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# Botulinum toxin type A therapy for hemifacial spasm (Review)

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[Intervention Review]

# Botulinum toxin type A therapy for hemifacial spasm

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## ABSTRACT

### Background

This is an update of a Cochrane Review, first published in 2005.

Hemifacial spasm (HFS) is characterised by unilateral, involuntary contractions of the muscles innervated by the facial nerve. It is a chronic disorder, and spontaneous recovery is very rare. The two treatments routinely available are microvascular decompression and intramuscular injections with botulinum toxin type A (BtA).

### Objectives

To compare the efficacy, safety, and tolerability of BtA versus placebo in people with HFS.

### Search methods

We searched CENTRAL, MEDLINE, Embase, reference lists of articles, and conference proceedings in July 2020. We ran the electronic database search, with no language restrictions, in July 2020.

### Selection criteria

Double-blind, parallel, randomised, placebo-controlled trials (RCTs) of BtA versus placebo in adults with HFS.

### Data collection and analysis

Two review authors independently assessed records. We planned to select included studies, extract data using a paper pro forma, and evaluate the risk of bias. We resolved disagreements by consensus, or by consulting a third review author. We planned to perform meta-analyses. The primary efficacy outcome was HFS-specific improvement. The primary safety outcome was the proportion of participants with any adverse event.

### Main results

We found no parallel-group randomised controlled trials comparing BtA and placebo in HFS.

**Authors' conclusions**

We did not find any randomised trials that evaluated the efficacy and safety of botulinum toxin type A in people with hemifacial spasm, so we are unable to draw any conclusions. O*bservational data show a strong association between BtA treatment and symptom improvement, and a favourable safety profile. While it is unlikely that future placebo-controlled RCTs will evaluate absolute efficacy and safety, they should address relevant questions for both people with HFS (such as long-term effects, quality of life, and other patient-reported outcomes), and clinicians (such as relative effectiveness of different BtA formulations and schemes of treatment) to better guide clinical practice.)*

## PLAIN LANGUAGE SUMMARY

**Botulinum toxin injections for unilateral involuntary contractions of facial muscles**

**The review question**

We reviewed the evidence about the effect of botulinum toxin type A (BtA) in people with one-sided, involuntary contractions of facial muscles, or hemifacial spasm. This is an update of a previous Cochrane Review: we assessed the efficacy (reduction in severity and disability) and safety of BtA versus placebo (a pretend medicine) in hemifacial spasm.

**Background**

Hemifacial spasm is a condition characterised by involuntary contractions of muscles on one side of the face. Although it is not dangerous, it usually causes cosmetic and functional problems, and may interfere with people's professional and social life, and have important health and economic implications. It is a chronic disorder, and recovery is rarely spontaneous.

Botulinum toxin is a powerful, natural chemical that can cause severe paralysis (an inability to move in the part of the body where it is applied) in animals and humans. It can also be used to treat many conditions, in particular those with involuntary muscle contractions, such as hemifacial spasm. Botulinum toxin is delivered by injections into the muscles that contract to produce most of the symptoms. There are different types of botulinum toxin, not all are available for treating health conditions. BtA is typically considered the first treatment option in hemifacial spasm.

**Study characteristics**

We performed a systematic search of the medical literature in July 2020 and found no studies that could be included in this review.

**Key results**

We found no clinically useful evidence from randomised clinical trials.

**Certainty in the evidence**

The clinical benefit of BtA treatment for HFS has not been properly addressed in randomised clinical trials.

We did not systematically search for data from other sources of evidence, which, by definition, are more prone to bias and carry a higher level of uncertainty. Observational studies suggest that BtA is effective and safe in this setting. Future randomised studies should evaluate the impact on outcomes that are relevant for people with HFS, and help to guide clinical practice in the selection of the BtA formulation, dose, and technique of administration

## BACKGROUND

This review is an update of a previously published Cochrane review, evaluating the efficacy and safety of botulinum toxin type A (BtA) versus placebo in the treatment of hemifacial spasm (HFS; (Costa 2005)).

### Description of the condition

See Table 1 for glossary of terms.

HFS is a condition characterised by involuntary paroxysmal contractions of muscles innervated by the facial nerve. Bilateral involvement is rare (Jamjoon 1990). The involuntary contraction affects orbicularis oculi in the upper face, and orbicularis oris, platysma, and other superficial muscles of the lower area of one half of the face. Although HFS is not dangerous, it usually causes significant cosmetic and functional disability. Its severity ranges from slight unilateral blinking, with no involvement of the lower half of the face, to intense spasm of the lower half of the face and neck with one eye closed, and progressive facial weakness (Cardoso 1995; Wang 1998). HFS may interfere with the person's professional and social life, and have important health and economic implications (Serrano 1999). It is a chronic condition, and recovery is rarely spontaneous.

HFS affects women more than men, and it usually appears in the fourth to seventh decade of life. For the white population of the United States, the average annual incidence is 0.78 per 100,000 population, and the average prevalence is 7.4 per 100,000 in men, and 14.5 per 100,000 in women (Auger 1990). Familial cases are rare (Carter 1990).

We do not fully understand the pathophysiology of HFS. The motor nucleus of the facial nerve may be hyperexcitable in some people (Cakmur 1999). Magnetic resonance imaging with special angiographic sequences shows that 65% (Bernardi 1993), to 100% of participants with HFS have a blood vessel that touches the facial nerve at its root exit zone, the point at which it leaves the brainstem in the cerebellopontine angle (Hosoya 1995). These vessels may cause focal demyelination with ephaptic transmission (i.e. current leakage and 'cross-talk') between axons, and slow nerve conduction (Nielsen 1984, Nielsen 1984a). Increasing nerve compression may be the cause of the progressive facial weakness.

The diagnosis is made by observation and clinical history. Radiological imaging is not important for the diagnosis, but it may help to exclude the rare cases associated with a tumour, aneurysm, or arteriovenous malformation (Matsuura 1996; Nagata 1992; Sprik 1988; Wang 1998).

Although many surgical and pharmacological approaches to treatment have been reported, the two treatments routinely available are microvascular decompression of the facial nerve at the pons (Barker 1995), and intramuscular injections of BtA.

### Description of the intervention

Botulinum toxin (Bt) is a powerful biological toxin produced by *Clostridium botulinum*. The active form of botulinum toxin is a di-chain polypeptide, composed of two chains: a heavy chain (100 kDa) and a light chain (50 kDa), and by associating with certain auxiliary proteins (haemagglutinins and non-haemagglutinins), the toxin forms a non-covalent multimeric complex of variable size (Simpson 2004). The nontoxic proteins aid the formation of neutralising antibodies, though beyond this, their role is unclear (Frevert 2010). Bt binds to peripheral cholinergic nerve terminals of the neuromuscular junction, as well as sympathetic ganglionic, parasympathetic ganglionic, and postganglionic terminals (Simpson 2004). After binding to an acceptor protein, Bt is endocytosed at the presynaptic membrane of the acetylcholine nerve terminals (Pellizzari 1999). By action of the N-terminal on the heavy-chain, a pore is formed on the endocytic membrane, which permits the release of the light chain into the cytosol. This light chain, which is a zinc protease, performs the key-action of the toxin, by cleaving soluble N-ethylmaleimide-sensitive factor attachment receptor proteins (SNARE proteins; (Pellizzari 1999)).

SNAREs are docking proteins for acetylcholine vesicles that allow for the release of acetylcholine into the synaptic cleft (Pellizzari 1999). The overall effect of Bt is a local chemodenervation, by the temporary blockade of acetylcholine release at cholinergic synapses. Temporary synapses are consequently formed via the process of axonal sprouting (Duchen 1971; Holland 1981; Juzans 1996).

There are seven immunologically distinct botulinum toxin serotypes (labelled A to G). These different Bt serotypes cleave specific SNARE proteins. Serotype A cleaves SNARE protein SNAP 25, located on the inner membrane, and serotype B targets synaptobrevin, located on the vesicular membrane (Pellizzari 1999).

Botulinum toxin is injected into the muscles involved in dystonia, with or without guidance by either electromyography (EMG) or ultrasound. As a general rule, the number of muscles injected tailored to the severity of the case in question, and the number of injection sites per muscle depend on the mass of the muscle. Within roughly three months after an injection of Bt into skeletal muscle, the nerve terminal resumes exocytosis, the muscle returns to its baseline function, and the effects of the Bt injection start to wear off (Jankovic 2004). Eventually, the muscle paralysis subsides; this is associated with the formation of new sprouts capable of neurotransmission. Over time, synaptic activity resumes in the original nerve terminals, leading to sprout regression (de Paiva 1999).

Currently, there are two commercially available Bt serotypes, botulinum toxin type A (BtA) and botulinum toxin type B (BtB). The following products are commonly available (three BtA and one BtB): onabotulinumtoxinA (Botox®, Allergan Inc., Irvine, CA, USA), abobotulinumtoxinA (Dysport®, Reloxin®, and Azzalure®, Ipsen Pharma, Boulogne Billancourt, France), incobotulinumtoxinA (Xeomin® and Bocoture® Merz GmbH, Frankfurt, Germany), and rimabotulinumtoxinB (Myobloc® and Neurobloc®, Solstice Neurosciences Inc., Louisville, KY, USA). Other BtA formulations are available in more restricted markets, and are yet to receive a generic name: Prosigne® and Lantox® (Lanzhou Institute of Biological Products, China), PurTox® (Mentor Worldwide LLC, Santa Barbara, CA, USA), and Neuronox® (Medy-Tox Inc, South Korea; (Walker 2014)).

### How the intervention might work

The therapeutic potential of all Bt serotypes derives from their ability to inhibit the release of acetylcholine from the

presynaptic nerve terminal into the synaptic cleft, causing local chemodenervation (Jankovic 2004). In addition to this, recent research has also suggested that Bt is active at multiple levels, namely sensory nerve terminals, and muscle spindles, which leads to a reduction in sensory input and fewer muscle contractions (Filippi 1993; Matak 2014; Rosales 1996; Rosales 2010).

It has also been suggested that cortical reorganisation may result from changes in the spinal cord, brainstem, and central nervous pathways (Palomar 2012). Animal research has shown the presence of supra-therapeutic levels of Bt by way of retrograde axonal transport and penetration of the central nervous system (Antonucci 2008; Boroff 1975). However, Bt has not been shown to penetrate the blood-brain barrier in humans.

Until recently, SNARE proteins were considered the only target molecules of Bt. Thus, it was widely accepted that the therapeutic and toxic actions of Bt were exclusively mediated by SNARE cleavage preventing the release of synaptic neurotransmitters. However, recent studies have suggested that a number of Bt actions might not be mediated by SNARE cleavage, specifically, neuroexocytosis, cell cycle and apoptosis, neuritogenesis and gene expression (Matak 2015). The existence of unknown Bt molecular targets and modulation of unknown signalling pathways is a possibility that may prove to be pharmacologically relevant.

### Why it is important to do this review

BtA is the toxin serotype that has been most intensively studied and approved for the treatment of the large number of focal dystonias. For the most prevalent and well-studied form of focal dystonia, cervical dystonia, BtA is considered first line therapy (Albanese 2013; Castelão 2017). BtB has also been shown to be efficacious, though with a different safety profile (Duarte 2016; Marques 2016). Despite the demonstrated efficacy, there is evidence that people attach a considerable expectation of harm due to botulinum toxin (Duarte 2018).

This is an update of a Cochrane Review that previously set out to assess the efficacy and safety of BtA compared to placebo in people with HFS (Costa 2005). As Cochrane's criteria for evaluating studies' risk of bias and the certainty in evidence have evolved and been updated, the authors considered it important to update this review.

## OBJECTIVES

To compare the efficacy, safety, and tolerability of botulinum toxin type A versus placebo in people with hemifacial spasm.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised, parallel-group, controlled trials (RCTs), blinded, single, or multiple dose, of any duration, assessing the efficacy, safety, or both, of botulinum toxin type A (BtA) treatment versus placebo in people with hemifacial spasm (HFS) were eligible for inclusion in this review.

#### Types of participants

Adults (i.e. 18 years of age or older), in any setting, with a clinical diagnosis made by any physician, specialist or other healthcare provider, of HFS. We allowed trials enrolling participants with any form of HFS. Participants could have prior exposure to botulinum toxin, and could be taking concomitant medications, if on stable regimens.

There were no restrictions regarding the number of participants recruited to trials, or the number of recruitment centres.

#### Types of interventions

Intramuscular injections of BtA compared to placebo. We allowed all administration schedules and injection techniques.

#### Types of outcome measures

##### *Primary outcomes*

###### Hemifacial spasm-specific improvement

Overall improvement on any validated symptomatic rating scale, measured between weeks three and six.

###### Adverse events

The proportion of participants with any adverse event, measured at any point during study follow-up. We also evaluated adverse events of special interest, such as facial or neck weakness, sore throat, injection site pain, and systemic complaints (e.g. diffuse muscle weakness, malaise, dizziness, and headache), measured at any point during study follow-up.

##### *Secondary outcomes*

###### Subjective evaluation of clinical status

Evaluated by either participants, or clinicians, or both, assessed with validated assessment tools, such as Patient Subjective Assessment of Change, Patient Global Assessment of Improvement, Patient Evaluation of Global Response (PEGR), Patient and Physician Global Assessment of Change, Investigator Global Assessment of Efficacy (IGAE), Physician Global Assessment of Change (PGAC), and visual analogue scale (VAS) for symptom severity, measured between weeks three and six after treatment.

###### Pain relief

Assessed with validated assessment tools, such as Patient Assessment of Pain or VAS pain score, measured between weeks three and six.

###### Health-related quality of life

Assessed with validated assessment tools, measured at any point during study follow-up.

###### Tolerability

We defined tolerability as the number of participant who dropped out due to adverse events, measured at any point during study follow-up.

###### Duration of effect

Assessed by the number of days until need for reinjection, or waning of the effects.

### Search methods for identification of studies

For this update, we expanded the search strategy to capture all the search terms for BtA formulations that were currently available.

The search strategy was designed to include other botulinum toxin formulations and other dystonic disorders that are also under current revision by the Cochrane Movement Disorders group .

### Electronic searches

We ran the final search for the original version of this review in June 2003, based on the search strategy developed for Cochrane Movement Disorders to identify all papers since 1977, the first year that botulinum toxin was used therapeutically in any condition. The search for the current update was run for the last time in July 2020.

We developed detailed search strategies for each database searched. Please see Appendix 1 for the Cochrane Central Register of Controlled Trials (CENTRAL) strategy, Appendix 2 for the MEDLINE search strategy, and Appendix 3 for the Embase strategy.

We assessed non-English language papers, translated them as necessary, and evaluated them for inclusion.

We did not search trials registries.

#### *Databases searched*

- Cochrane Movement Disorders' Trials Register ( July 2020);
- CENTRAL (2020, Issue 6) in the Cochrane Library (searched July 2020);
- MEDLINE (1977 to July 2020);
- Embase (1977 to July 2020).

### Searching other resources

The search strategy also included:

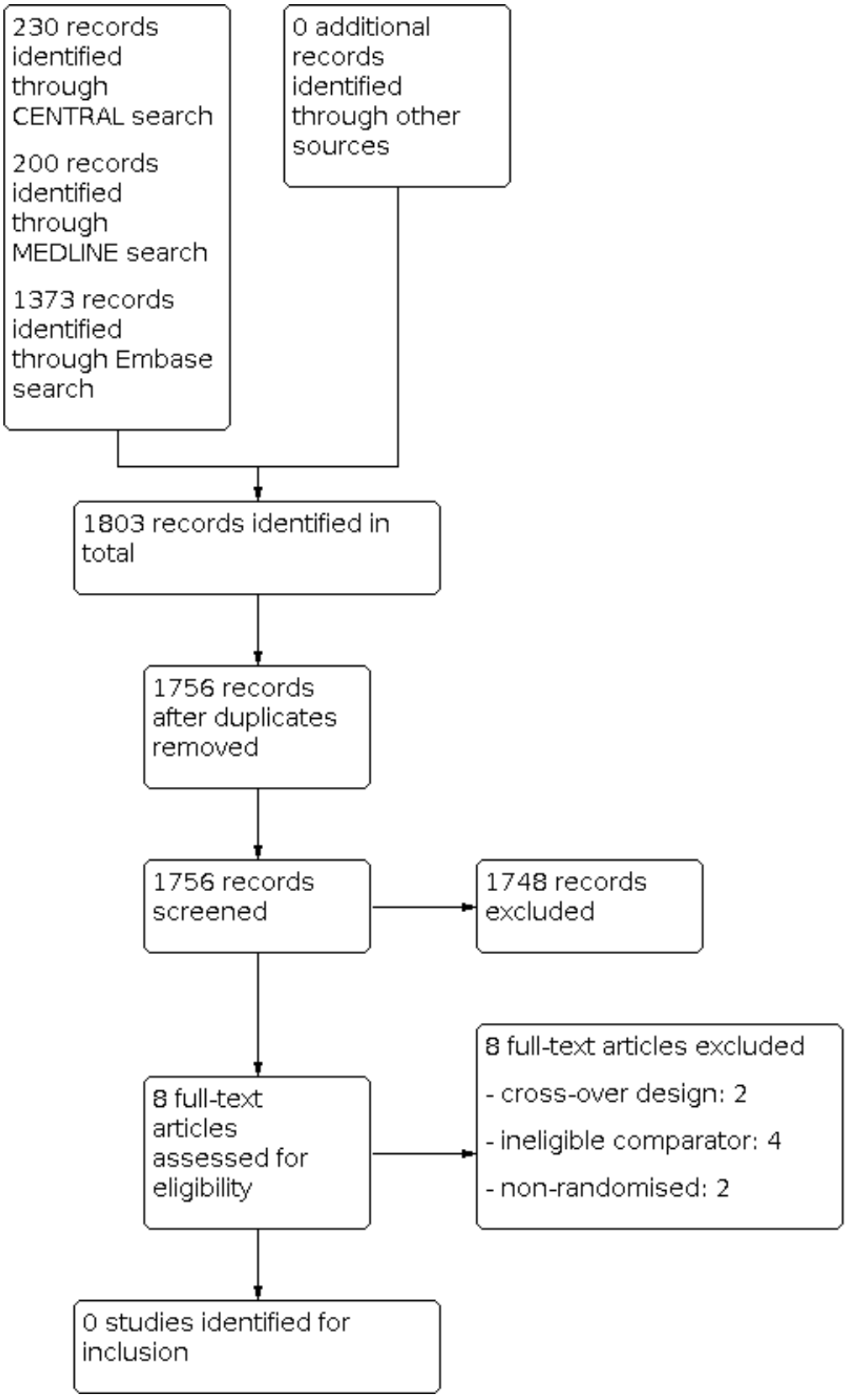
- searches through reference lists of located trials and review articles concerning botulinum toxin;
- handsearch of abstracts of international congresses relevant in the fields of movement disorders and botulinum toxins (American Academy of Neurology, Movement Disorders Society, International Association of Parkinsonism and Related Disorders, and International Neurotoxin Association (1985 to July 2020));
- personal communication with other researchers in the field;
- contact with drug manufacturers;
- whenever necessary, we contacted authors of published trials for further information and unpublished data.

## Data collection and analysis

### Selection of studies

Two review authors independently screened all titles and abstracts identified from searches to determine which ones met the inclusion criteria. We retrieved, in full text, any papers identified as potentially relevant by at least one review author, or those without an available abstract. Two review authors independently screened full-text articles, with discrepancies resolved by discussion, and by consulting a third review author where necessary, to reach consensus. We collated duplicate publications and presented them by individual study. We outlined the screening and selection process in a PRISMA flow chart (Liberati 2009); see Figure 1.

**Figure 1. Study flow diagram**



### Data extraction and management

Two review authors planned to independently extract data from included studies, using a piloted data extraction form. We planned to resolve any discrepancies by discussion until consensus was reached, or through consultation with a third review author where necessary. We planned to extract the following items from each study.

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

### Assessment of risk of bias in included studies

We planned to assess the risk of bias of included studies according to the domains described in the Cochrane tool for assessing risk of bias, and planned to classify the risk of bias for each domain as high, unclear, or low, and the overall assessment as high or low (Higgins 2011a). We planned to assess two further domains, which we describe below: enriched population and independent funding. We planned to use the following definitions for each domain in the 'Risk of bias' assessment.

- Random sequence generation (checking for possible selection bias). We would assess the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated); high risk of bias (non-random process used, e.g. allocation by birth year or by judgement).
- Allocation concealment (checking for possible selection bias). We would assess the method used to conceal allocation to interventions prior to assignment, to determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We would assess the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated); high risk of bias (e.g. open list).
- Blinding of participants and personnel (checking for possible performance bias). We would assess the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We would assess methods as: low risk of bias (study states that it was blinded, and describes the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study states that it was blinded, but does not provide an adequate description of how it was achieved). We would consider studies that are not double-blind at high risk of bias.
- Blinding of outcome assessment (checking for possible detection bias). We would assess the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We would assess the methods as: low risk of bias (study has a clear statement that outcome assessors were unaware of treatment allocation, and ideally describes how this was achieved); unclear risk of bias (study states that outcome assessors were blind to treatment allocation, but lacks a clear statement on how it was achieved). We would consider studies where outcome assessment is not blinded at high risk of bias.
- Selective reporting (checking for reporting bias). We assessed whether primary and secondary outcome measures were pre-specified and whether these were consistent with those reported. We assessed selective reporting as: low risk of bias (studies reporting primary and secondary outcomes); unclear risk of bias (study reporting insufficient information to permit judgement); high risk of bias (not all pre-specified outcomes reported or only for certain data collection time points).
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We would assess the methods used to deal with incomplete data as: low risk (< 10% of participants did not complete the study, the investigators used ‘baseline observation carried forward’ analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).

In addition to these criteria, we also added two more items for consideration.

- Enriched population. Because the clinical effect of botulinum toxin treatment is easily perceived, participants who are not naive to botulinum toxin treatment are likely to recognise the presence of beneficial clinical effects, frequent adverse events, or both, effectively revealing the respective allocation arm. It is also relevant, that by preferentially including responders to botulinum toxin or excluding non-responders to botulinum toxin, there is an increased likelihood that these participants would respond more favourably to botulinum toxin than a naive population would. We subdivided this domain in two: preferential enrolment of known positive responders to botulinum toxin; and exclusion of known poor responders to botulinum toxin.
  * Low risk of bias: at least 70% of trial participants were naive to treatment with botulinum toxin.
  * Unclear risk of bias: the trial did not make explicit the percentage of participants who were known to be botulinum toxin-naive.
  * High risk of bias: arbitrarily defined as more than 30% of participants not naive to botulinum toxin.

- For-profit bias. To assess the study source of funding, we added this domain.
  - Low risk of bias: the trial appears to be free of industry sponsorship, or other type of for-profit support that may introduce bias into trial design, conduct, or trial results.
  - Unclear risk of bias: the trial may be free of for-profit bias, but the trial did not provide any information on clinical trial support or sponsorship.
  - High risk of bias: the trial was sponsored by industry, or received other types of for-profit support.

### Measures of treatment effect

We planned to compare condition-related symptoms at baseline to those at weeks three to six post-injection, in the BtA and placebo arms. We planned to extract continuous outcomes whenever possible, pool the data from the studies, where adequate, and use them for comparison.

#### *Dichotomous data*

We planned to base the analysis of these data on the number of events and the number of people assessed in the intervention and comparison groups. We would have used these to calculate the risk ratio (RR) and 95% confidence interval (CI).

#### *Continuous data*

We would have based the analysis of these data on the mean, standard deviation (SD), and number of people assessed for both the intervention and comparison groups, to calculate mean difference (MD) and 95% CI. If more than one study had measured the same outcome using different validated tools, we would have calculated the standardised mean difference (SMD), namely Hedges' (adjusted) g, and 95% CI (Hedges 1985). For interpretation of effect sizes with SMDs, we would have used a common rule of thumb to define a small effect (SMD = 0.2), a moderate effect (SMD = 0.5), or a large effect (SMD = 0.8; (Cohen 1988)). If necessary for comparison, we planned to dichotomise rating scales, using each study author's own criteria for improvement or no improvement.

#### *Time-to-event data*

We planned to analyse these data based on log hazard ratios (HR) and standard errors, obtained from results of Cox proportional hazards regression models. We had planned to use these in order to calculate a HR and 95% CI.

### Unit of analysis issues

If included studies had multiple arms with different dosages of botulinum toxin, we planned to combine all groups to create a single pair-wise comparison, using the Review Manager 5 calculator (Review Manager 2014), according to the methods suggested by Cochrane (Higgins 2011b). We would also have created a single, pair-wise comparison in cases of multiple treatment groups that used different interventions (e.g. onabotulinumtoxinA and abobotulinumtoxinA), if these were compared to the same comparator.

For dichotomous outcomes, we planned to sum both the sample sizes and the numbers of people with events across groups. For continuous outcomes, means, and standard deviations, we could combine data using a pooled mean or SD (Higgins 2011b; Higgins 2011c).

### Dealing with missing data

For missing outcome or summary data, we planned to use imputation methods to derive the missing data (where possible), and report any assumptions in the review. In these cases, we planned to carry out sensitivity analyses, to investigate the effects of any imputed data on pooled effect estimates.

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

If this were to fail, and if there was at least one sufficiently large and similar study, we would have used a method of single imputation (Higgins 2011b).

Lastly, if there were a sufficient number of included studies with complete information, we would have used multiple imputation methods to derive missing data (Carpenter 2013; Rubin 1991).

If none of these methods proved successful, we would have conducted a narrative synthesis for the data in question.

### Assessment of heterogeneity

We planned to assess whether studies were similar enough to pool data. We intended to pool data using meta-analysis, and assess the degree of heterogeneity by visual inspection of forest plots and by examining the $Chi^2$ test for heterogeneity (Deeks 2011). We planned to quantify heterogeneity using $I^2$ (Higgins 2003). We planned to consider an $I^2$ value of 50% or more to represent substantial levels of heterogeneity, and to interpret this value in light of the size and direction of effects, and the strength of the evidence for heterogeneity, based on the P value from the $Chi^2$ test.

### Assessment of reporting biases

We planned to construct a funnel plot (Sterne 2001), and formally test asymmetry (Peters 2006), to see if results indicated publication bias. Should enough studies be included in future updates of this review, we plan to undertake these analyses.

### Data synthesis

We planned to perform the analyses with Review Manager 5, and Stata version 15 (Review Manager 2014; Stata).

#### *Meta-analysis*

We would have based the decision to meta-analyse data on an assessment of whether the interventions in the included trials were similar enough in terms of participants, settings, intervention, comparison, and outcome measures to ensure meaningful conclusions from a statistically pooled result. We planned to use a random-effects model.

We planned to pool effect measures by applying the Mantel-Haenszel method for dichotomous outcomes, and the inverse-variance or generic inverse-variance method for continuous outcomes. We also planned to pool time-to-event data using the

generic inverse-variance method. We intended to present all results with 95% CI.

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

Where there were no data to combine in a meta-analysis, we planned to undertake a narrative approach to result synthesis.

#### *Assessing the certainty in the evidence*

Using the GRADE approach, two review authors planned to independently assess the evidence for each outcome for the following domains: study limitations, inconsistency, indirectness, imprecision and publication bias (Schünemann 2011). In case of disagreement, the authors attempted to reach consensus, consulting an independent third review author, if necessary. We would have used the GRADEpro GDT software tool to develop a 'Summary of findings/ table, which we then would have imported into the review manuscript (GRADEpro GDT).

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

- Study limitations: we downgraded once if more than 30% of participants were from studies classified as being at a high risk of bias across any domain, with the exception of for-profit bias.
- Inconsistency: we downgraded once if heterogeneity was statistically significant (i.e. p-value < 0.05) or if the $I^2$ value was more than 40%. When we did not perform a meta-analysis, we downgraded once if trials did not show effects in the same direction.
- Indirectness: we downgraded once if more than 50% of the participants were outside the target group.
- Imprecision: we downgraded once if the optimal information size (i.e. using a standard sample size calculation) was not met or, alternatively, if it was met, but the 95% CI failed to exclude important benefit or important harm (Guyatt 2011).
- Publication bias: we downgraded once if there was direct evidence of publication bias, or if estimates of effect were based on small scale, industry-sponsored studies that raised a high index of suspicion of publication bias.

We planned to apply the following definitions to the certainty in the evidence (Balshem 2011):

- 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.

#### *'Summary of findings' table*

We planned to include a 'Summary of findings' table to present the main findings of this review in a simple tabular format, based on the results of the GRADE analysis.

#### Subgroup analysis and investigation of heterogeneity

We planned no subgroup analyses for this update.

#### Sensitivity analysis

We planned no sensitivity analyses for this update.

## RESULTS

### Description of studies

See: Figure 1, flow diagram of study selection.

#### Results of the search

We last ran the electronic search in July 2020. The search returned 1803 records (230 through CENTRAL; 200 though MEDLINE; 1373 through Embase), resulting in 1756 records after removing all duplicates. After title and abstract screening, we retrieved eight articles for full-text screening.

#### Included studies

We did not include any studies in the review.

#### Excluded studies

We excluded all eight records that we assessed as full texts: two trials had a cross-over design; four had an ineligible comparator, and two were not randomised. We listed them, together with reasons for their exclusion, in the Characteristics of excluded studies table.

### Risk of bias in included studies

We included no studies in the review.

### Effects of interventions

We included no studies in the review.

## DISCUSSION

Botulinum toxin type A (BtA) received approval for hemifacial spasm treatment in the early 1990s in the USA and Europe. Although there were no placebo-controlled trials, the available data were considered sufficient to support the decision to consider it as the treatment of choice for hemifacial spasm. A number of observational studies of interventions enrolled a total of several thousand participants (Jost 2001). In all these studies, BtA was considered highly effective, with a success rate of 76% to 100%. The mean duration of improvement ranged between 2.6 and four months (Batisti 2017). The most common adverse effects reported

in those studies were: ptosis, lagophthalmos, and dry eye (Ababneh 2013; Cillino 2010).

Bt therapy is probably the second most important discovery in movement disorders therapy after levodopa. Few drugs can match the obvious effect of Bt in some dystonias. The paucity of trials comparing BtA with placebo in hemifacial spasm is probably due to the very high success rate and degree of benefit reported in open, non-randomised studies. Although our review highlights this paucity of placebo-controlled data, we also think that it is important for the reader to understand that this is a particular situation; the effectiveness of BtA for the treatment of HFS is difficult to question; the strength of open-label data makes it ethically difficult to randomise participants to placebo or BtA, in trials designed to examine efficacy.

However, further controlled studies are needed, justifiable, and valuable to compare different Bt serotypes and formulations, techniques of injection, doses, long-term efficacy, to better understand the development of secondary non-responsiveness, and various models of service delivery. Furthermore, the impact of BtA on outcomes relevant for people with HFS has not been properly evaluated.

The surgical option of posterior fossa microvascular decompression (MVD) is often successful, and may be curative. To our knowledge, no randomised controlled study has compared MVD with BtA. Such a pragmatic trial could be most helpful in determining the best long-term management of HFS, especially in younger people, who otherwise face many years of BtA injections.

### Summary of main results

We included no studies in the review.

### Overall completeness and applicability of evidence

We included no studies in the review.

### Quality of the evidence

We included no studies in the review.

### Potential biases in the review process

Although we followed the methods recommended by Cochrane in order to minimise bias in the review process, certain areas do deserve attention. In particular, we did not search clinical trials registries. Although this opens the current review to the potential bias of having missed trials, we consider this possibility highly unlikely, because we extensively contacted other experts in this field, and USA and European trials in this area are well-known.

By demanding parallel-group, placebo-controlled RCTs, we raised the bar considerably on the type of evidence that can be considered adequate to evaluate the comparative effectiveness in movement disorders. As such, we cannot draw conclusions, in this review.

### Agreements and disagreements with other studies or reviews

We know of no other systematic review looking into the efficacy, safety, and tolerability of botulinum toxin in hemifacial spasm. However, a large 10-year retrospective cohort study found a response rate of 95%, and duration of response of around three months (Defazio 2002). This study also found an improved safety profile over time.

The proportion of participants with any adverse events is considerable in several observational studies, with estimates ranging from 2% (Jog 2016), to 37% (Batisti 2017). This aspect is particularly relevant, as a large nocebo effect, which may mask safety conclusions, has been shown in movement disorders research (Duarte 2018; Rato 2018; Rato 2019; Silva 2017).

## AUTHORS' CONCLUSIONS

### Implications for practice

We did not find any randomised, controlled, parallel-group trials that met our inclusion criteria, therefore, we do not have any evidence upon which to draw conclusions on the efficacy and safety of botulinum toxin type A for people with hemifacial spasm.

### Implications for research

International guidelines recommend the use of BtA for hemifacial spasm; but they rely on observational data that show a strong association between BtA treatment and symptom improvement, and a favourable safety profile. That said, it is ethically difficult to randomise participants to placebo or BtA, in trials designed to examine efficacy.

We believe that the gaps in evidence most relevant for people with hemifacial spasm are two-fold: the comparison of botulinum toxin type A (BtA) versus surgery, and the optimal scheme of treatment (including the option of different BtA formulations) for those under BtA therapy. Future trials should explore technical factors, such as the optimum treatment interval, injection technique, dose, Bt type, and Bt formulation. Other issues include service delivery, quality of life, long-term efficacy, safety, and immunogenicity.

Future research on all formulations of botulinum toxin should endeavour to establish clinical effectiveness, not only based on changes from baseline, but also, preferably, based on validated measures of minimal clinically important difference or change (Brożek 2006), as well as on outcomes relevant for people with hemifacial spasm.

It is currently uncertain whether the clinical effectiveness of botulinum toxin decays over time, with repeated treatment sessions, and whether a possible loss of effectiveness occurs in all clinical domains. Future studies comparing any form of BtA should address the comparative proportion of participants who develop secondary non-responsiveness to treatment.

Finally, in conducting this review, we were faced with the fact that there is no defined core outcome set in hemifacial spasm research, as there is for other areas (Tugwell 2007). A set of core outcome measures, to determine which patient-reported outcomes are important to measure, should be defined and included in future research, via well-established methodology. This would promote research in this field, and support the clinical effectiveness of botulinum toxin (Macefield 2014).

## ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Colakoglu 2011 | Cross-over trial. Ineligible comparator.<br><br>In this trial, participants were allocated to two different application methods. All of them were administered BtA into perioral muscles, but only one of the arms was administered also BtA into the orbicularis oculi, while the other arm received placebo. Then, participants were crossed over. The purpose was to evaluate the necessity of Bt application into lower facial muscles in people with HFS. The authors found that in participants with mild lower facial involvement, toxin application to these muscles might not be necessary.<br><br>However, these comparisons are not within the scope of our review. Also, this study did not include a placebo arm, and its design (single-blinded cross-over) was not contemplated in our protocol criteria. |
| Jitpimolmard 1998 | This study was an open, non-randomised trial that compared the effects of 2 different techniques of BtA injections. However, these comparisons were not within the scope of our review. |
| Mezaki 1999 | This randomised trial assessed the effects of different BtA doses. However it did not include a placebo arm. |
| Park 1993 | We found this controlled study of BtA versus placebo. In reality, this was a prospective case series of 101 participants with hemifacial spasm, which had first included, in the protocol, a randomised double-blind phase. It was not clear whether any participants had previously received BtA treatments. Only eight participants with hemifacial spasm were enrolled in the controlled phase. There were no clear data for baseline characteristics, treatment program, or results for BtA and placebo groups regarding these eight participants. Therefore, we excluded this study. |
| Price 1997 | A randomised trial enrolling 42 participants with hemifacial spasm analysed the effectiveness and side effects of four different BtA treatment site applications. The authors found that the brow treatment was equally effective to standard treatment with fewer side effects. However, this study did not include a placebo arm. |
| Sampaio 1997 | This randomised controlled trial compared different BtA formulations (Botox and Dysport at a ratio of 1 to 4) in participants with blepharospasm and hemifacial spasm. No placebo group was included. |
| Xiao 2018 | Compared BtA at different dosages, without an eligible comparator for this review. |
| Yoshimura 1992 | Cross-over trial.<br><br>This trial enrolled 11 participants with HFS, who were randomly assigned to 4 sets of injections. Three of these injections were of BtA (formulation Botox) using 3 different doses (low, intermediate, and high dose), and one injection was of placebo (saline). Muscles were selected for injection based on clinical involvement. For each participant, the site of injections was kept constant. BtA dose was determined for each participant on the basis of the number of muscles involved, frequency and severity of the spasms. The average dose ranged from 2.5 U to 10 U per muscle. Doses of one-half (low dose) and twice this dose (high dose) were administered on different occasions. The total dose administered to participants at any one time varied between 5 U and 90 U. BtA was diluted to a concentration of 2.5 U to 5 U per 0.1 mL. Participants were not re-injected until any response to the previous injection (as determined by both the participants and physicians) was lost. |

BtA: botulinum toxin type A
HFS: hemifacial spasm

## ADDITIONAL TABLES

**Table 1. Glossary of terms**

| Term | Definition |
|---|---|
| **BtA non-responsive** | People who do not experience the expected benefit from treatment with botulinum toxin type A. |
| **Hemifacial spasm** | A movement disorder in which people have abnormal movements of the face muscles that they cannot control. It is frequently accompanied by social embarrassment and pain. |
| **Chemodenervation** | The process by which botulinum toxin causes muscular paralysis. Although all the anatomical elements necessary for muscular control are intact (i.e. nerve, synapse, and muscle), there is a chemical process that disables the transmission of the electrical signal from the nerve to the muscle. |
| **Dysphagia** | A discomfort or difficulty when swallowing. |
| **Non-naive** | People who have been treated in the past with botulinum toxin. |
| **Voluntary action** | Movements that people are able to control, start, and stop when they want to. |

## APPENDICES

### Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Botulinum Toxins] explode all trees

#2 Botulinum Toxins, Type A

#3 (botul* near/2 tox*):ti,ab

#4 (botox or dysport or xeomin or myobloc or rimabotulinum* or abobotuli* or onabotulinum* or oculinum or purtox or CNBTX or Neuronox):ti,ab

#5 {or #1-#4}

#6 MeSH descriptor: [Dystonic Disorders] explode all trees

#7 MeSH descriptor: [Dystonia] explode all trees

#8 MeSH descriptor: [Torticollis] explode all trees

#9 MeSH descriptor: [Blepharospasm] explode all trees

#10 MeSH descriptor: [Meige Syndrome] explode all trees

#11 MeSH descriptor: [Hemifacial Spasm] explode all trees

#12 (cervic* near/2 dysto*):ti,ab

#13 blepharosp*:ti,ab

#14 (hem* near/2 spasm*):ti,ab

#15 (meige and (dysto* or syndrom*)):ti,ab

#16 (crani* near/2 dysto*):ti,ab

#17 (foca* near/2 dysto*):ti,ab

#18 (write* and (cramp* or dysto*)):ti,ab

#19 torticol*:ti,ab

#20 {or #6-#19}

#21 #5 and #20

#22 MeSH descriptor: [Animals] explode all trees

#23 MeSH descriptor: [Humans] explode all trees

#24 #22 not #23

#25 #21 not #24 in Trials

## Appendix 2. MEDLINE search strategy

#1 randomized controlled trial.pt.

#2 controlled clinical trial.pt.

#3 randomized.ab.

#4 placebo.ab.

#5 clinical trials as topic.sh.

#6 randomly.ab.

#7 trial.ti.

#8 1 or 2 or 3 or 4 or 5 or 6 or 7

#9 exp botulinum toxins/

#10 exp botulinum toxins, type A/

#11 (botul$ adj2 tox$).ti,ab.

#12 (botox or dysport or xeomin or myobloc or rimabotulinum$ or abobotuli$ or onabotulinum$ or oculinum or purtox or CNBTX or Neuronox).ti,ab.

#13 9 or 10 or 11 or 12

#14 (cervic$ adj2 dysto$).ti,ab.

#15 blepharosp$.ti,ab.

#16 (hem$ adj2 spasm$).ti,ab.

#17 (meige and (dysto$ or syndrom$)).ti,ab.

#18 (crani$ adj2 dysto$).ti,ab.

#19 (foca$ adj2 dysto$).ti,ab.

#20 (write$ and (cramp$ or dysto$)).ti,ab.

#21 torticol$.ti,ab.

#22 exp dystonic disorders/

#23 exp dystonia/

#24 exp torticollis/

#25 exp blepharospasm/

#26 exp meige syndrome/

#27 exp hemifacial spasm/

#28 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

#29 8 and 3 and 28

#30 exp animals/ not humans/

#31 29 not 30

## Appendix 3. Embase search strategy

#1 random$.tw.

#2 clinical trial:.mp.

#3 placebo$.mp.

#4 double-blind$.tw.

#5 1 or 2 or 3 or 4

#6 exp Hemifacial Spasm/

#7 exp Meige Syndrome/

#8 exp blepharospasm/

#9 exp torticollis/

#10 exp Dystonia/

#11 exp Dystonic Disorders/

#12 (cervic$ adj2 dysto$).ti,ab.

#13 blepharosp$.ti,ab.

#14 (hem$ adj2 spasm$).ti,ab.

#15 (meige and (dysto$ or syndrom$)).ti,ab.

#16 (crani$ adj2 dysto$).ti,ab.

#17 (foca$ adj2 dysto$).ti,ab.

#18 (write$ and (cramp$ or dysto$)).ti,ab.

#19 torticol$.ti,ab.

#20 5 or 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

#21 exp Botulinum Toxins, Type A/

#22 exp Botulinum Toxins/

#23 (botul$ adj2 tox$).ti,ab.

#24 (botox or dysport or xeomin or myobloc or rimabotulinum$ or abobotuli$ or onabotulinum$ or oculinum or purtox or CNBTX or Neuronox).ti,ab.

#25 21 or 22 or 23 or 24

#26 19 and 20 and 25

#27 limit 26 to human

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 19 October 2020 | New citation required but conclusions have not changed | Methods updated. No new trial included. |
| 25 July 2020 | New search has been performed | Methods updated. No new trial included. |

## HISTORY

Protocol first published: Issue 3, 2004
Review first published: Issue 1, 2005

| Date | Event | Description |
|---|---|---|
| 7 October 2008 | Amended | Converted to new review format. |
| 25 October 2004 | New citation required and conclusions have changed | Substantive amendment |

## CONTRIBUTIONS OF AUTHORS

A Peter Moore - APM; Cristina Sampaio - CS; Filipe Brogueira Rodrigues - FBR; Gonçalo S Duarte - GSD; João Costa - JC; Joaquim Ferreira - JJF; Mafalda Castelão - MC; Raquel E Marques - REM.

Conceiving the review - APM, CS, JC, JJF

Designing the review - APM, CS, JC, JJF

Co-ordinating the review - JC

Designing search strategies – FBR, JC

Undertaking searches – FBR, GSD

Screening search results – FRB, GSD, MF, REM

Organising retrieval of papers - FRB, GSD, JC, MF, REM

Screening retrieved papers against eligibility criteria - FRB, GSD, MF, REM

Appraising quality of papers - FRB, GSD, JC, MF, REM

Extracting data from papers - FRB, GSD, JC, MF, REM

Writing to authors of papers for additional information – GSD, JC, REM

Data management for the review – FRB, GSD, MF, REM

Entering data into RevMan - FRB, GSD, MF, REM

Analysis of data - FRB, GSD, JC, MF, REM

Interpretation of data - APM, CS, FRB, GSD, JC, JJF, MF, REM

Writing the review - FRB, GSD, JC

Providing general advice on the review – CS, JC, JJF

Performing previous work that was the foundation of the current review – Ana Borges, Claudia Espírito Santo, Miguel Coelho.

## DECLARATIONS OF INTEREST

JC, JJF, and CS were investigators in clinical trials in botulinum toxin A and B use in dystonia sponsored by Elan (manufacturer of botulinum toxin type B), Allergan (manufacturer of botulinum toxin type A), and Ipsen (manufacturer of botulinum toxin type A). Review authors (FBR, GSD, MC, REM) who were not trialists searched for studies, selected studies, extracted and analysed data (including risk of bias), and assessed the quality and certainty of the evidence with a GRADE approach.

JJF and CS were speakers in symposia promoted by Elan, Allergan, and Ipsen.

APM received royalties from Ipsen for the use of the 'LIVEchart' scoring system for botulinum toxin treatment efficacy. He also received consulting fees from Ipsen, Merz (manufacturer of botulinum toxin type A), Eisai (manufacturer of botulinum toxin type B), and Allergan. The same companies provided support for travel to meetings, for studies, or other purposes.

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this updated review, we only accepted parallel-group studies i.e. no cross-over studies, and we opted not to exclude based on allocation concealment. No changes were made to the type of participants included or the interventions allowed.

Adverse events, which we originally included as a secondary outcome, were included in this updated review as a primary safety outcome. We also planned to consider the proportion of participants with the most frequent adverse events, which was not stated in the original protocol. We included an assessment of pain, tolerability, and the duration of effect as new secondary outcomess.

We planned to use new approaches to deal with missing data and unit of analysis issues.

We planned to use theCochrane tool for assessing risk of bias in this review, to which we added two criteria. We included enriched population, since a known positive response to botulinum toxin type A and certain disorder subtypes are known to influence the magnitude of response to the intervention. As has been verified in a Cochrane Methodology Review, industry-sponsored trials display "the existence of an industry bias that cannot be explained by standard 'Risk of bias' assessments" (Lundh 2017). We planned to analyse blinding of outcome assessment in two new subcategories: subjective and objective assessment, and also planned to add a ‘Summary of findings' table.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Botulinum Toxins, Type A [*therapeutic use]; Hemifacial Spasm [*drug therapy]; Neuromuscular Agents [*therapeutic use]; Randomized Controlled Trials as Topic

### MeSH check words

Humans