Botulinum toxins for sleep bruxism (Protocol)

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Botulinum toxins for sleep bruxism

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ABSTRACT

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

To determine the effectiveness and safety of botulinum toxins as an intervention to reduce the negative consequences of sleep bruxism in adults.
BACKGROUND

Definition of sleep bruxism

Sleep bruxism is a condition characterised by teeth grinding or clenching during sleep, that may wear down the teeth, may cause jaw pain, headaches and masticatory muscle growth (particularly the masseter), and may disrupt the sleep process of the person with the condition and their sleeping partner. In 2014, according to the third edition of the ICSD (The International Classification of Sleep Disorders; ICSD-3) (Svensson 2017), sleep bruxism was considered a sleep movement disorder; however, in 2018, an international consensus defined sleep bruxism as “a masticatory muscle activity during sleep that is characterised as rhythmic (phasic) or non-rhythmic (tonic) and is not a movement disorder or a sleep disorder in otherwise healthy individuals” (Lobbezoo 2018). Dentists should perform a comprehensive assessment of patients referred with this condition, since sleep bruxism can be clinically classified as harmless, or as protective (when positive health outcomes, such as airway permeability in patients suffering from obstructive sleep apnoea, are involved), or as a risk factor for oral health problems (when associated with craniofacial problems such as excessive tooth wear, tooth fractures, myofascial pain, and masticatory hypertrophy (muscles larger or more developed than usual)) (Frohmam 1931; Lobbezoo 2018; Lobbezoo 2020; Svensson 2017).

Diagnosis

Due to factors such as complexity of the condition, variability amongst individuals, difficulty of monitoring, and lack of consensus, it has been challenging to define biomarkers for the assessment of sleep bruxism. Polysomnography is a type of sleep study that is used to diagnose, or rule out, many types of sleep disorders. Polysomnography uses electromyography (EMG) to evaluate and record the electrical activity produced by skeletal muscles, such as those used in chewing. PSG studies have shown objective evidence of rhythmic masticatory muscle activity (RMMAs) recordings during sleep bruxism events, which were preceded by systemic responses such as transitory hypertension (high blood pressure), hyperpnoea (abnormally fast or deep breathing), and tachycardia (heart beating faster than normal at rest) (Imai 2021; Lavigne 2008). RMMAs is characterised by an EMG amplitude of the masseter and the temporalis muscles (muscles involved in chewing) that is at least 10% of the maximum voluntary clenching capacity of the patient, and can be classified as phasic (with three or more RMMAs recordings that last between 0.25 and up to 2 seconds), tonic (one sustained RMMAs recording over 2 seconds), or mixed (phasic and tonic) (Carra 2012; Lobbezoo 2017). When assessed under sleep-laboratory conditions, and combined with audio and video, RMMAs recordings that are separated by less than two seconds are considered to correspond to a single bruxism event, which can be used as a biomarker when the frequency is quantified per hour of sleep (bruxism index) (Carra 2012; Casset 2017; Lobbezoo 2017). Also, RMMAs recordings can be quantified per hour of sleep (RMMAs index), and total time spent under bruxism status can be quantified as a proportion of total sleep time (bruxism time index) (Carra 2012; Casset 2017; Lobbezoo 2017).

PSG is considered the gold standard for the assessment of sleep bruxism. However, since PSG is not always available for clinical purposes, sleep bruxism can also be assessed using self-report (i.e. patients or relatives indicating signs of sleep bruxism such as tooth clenching noises during sleep), clinical evaluation (i.e. signs of tooth wear, masticatory muscles pain/stiffness/hypertrophy, tooth fractures, etc.), or a combination (Lobbezoo 2013; Lobbezoo 2017; Lobbezoo 2018). In addition, instrumental assessment of sleep bruxism can be achieved using portable EMG devices, albeit with the limitation that it is not performed in laboratory conditions and lacks audio or video input (Lobbezoo 2013; Lobbezoo 2017; Lobbezoo 2018).

Based on the assessment approach, sleep bruxism can be graded as ‘possible’ (when using only self-report), ‘probable’ (clinical findings with or without self-report) or ‘definite’ (when instrumental assessment is used, with or without self-report or clinical positive findings, or both) (Lobbezoo 2018). This systematic review will focus on definite diagnoses of sleep bruxism.

Aetiology

The aetiology of sleep bruxism is not completely understood (Castroflorio 2017; Goldstein 2021), which complicates effective management (Manfredini 2015). In the adult population, the prevalence of sleep bruxism ranges between 8% and 31% when self-report and clinical assessment are considered (Manfredini 2013), and it is 7.4% when assisted by PSG (Svensson 2017). Some studies suggest that sleep quality and quality of life are both impaired in adults with sleep bruxism (Camara-Souza 2019; Neu 2018). Although sleep bruxism has been associated with myofascial pain and masticatory hypertrophy (enlargement), the evidence is contradictory because some clinical studies have not seen these symptoms in sleep bruxism-affected populations (Almzinozini 2017; Goller 2018; Muzalev 2017; Palinkas 2016). Moreover, sleep bruxism may not be related to general bruxism, as shown by a recent clinical study that reported teeth grinding in adult women affected by this condition, with no relation with other behaviours such as clenching the teeth when awake (Chattratrai 2023). Furthermore, sleep bruxism is considered to be a risk factor for dental-related problems such as tooth wear (Wetselaar 2019), dental implant failure (Chrcanovic 2016), and poor oral health-related quality of life (Camara-Souza 2019; Tay 2020).

Usual treatment

Several strategies such as biofeedback therapy (Jokubauskas 2018), physical therapy (Amorim 2018), occlusal splints (Jokubauskas 2018; Manfredini 2015), cognitive behavioural therapy (Manfredini 2015), and pharmacotherapy (Macedo 2007) have been used to manage clinical problems associated with sleep bruxism. However, how to select the optimal intervention to target a specific set of symptoms has not been clarified (Goldstein 2021).

Description of the intervention

In mammals, including humans, a subset of specialised skeletal muscles (i.e. the masticatory muscles, including the masseter and the temporalis) are responsible for vital functions such as speaking, self-defence, social interaction, and mastication. The coordinated contraction of these muscles allows the mandible (jaw) to perform movements necessary for activities such as chewing and speaking; this is controlled by the cortex of the brain, which has specific areas for motor functions (Nordstrom 2007). During chewing (mastication), projections of motor neurones control the movements of the mandible. These projections run within the brain from the cortex to both the trigeminal motor nuclei and the brainstem, and control chewing via a neural network known as a
central pattern generator. This control is based on feedback from sensory points in the mouth (e.g. periodontal ligament, tongue) and the lips (Mercer 2019; Nordstrom 2007). In order to induce a muscle contraction, motor neurones release acetylcholine into the neuromuscular junction, a specialised synapse that translates electrical signals from motor neurones to contractile function in the skeletal muscles (Mukund 2020). When the acetylcholine reaches the receptors in the postsynaptic membrane in the muscle, it generates the release of calcium deposits that trigger the processes of excitation-contraction of muscle fibres (Arias-Calderon 2016; Mukund 2020), converting initial electrical signalling (nerve impulse), to chemical signalling (neurotransmitter release) and, finally, to mechanical response (muscle contraction).

Botulinum toxin is naturally produced by the anaerobic bacterium Clostridium botulinum. When injected into muscles, it blocks the release of acetylcholine at the neuromuscular junction, leading to transient paralysis and atrophy of skeletal muscle (Montecucco 2005; Pirazzini 2017; Rossetto 2014). Botulinum toxins can be classified by type (A to G) and subtype (e.g. A1). The molecules for all types have a heavy chain of 100 kDa (kilodalton - a unit of measurement used in biochemistry and molecular biology to describe the molecular weight of proteins and other macromolecules) with metalloprotease activity, and a light chain of 50 kDa that serves as a specific ligand (binding point) for the presynaptic membrane of the motor neurone (Pirazzini 2017; Rossetto 2014). When injected intramuscularly, botulinum toxin bonds to specific receptors in the presynaptic membrane and is absorbed by the motor neurone (Rossetto 2014). Once inside the motor neurone, botulinum toxin cleaves specific proteins responsible for the release of acetylcholine, and so blocks the required input for muscle contraction (Rossetto 2014).

Clinical use of botulinum toxin started in the 1980s when it was used as a treatment for blepharospasm (involuntary tight closing of the eyelids) (Cartee 2011). Follow-up of those treated for blepharospasm showed a reduction in wrinkles on the side injected, which led to subsequent cosmetic use (Cartee 2011). Soon, the use of botulinum toxin for cosmetic purposes was found to relieve headaches, which suggested it might be used in pain management (Cartee 2011). Botulinum toxin is currently approved for conditions such as strabismus, blepharospasm, cervical dystonia, hemifacial spasm, overactive bladder, focal spasticity, sialorrhea, and chronic migraine (Cartee 2011; Montecucco 2005; Pirazzini 2017).

The first report of botulinum toxin intervention in a patient suffering from bruxism, which developed as she emerged from a coma after a car accident, was published in 1990 (Van 1990). Currently, intramuscular injection of botulinum toxin into the masticatory muscles (masseter only or masseter and temporalis, bilaterally) is an off-label strategy for reducing negative impact of their increased activity during bruxism events (Manfredini 2015). Botulinum toxin damages the internal machinery of the motor neurone responsible for the release of acetylcholine in the presynaptic membrane (Pirazzini 2017; Rossetto 2014). The light chain (the portion with less molecular weight) of botulinum toxin exhibits a zinc-dependent protease function that rapidly cleaves its protein target; in the case of the most commonly used botulinum toxin in sleep bruxism (type A), its target is a protein named SNAP25, which is part of the SNARE complex (a complex of three proteins needed for the neurotransmitter release process) (Pirazzini 2017; Rossetto 2014). The botulinum toxin intervention is expected to reduce muscle function and volume, as blocking the release of acetylcholine leads to transient paralysis and atrophy (wasting or reduction) of masticatory muscle (Miller 2016).

Moreover, botulinum toxin type A blocks the release of molecules such as substance P in nociceptive neurones, showing potential benefit for myofascial pain symptoms (Matak 2017; Matak 2019; Pihut 2016). A recent systematic review has reported the experimental use of botulinum toxin type A for conditions involving neuropathic orofacial pain (Dawson 2020). There are potential mechanisms that may explain how botulinum toxin type A impacts nociceptive neurones, in addition to the disruption of the SNARE complex, such as the interruption of the activity of the microtubule-dependent neuronal axonal transportation system, positive feedback and interaction with endogenous opioids, and...
selective binding to specific receptors expressed in certain neurone populations (Matak 2019).

A recent synthesis of the evidence reported that the effectiveness of botulinum toxin for reducing negative outcomes in people with sleep bruxism remains uncertain (Agren 2020; Balanta-Melo 2022; Cheng 2022; De La Torre 2017; Fernandez-Nunez 2019; Sendra 2021). Moreover, the clinical significance of adverse effects in the short term and the long term is not fully understood.

Why it is important to do this review

The best approach for reducing the negative effects of sleep bruxism is still under debate (Goldstein 2021; Manfredini 2015; Winocur 2017). Some strategies, such as occlusal splint therapy, may have beneficial effects in terms of preventing damage to teeth in patients with sleep bruxism, but the evidence is uncertain (Macedo 2007). A systematic review of biofeedback therapy found high heterogeneity between different techniques, with questionable effectiveness in reducing the negative clinical effects of sleep bruxism (Jokubauskas 2018). Given the feasibility of injecting botulinum toxin into the masticatory muscles as an outpatient procedure, interest in this intervention in the dental context has increased in recent years (Miller 2016). Botulinum toxin intervention has also been associated with pain-relief properties in patients with sleep bruxism (Baad-Hansen 2019; Bussadori 2020; De La Torre 2017; Goldstein 2021). Since sleep bruxism might negatively impact relevant outcomes such as sleep quality (Camara-Souza 2019; Smardz 2022), dental implant survival (Chrcanovic 2016), oral health-related quality of life (Camara-Souza 2019; Duarte 2020; Taj 2020), stress-related symptoms (Chattrattrai 2022; Polmann 2021), tooth wear (Wetselaar 2019), and quality of sleep for sleep partners (Palinkas 2019), understanding the effectiveness of botulinum toxin for reducing such negative impact is crucial in modern dentistry.

OBJECTIVES

To determine the effectiveness and safety of botulinum toxins as an intervention to reduce the negative consequences of sleep bruxism in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled clinical trials and cross-over randomised controlled trials. To be included, a study must contain at least one of the comparisons of interest for this review: intervention versus placebo; intervention versus no intervention; intervention versus another concentration of the same intervention.

Based on the mechanism of action of the botulinum toxin, we have selected a minimum study length of one month for inclusion.

Types of participants

Adults aged 18 years or older with sleep bruxism who have been assessed using polysomnography (PSG) by laboratory-based evaluation or portable devices. The PSG evaluation may either stand alone or be combined with questionnaires or clinical examination, or both. Although a first-night effect on PSG sleep bruxism evaluation in adults has been reported (Haraki 2020), one-night PSG assessment is valid to discriminate between sleep bruxism patients and a control population (Chattrattrai 2023a; Haraki 2020). We will not use any demographic or ethnicity restrictions. We will exclude studies that involve only a subset of relevant participants, unless the study reports separate data for the eligible participants.

Types of interventions

Intervention

- Intramuscular injection of botulinum toxin of any type in the masseter or temporalis muscles, or both, either unilaterally or bilaterally

Comparison

- No treatment
- Injection of the same volume of placebo (usually saline solution)
- Injection of a different concentration of the same active treatment

We will consider all types of botulinum toxins. Given that doses of different brands of botulinum toxin are not equivalent, we cannot define a single set of doses for all the interventions we might find. In terms of frequency, the indication for intramuscular injection of botulinum toxin, based on its mechanism of action, ranges from three to six months (for multiple interventions), so we will consider outcomes at one month, three months, and six months.

If a subsequent injection is performed, we will consider the same time points.

Types of outcome measures

We will not exclude studies based on the outcomes they measure.

Primary outcomes

- Bruxism events (bruxism index, rhythmic masticatory muscle activity (RMMA) index, bruxism time index (Carra 2015; Lobbezoo 2018; Svensson 2017)), determined by instrumental evaluation (laboratory-based or portable devices for polysomnography/EMG including the masseter and the temporalis muscles)

The quantification of bruxism events is our primary outcome because it is an objective method to determine sleep bruxism, which has been used recently in randomised controlled trials.

- Pain (either muscular or articular (joint)) assessed by visual analogue scale (VAS)

Although the relationship between muscle or articular pain and sleep bruxism is still debated (Muzalev 2017), this outcome is relevant for participants and has been reported consistently (Balanta-Melo 2022). A minimum clinically important difference (MCID) of 1.2 units on a 1 to 10 VAS has been defined in previous reports (Balanta-Melo 2022; Calixtre 2020).

Secondary outcomes

- Sleep Quality, Quality of Life and Oral Health-Related Quality of Life assessed by validated questionnaires (e.g. Pittsburg Sleep Quality Index (Buysse 1989), Epworth Sleepiness Scale (Johns 1991))
• Adverse effects, such as:
  o aesthetic impairment (e.g. smile deviation);
  o low masticatory force;
  o permanent loss of innervation/sensitivity;
  o difficulty in swallowing, dysarthria (difficulty in speaking);
  o reduction in removable prosthesis intraoral retention;
  o mandibular bone loss assessed by cone-beam computerised tomography (CBCT) or computerised tomography (CT).

We will evaluate adverse effects based on the measures that are reported; for aesthetic and functional impairments (e.g. swallowing, speaking, removable prosthesis retention), we expect subjective evaluations; for low masticatory force, we expect to retrieve quantitative measurements with bite force devices; for mandibular bone loss, we expect differences between baseline and time points on cortical bone thickness evaluated with diagnostic imaging such as CBCT and CT.

If studies report different measurements, the review authors will reach a consensus about the analysis strategy to be used.

We will also analyse cost-effectiveness data reported in any of the included studies, but we do not intend to provide a comprehensive assessment of the economic burden of the condition.

Search methods for identification of studies

We will design a search strategy for each database to identify relevant studies for this review. We will base corresponding search strategies on the design for MEDLINE (see Appendix 1), with revisions for differences in vocabulary and syntax guidelines. This search strategy will use the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision), as described in the Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (Lefebvre 2023). We will not restrict searches by language or time of publication.

Electronic searches

We will search the following databases.
- MEDLINE via Ovid (see Appendix 1)
- PubMed
- EMBASE via Ovid
- The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library)
- Cochrane Oral Health’s Trials Register
- Web of Science

Searching other resources

We will conduct an additional search for relevant studies in topic-related reviews and reference lists of retrieved papers. In addition, we will conduct electronic searches using the following sources.

- Google Scholar for grey literature
- Online abstracts from sleep-related congresses, unpublished studies, thesis dissertations, preprint services, and non-indexed journals

Moreover, we will perform an online search for abstracts and unpublished studies in the indexes of the annual meetings held by the following organisations.

- International Association for Dental Research (IADR, 1991 to present)
- International Association for the Study of Pain (IASP, 1974 to present)

We will search the Epistemonikos database for additional primary studies and systematic reviews (Rada 2020).

Finally, for unpublished results and ongoing studies, we will search the following trial registries.

- WHO International Clinical Trials Registry Platform
- ClinicalTrials.gov

When needed, we will contact experts in the field for information about any ongoing or unpublished trials.

Data collection and analysis

Selection of studies

To identify eligible studies, two review authors will screen the titles and abstracts of papers retrieved after running the search strategy, and will then evaluate full-text articles of potentially eligible studies to determine if these meet the review inclusion criteria. A third review author will resolve disagreement regarding eligibility by coordinating a group discussion to obtain a final decision. We will list studies that we do not classify as eligible studies as ‘excluded’, and provide the main reasons for exclusion in a ‘Characteristics of excluded articles’ table.

Data extraction and management

We will develop a standardised data extraction form using Microsoft Excel for Mac (version 16.45) to extract and tabulate the data regarding the characteristics of the studies, such as the type of interventions and comparisons, participants, co-interventions, and randomisation procedures. We will record the definitions used, as well as information about the risk of bias in the studies. Two independent review authors will perform this data extraction in duplicate, and a third review author will resolve any disagreement. We will consider and record any other information relevant to the aims of this review. We will use a data extraction form that has been initially piloted on at least three studies. If required, we will use specialised translation services for studies not written in English.

Assessment of risk of bias in included studies

To evaluate the following sources of bias in the studies included in the review, we will use the Cochrane tool for assessing the risk of bias in randomised trials (RoB1) (Higgins 2011).

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
-Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other potential sources of bias
Two review authors will evaluate each domain, independently and in duplicate, and classify it as low, unclear, or high risk of bias. A third review author will resolve any disagreement. We will present a graphic to show the proportion of studies for each classification. In addition, we will include a description of the risk of bias for each study in the 'Characteristics of the included studies' table. We will contact the corresponding authors or co-authors of the included studies by email if we require more details about their studies. We will assess the overall risk of bias in each study as low (if all domains are low risk), high (if one or more domains is high risk), or unclear (if no domains are high risk but one or more is unclear).

**Measures of treatment effect**

To evaluate each study's outcomes, we will use the mean difference (MD) and its 95% confidence interval (CI) to estimate the treatment effect when continuous outcomes are reported using the same scale. If different scales are used for the same outcome, we will calculate the standardised mean difference. For dichotomous outcomes such as adverse events, we will use the risk ratio (RR) with a 95% CI to estimate the treatment effect. We will summarise time-to-event data (survival data) using hazard ratios (HR). For events that may recur, we will use the rate ratio, as described in section 6.7.1 of the Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023) (Higgins 2023).

**Unit of analysis issues**

We anticipate that we will manage trials that compare multiple interventions as trials with two arms (e.g. intervention versus placebo, intervention dose A versus intervention dose B). Due to the degenerative effects of a single intramuscular botulinum toxin injection (intervention) on the human masseter muscle structure in the long-term (up to 12 months) (Ma 2018), we plan to include only data from the first intervention periods of cross-over trials, which we will treat as randomised trials with two arms. If studies with more than two arms are considered relevant, we will distribute the participants from the control group amongst the other groups (interventions) in any meta-analysis, to avoid double counting participants.

For outcomes reported at several time points, we will assess those reported at one month, three months, and six months, for each study.

For all studies, we will consider the participant as the unit of analysis. For events that may recur, we will use the rate ratio as described above.

We do not expect to find comparisons of unilateral versus bilateral injections, as the intervention is done bilaterally when intended for sleep bruxism management. However, we do expect reports of the intervention in the masseter only or in both the masseter and temporalis; we will consider these as different interventions for subgroup analysis (see below).

**Dealing with missing data**

If relevant studies have missing data, we will contact the corresponding authors when contact information is available. We will use the intention-to-treat approach if the data are reported accordingly. If missing data cannot be obtained after contacting study authors, we will impute replacement values and treat these as if they had been observed. We will carry out sensitivity analysis to assess how sensitive results are to the assumptions that we have made. We will address the potential impact of missing data on the findings of the review in our 'Discussion' section.

**Assessment of heterogeneity**

We will assess statistical heterogeneity using the Chi² test, with a significance level of 0.1. We will estimate the variability between studies using the I² test, as described in section 10.10 (Chapter 10) of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2023).

**Assessment of reporting biases**

We will assess publication bias according to recommendations described in section 13.3.5 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2023).

**Data synthesis**

If heterogeneity between studies is not relevant and the I² is less or equal to 40%, we will use the fixed-effect model for meta-analysis. If heterogeneity is detectable and I² is greater than 40%, we will use the random-effects model using a restricted maximum likelihood variance estimator with improved performance (Langan 2019). We will consider the availability of data and heterogeneity between studies when deciding whether to perform meta-analysis. We will use RevMan Web 2.2.1 software for meta-analysis (ReviewMan Web 2024). We will generate forest plots to illustrate the effects. If meta-analysis is not carried out, we will tabulate data and display the results in figures when possible.

**Subgroup analysis and investigation of heterogeneity**

We will consider conducting subgroup analyses or meta-regression for the primary outcomes, if the retrieved data allow it, based on the following factors.

- Treatment approach: the intervention might involve either the masseter muscle alone or a combination of the masseter and temporalis muscles; in either case, the intervention is done bilaterally.
- Dose of intervention: the intervention can be performed using different doses. Since there is no official dose equivalence in different brands of botulinum toxin, we will consider this parameter for subgroup analysis.
- Botulinum toxin type: although botulinum toxin type A is the type used most often for intervention in sleep bruxism, if we find any other type used for the same purpose, we will consider a subgroup analysis based on this parameter.

**Sensitivity analysis**

We will consider conducting sensitivity analyses for our primary outcomes where indicated. The risk of selection bias is one of the most important characteristics of the studies that will be considered relevant for this review. Therefore, we will conduct sensitivity analysis by removing studies classified as high risk of bias for random sequence generation and allocation concealment. We plan to also conduct sensitivity analysis to assess the impact of imputing missing data.
Summary of findings and assessment of the certainty of the evidence

To assess our certainty in the retrieved evidence, we will use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach and the summary of findings table format (Carrasco-Labra 2016; Schünemann 2022). According to the GRADE method, a randomised clinical trial is ranked as high-quality evidence, assuming there are no limitations in terms of the study design, inconsistent or imprecise results, indirectness of evidence, or publication bias (Schünemann 2022). The certainty of the evidence can be downgraded by one level (to ‘moderate’), two levels (to ‘low’), or three levels (to ‘very low’), depending on the presence of these factors. Two review authors will evaluate our certainty in the evidence independently and in duplicate.

We will create summary of findings (SoF) tables to summarise the results and our level of certainty about the body of evidence (Schünemann 2022).

Our SoF tables will present two comparisons:

• botulinum toxin intramuscular injection (in the masseter or temporalis muscles or both) versus placebo; and
• botulinum toxin intramuscular injection (in the masseter or temporalis muscles or both) versus no intervention.

We will present results for our prespecified outcomes at two time points: one month and three months.

ACKNOWLEDGEMENTS

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Cochrane Movement Disorders Group supported the authors in the development of this Cochrane protocol, and the following people conducted the editorial process.

• Sign-off Editor (final editorial decision): Dr Robert Boyle, Imperial College London, UK
• Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the protocol): Dr Marwah Anas El-Wegoud, Cochrane Central Editorial Service
• Editorial Assistant (conducted editorial policy checks and supported editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service
• Copy Editor (copy edited and proofread the protocol): Laura MacDonald, Cochrane Central Production Service
• Peer-reviewers (provided comments and recommended an editorial decision): Alberto Herrero Babiloni, DDS, MS, McGill University (clinical review); Dr Magdalini Thymi, Academic Centre for Dentistry Amsterdam (clinical review); Reny de Leeuw, DDS, PhD, MPH, Professor Emeritus Orofacial Pain Program, College of Dentistry Oral Health Science, University of Kentucky, Lexington Kentucky (clinical review); Jennifer Hilgart, Cochrane (methods review); Jo Abbott, Information Specialist (search review). Two additional peer reviewers provided clinical peer-review and consumer peer-review but chose not to be publicly acknowledged.
Additional references

Agren 2020

Ahn 2007

Almezzini 2017

Amorim 2018

Arias-Calderon 2016

Aziz 2017

Baad-Hansen 2019

Balanta-Melo 2019

Balanta-Melo 2022

Brin 2014

Bussadori 2020

Buysse 1989

Calixtre 2020

Camara-Souza 2019

Carra 2012

Carra 2015

Carrasso-Labra 2016

Cassette 2011

Casset 2017

Castroflorio 2017
Fedorowicz 2013

Fernandez-Nunez 2019

Frohman 1931

Goldstein 2021

Goller 2018

Haraki 2020

Higgins 2011

Higgins 2023

Hong 2020

Imai 2021

Johns 1991

Jokubauskas 2018

Kahn 2020
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Kane 2015

Langan 2019

Lavigne 2008

Lee 2010

Lee 2017

Lefebvre 2023

Lobbezoo 2013

Lobbezoo 2017

Lobbezoo 2018

Lobbezoo 2020

Ma 2018

Macedo 2007

Manfredini 2013

Manfredini 2015

Matak 2017

Matak 2019

Mercer 2019

Miller 2016

Montecucco 2005

Mukund 2020

Muzalev 2017
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Neu 2018

Nordstrom 2007

Palinkas 2016

Palinkas 2019

Peng 2018

Pihut 2016

Pirazzini 2017

Polmann 2021

Rada 2020

Raphael 2014

Raphael 2020

ReviewMan Web 2024 [Computer program]

Rossetto 2014

Scaglione 2016
Scaglione F. Conversion ratio between botox(R), dysport(R), and xeomin(R) in clinical practice. *Toxins (Basel)* 2016;8(3):1-10.

Schünemann 2022

Sendra 2021

Shim 2014

Sinclair 2013

Smardz 2022

Svensson 2017
Tay 2020

Van 1990

Wetselaar 2019

Winocur 2017

**APPENDICES**

**Appendix 1. MEDLINE (Ovid) search strategy**

1. exp Bruxism /
2. bruxism$.mp.
3. ((teeth$ or jaw$) adj5 clench$).mp.
4. ((teeth$ or jaw$) adj5 grind$).mp.
5. 1 or 2 or 3 or 4
6. exp Botulinum Toxins /
7. exp Botulinum Toxins, Type A /
8. onabotulinum$.mp.
9. abobotulinum$.mp.
10. Incobotulinum$.mp.
11. BTXA$.mp.
12. BTX-A$.mp.
13. BoNTA$.mp.
15. BoNT/A$.mp.
16. botox$.mp.
17. dysport$.mp.
18. xeomin$.mp.
19. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 5 and 19

The above subject search will be linked with the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials in MEDLINE *(Higgins 2023).*

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
CONTRIBUTIONS OF AUTHORS

Julián Balanta-Melo was the lead review author for the following tasks: conceptualisation, supervision, methodology, analysis, writing draft manuscript, and writing and editing review. He was supported by his co-authors in undertaking key tasks as detailed below.
Matías Dallasserri: methodology, analysis, writing draft manuscript, and writing review.
Conchita Martin Alvaro: methodology, analysis, writing draft manuscript, and writing review.
Francisca Verdugo-Paiva: methodology, analysis, writing draft manuscript, and writing review.
Julio Villanueva: conceptualisation, supervision, methodology, analysis, writing draft manuscript, writing and editing review.

DECLARATIONS OF INTEREST

Julián Balanta-Melo: none known
Matías Dallasserri: none known
Conchita Martin Alvaro: none known
Francisca Verdugo-Paiva: none known
Julio Villanueva: none known

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