmacological treatment for sialorrhoea. There is a lack of consensus in the literature regarding Botulinum toxin and its doses, dosing intervals, the salivary glands that should be targeted, whether anatomical landmarks or ultrasound guidance is used and the dosage proportion that should be delivered to each salivary gland. There are practical considerations such as the procurement, cold storage and preparation of the Botulinum toxin injection. Anti-cholinergic medications such as glycopyrrolate offer a non-invasive alternative. Decisions on treatment need to balance potential efficacy with risk of adverse events.

Implications for Research

The included papers highlighted areas where reporting and conduct of future trials could be improved. For example, making protocols available and standardisation of outcomes. Use of a core outcomes set would allow data to be compared and pooled between studies but more importantly would ensure the outcomes measured and reported are the ones that are most relevant to individuals who experience sialorrhoea. Although no intervention was well studied, with so few studies, the use of topical preparations of anti-cholinergic or PD

medications is a key area for future research. Botulinum toxin has been shown to be efficacious but further research to address the practical concerns highlighted above is needed. The economic implications of these treatments, especially if repeat or prolonged appointments are required, also needs to be addressed.

Key points

- Sialorrhoea in PD is a poorly studied area.
- Most studies involve small numbers of participants with limited follow up.
- There is significant heterogeneity in outcomes measures used to evaluate the burden of sialorrhoea with lack of consensus on what constitutes clinically meaningful change.
- More research is required to better understand the underlying mechanism and potential treatments of sialorrhoea in idiopathic PD.

Supplementary data

Supplementary data are available in attached appendices.

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Author roles

1. Research project: A. Conception, B. Organisation, C. Execution
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critical Analysis
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Feedback

FN: 1C, 2A, 2C, 3A

JR: 1A, 1B, 1C, 3B

MB: 1A, 1B, 1C, 3B

AR: 1B, 1C, 3B

CS: 1B, 1C, 3B

MRT: 2A, 2B, 2C

EN: 2A, 2C, 3B

TQ: 1B, 1C, 2C, 3B

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Ethical compliance statement

Institutional review board approval and informed patient consent was not necessary for this work. We confirm we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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626 **Legends for Figures and Supplemental Files**

627 Figure 1. Preferred Reporting of items in Systematic Reviews and Meta-Analyses flow
628 diagram. A total of 13 studies were included in the systematic review and 5 studies in the
629 meta-analysis.

630 Figure 2. Summary of risk of bias of the included studies. Red circle with 'cross' symbol
631 indicates high risk of bias, yellow circle with 'minus' symbol indicates unclear risk of bias and
632 green circle with 'plus' symbol indicates low risk of bias in that specific domain.

633 Figure 3. Summary of outcomes from each study. Green = Significant difference between
634 intervention and comparative group, Red = No significant difference, Grey = not assessed.

635 Figure 4. Meta-analysis of outcomes of interest after Botulinum toxin administration in
636 adults with sialorrhoea and Parkinson's Disease. St diff in means, standard difference in
637 means; CI; confidence interval. Panel A: Saliva production; Panel B: Functional Outcomes;
638 Panel C: Adverse events

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640 Supplementary Table S1. Baseline study characteristics

641 Supplementary Table S2: Summary of results, additional data

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646 **Tables**

647 **Table 1 GRADE Assessment**

Outcome	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Saliva production: studies measured the weight of saliva produced over a defined time period. Lower scores indicate a decrease in saliva production	95 (3 studies)	⨁◯◯◯	Downgraded due to the risks of imprecision, indirectness and reporting bias
Adverse events: studies recorded the incidence of adverse events as reported by participants	157 (5 studies)	⨁◯◯◯	Downgraded due to the risks of imprecision (95% CI contains an effect size of no difference)
Functional outcome: studies measured functional outcomes using different scales. Lower scores indicate an	157 (5 studies)	⨁⨁◯◯	Downgraded due to the risks of reporting bias

improvement in severity or frequency of sialorrhoea			

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect