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# Botulinum toxin type A therapy for cervical dystonia (Review)

Rodrigues FB, Duarte GS, Marques RE, Castelão M, Ferreira J, Sampaio C, Moore AP, Costa J

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[Intervention Review]

# Botulinum toxin type A therapy for cervical dystonia

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## ABSTRACT

### Background

This is an update of a Cochrane Review first published in 2005. Cervical dystonia is the most common form of focal dystonia, and is a highly disabling movement disorder, characterised by involuntary, usually painful, head posturing. Currently, botulinum toxin type A (BtA) is considered the first line therapy for this condition.

### Objectives

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

### Search methods

We searched Cochrane Movement Disorders' Trials Register, CENTRAL, MEDLINE, Embase, reference lists of articles, and conference proceedings in July 2020. All elements of the search, with no language restrictions, were last run in July 2020.

### Selection criteria

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

### Data collection and analysis

Two review authors independently assessed records, selected included studies, extracted data using a paper pro forma, and evaluated the risk of bias. We resolved disagreements by consensus or by consulting a third review author. We performed meta-analyses using a random-effects model, for the comparison of BtA versus placebo, to estimate pooled effects and corresponding 95% confidence intervals (95% CI). We performed preplanned subgroup analyses according to BtA dose used, the BtA formulation used, and the use (or not) of guidance for BtA injections. The primary efficacy outcome was improvement in cervical dystonia-specific impairment. The primary safety outcome was the proportion of participants with any adverse event.

### Main results

We included nine RCTs, with moderate, overall risk of bias, that included 1144 participants with cervical dystonia. Seven studies excluded participants with poorer responses to BtA treatment, therefore, including an enriched population with a higher probability of benefiting from this therapy. Only one trial was independently funded. All RCTs evaluated the effect of a single BtA treatment session, using doses from

150 U to 500 U of onabotulinumtoxinA (Botox), 120 U to 240 U of incobotulinumtoxinA (Xeomin), and 250 U to 1000 U of abobotulinumtoxinA (Dysport).

BtA resulted in a moderate to large improvement from the participant's baseline clinical status, assessed by the investigators, with a mean reduction of 8.09 points in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS total score) at week four after injection (95% CI 6.22 to 9.96; $I^2$ = 0%) compared to placebo. This corresponded, on average, to a 18.4% improvement from baseline. The mean difference (MD) in TWSTRS pain subscore at week four was 2.11 (95% CI 1.38 to 2.83; $I^2$ = 0%) compared to placebo. Overall, both participants and clinicians reported an improvement of subjective clinical status. It was unclear if dropouts due to adverse events differed (risk ratio (RR) 2.51; 95% CI 0.42 to 14.94; $I^2$ = 0%) However, BtA treatment increased the risk of experiencing an adverse event (R) 1.23; 95% CI 1.05 to 1.43; $I^2$ = 28%). Neck weakness (14%; RR 3.40; 95% CI 1.19 to 9.71; $I^2$ = 15%), dysphagia (11%; RR 3.19; 95% CI 1.79 to 5.70; $I^2$ = 0%), and diffuse weakness or tiredness (8%; RR 1.80; 95% CI 1.10 to 2.95; $I^2$ = 0%) were the most common treatment-related adverse events. Treatment with BtA resulted in a decreased risk of dropouts. We have moderate certainty in the evidence across all of the aforementioned outcomes, with the exception of subjective assessment and tolerability, in which we have high confidence in the evidence.

We found no evidence supporting the existence of a clear dose-response relationship between BtA and improvement in cervical dystonia-specific impairment, a destinction between BtA formulations, or a variation with use of EMG-guided injection for efficacy outcomes.

Due to clinical heterogeneity, we did not pool health-related quality of life data, duration of clinical effect, or the development of secondary non-responsiveness.

**Authors' conclusions**

We are moderately certain in the evidence that a single BtA treatment session resulted in a clinically relevant reduction of cervical dystonia-specific impairment, and pain, and highly certain that it is well tolerated, compared with placebo. There is moderate-certainty evidence that people treated with BtA are at an increased risk of developing adverse events, most notably, dysphagia, neckweakness and diffuse weakness or tiredness. There are no data from RCTs evaluating the effectiveness and safety of repeated BtA injection cycles. There is no evidence from RCTs to allow us to draw definitive conclusions on the optimal treatment intervals and doses, the usefulness of guidance techniques for injection, the impact on quality of life, or the duration of treatment effect.

## PLAIN LANGUAGE SUMMARY

**Treatment with botulinum toxin type A for people with involuntary posturing of the head, or cervical dystonia**

**The review question**

This is an update of a Cochrane Review, We assessed the effectiveness (reduction in severity, disability, and pain) and safety of botulinum toxin type A (BtA) versus placebo (a pretend medicine) in people with involuntary positioning of the head, or cervical dystonia

**Background**

Cervical dystonia, also called spasmodic torticollis, is a disorder that causes undesired, uncontrollable, often painful, abnormal placement of the head. It is a relatively uncommon condition (affecting 57 to 280 people per million) that can be very disabling, and can negatively affect a person's quality of life. In most cases, the cause is unknown; no cure exists. Since cervical dystonia is normally a long-term disorder, it requires long-term treatment.

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 injected) in animals and humans. It can also be used to treat many conditions, in particular, those with involuntary muscle contractions, such as cervical dystonia. Botulinum toxin is delivered by injections into the muscles that contract to produce most of the disorder 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 cervical dystonia.

**Study characteristics**

We searched the medical literature up to July 2020. We found nine studies that compared treatment with BtA versus placebo, and included a total of 1144 participants, with on average, a moderate disease impairment. The participants remained in most of the studies for 16 to 20 weeks after the treatment. The average age of people in the studies was 52.8 years, and they had cervical dystonia for an average of 4.8 to 12.1 years before taking part in the trials. Sixty-four percent of the people in the studies were women. Eight of the nine trials were funded by drug manufacturers with possible interests in the results of the studies.

**Key results**

The results show that a single treatment session improved cervical dystonia symptoms, including pain, and participant's self-evaluations. However, the risk of having an unpleasant or undesirable event, particularly swallowing difficulties, tiredness, and neck weakness, was also increased. Only three studies examined the impact of BtA on quality of life, suggesting some benefit from BtA.

**Certainty in the evidence**

There is moderate certainty in the evidence for overall and pain improvement, and the risk of undesired events. There is high certainty in the evidence that participants reported self-evaluated improvement, and the risk that participants did not tolerate treatment.

To be included in the studies, participants must have had a history of successful treatment with BtA. People with certain types of cervical dystonia, in particular the types that make the head turn mostly backward or forward, were not allowed to participate in the studies; it is known that they do not respond as well to botulinum toxin treatment. Therefore, the conclusions from this review may not apply to all people with cervical dystonia.

We can draw no conclusions regarding long-term effects of BtA for this condition.

## Summary of findings 1. Botulinum toxin type A compared to placebo for cervical dystonia

**Botulinum toxin type A compared to placebo for cervical dystonia**

**Patient or population:** cervical dystonia
**Setting:** hospital-based, movement disorders clinics
**Intervention:** botulinum toxin type A
**Comparison:** placebo

| Outcomes | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | | | Certainty of the evidence (GRADE) | What happens |
|---|---|---|---|---|---|---|
| | | Without botulinum toxin type A | With botulinum toxin type A | Difference (95% CI) | | |
| **Cervical dystonia-specific improvement**<br>*assessed with: TWSTRS total score (range 0 - 85, higher is worse) at 4 weeks;*<br>651 participants (5 RCTs) | - | The mean cervical dystonia-specific improvement without botulinum toxin type A was 12.00 | - | MD 8.09 higher (6.22 higher to 9.96 higher) | ⊕⊕⊕⊖ Moderate[a] | Botulinum toxin type A likely improves cervical dystonia-specific signs and symptoms' |
| **Adverse events**<br>*at 4 weeks;* 1085 participants (8 RCTs) | RR 1.23 (1.05 to 1.43) | Study population | | | ⊕⊕⊕⊖ Moderate[a] | Botulinum toxin type A likely increases adverse events |
| | | 43.8% | 53.9% (46 to 62.7) | 10.1% more (2.2 more to 18.8 more) | | |
| **Subjective participant assessment**<br>*at 4 weeks;* 755 participants (6 RCTs) | RR 2.19 (1.78 to 2.70) | Study population | | | ⊕⊕⊕⊕ High[a,b] | Botulinum toxin type A results in a large improvement in subjective participant assessment |
| | | 25.3% | 55.3% (44.9 to 68.2) | 30.1% more (19.7 more to 42.9 more) | | |
| **Cervical dystonia-specific pain**<br>*assessed with TWSTRS pain subcale (range 0 - 20, higher is worse) at 4 weeks;*<br>429 participants (3 RCTs) | - | -c | - | MD 2.11 higher (1.38 higher to 2.83 higher) | ⊕⊕⊕⊖ Moderate[a] | Botulinum toxin type A likely reduces cervical dystonia-specific pain |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Tolerability**<br><br>*assessed as dropouts at 4 to 6 weeks:*<br><br>*705* participants (5 RCTs) | RR 0.48 (0.32 to 0.73) | Study population | | | ⊕⊕⊕⊕ High[a,b] | Botulinum toxin type A results in a large reduction in tolerability (increased trial dropouts) |
| | | 25.6% | 12.3% (8.2 to 18.7) | 13.3% fewer (17.4 fewer to 6.9 fewer) | | |
| **Health-related quality of life**<br><br>assessed with multiple tools at 4 weeks; 409 participants (3 RCTs) | Three trials found a greater improvement in health-related quality of life with botulinum toxin type A compared with placebo, however, two trials found no benefit in social functioning when compared to placebo | | | | ⊕⊕⊕⊖ Moderate[a] | Botulinum toxin type A likely improves health-related quality of life (across most domains) |
| **Duration of effect**<br><br>618 participants (5 RCTs) | One trial reported a mean time to re-treatment of 14.4 weeks (range 4 to 30 weeks). Other trials reported duration of effect heterogeneously, such that we could not adequately assess or pool it. | | | | ⊕⊖⊖⊖ Very low[a,d,e] | The evidence is very uncertain how long the effects of botulinum toxin type A last |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **TWSTRS**: Toronto Western Spasmodic Torticollis Rating Scale

**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

[a]Downgraded one level due to serious study limitations; we had concerns with randomisation procedures and other biases, such as for-profit bias
[b] Upgrade one level due toa large effect size (RR>2 or <0.5)
[c]Not estimable, as data were only available as between-group differences
[d]Downgraded one level due to serious indirectness; different formats were used in each trial for reporting duration of effect, so we were unable to adequately assess and pool data across trials
[e]Downgraded one level due to serious imprecision; the optimal in formation size was not reached in the information assessed.

## BACKGROUND

This is an update of a Cochrane Review, evaluating the efficacy and safety of botulinum toxin type A (BtA) versus placebo in the treatment of cervical dystonia (Costa 2005; Castelão 2017).

### Description of the condition

See Table 1 for glossary of terms.

Dystonia is the third most common movement disorder, after Parkinson's disease and essential tremor, with an overall prevalence of 164 per million(Steeves 2012). Dystonia syndromes are a group of disabling, painful disorders, characterised by involuntary sustained or intermittent muscle contractions causing abnormal, often repetitive, movements or postures of the face, neck, trunk, or limbs. Dystonic movements are typically patterned or twisting, and are often initiated or worsened by voluntary action (Albanese 2013). These neurological disorders can be classified, based on topographic distribution, including focal dystonia (one body region, e.g. cervical dystonia and blepharospasm), segmental dystonia (two or more adjacent regions), multifocal dystonia (two or more nonadjacent regions), hemidystonia (ipsilateral regions), and generalised dystonia (trunk and two or more other regions; (Albanese 2013; Tarsy 2006)).

Focal dystonia is a highly disabling movement disorder, with serious functional and social impairment. Close to half of the people with it quit work by the age of forty, or retire early, and 10 years later, only 25% of people are working compared to 62% of the general population (Zoons 2012). Moreover, health-related quality of life is importantly diminished, mainly attributable to depression and anxiety, with scores comparable to people with multiple sclerosis, Parkinson's disease, or stroke (Zoons 2012).

Cervical dystonia, also called spasmodic torticollis, is the most common form of adult-onset focal dystonia, with estimates from population studies ranging from 57 per million in Europe (ESDE 2000), to as high as 280 per million in the USA (Jankovic 2006). It typically has its onset in the fifth decade (Albanese 2013), and affects more women than men (Defazio 2013). This condition is characterised by abnormal movements of the head, neck, and shoulder, resulting in posturing of the head away from its normal central position (Foltz 1959). It may present predominantly with sustained abnormal posture, spasm, jerks, tremor, or a combination of these features. Neck or shoulder pain, or both, occur in more than 70% of individuals with cervical dystonia (Chan 1991; Tarsy 2006).

Cervical dystonia can be classified according to the dominant head position, with the most common type involving horizontal turning, the so-called rotatory (or simple) torticollis (Albanese 2013; Chan 1991). Other common patterns include laterocollis (tilt to one side), retrocollis (tilt upwards, resulting in neck extension), and anterocollis (tilt downwards, resulting in neck flexion). Among all forms of cervical dystonia, complex torticollis, a combination of these abnormal patterns, is found relatively frequently in clinical practice.

The aetiology of most forms of dystonia is still not fully understood, with the exception of early-onset dystonia, for which a hereditary aetiology is common (Balint 2015). In most cases of focal adult-onset dystonia, such as cervical dystonia, the pathophysiology is generally considered to result from inhibition of the central nervous system (CNS) at multiple levels, resulting in abnormal sensorimotor integration (Hallett 1998). Cervical dystonia can also be secondary to brain injury, infections of the CNS, drugs (such as levodopa or antipsychotics), toxins, vascular or neoplastic disorders, and may also be psychogenic (i.e. functional; (Albanese 2013)). Although most cases of cervical dystonia are currently classified as idiopathic, it should be noted that some may come to be reclassified as inherited, since new gene discoveries are under investigation (Albanese 2013; Balint 2015).

The natural course of cervical dystonia remains unclear. It usually develops gradually and deteriorates over the initial years. The clinical presentation in adults seldom progresses to generalised dystonia, although it often extends to adjacent body regions. For most individuals, cervical dystonia is a life-long disorder, with only about 10% undergoing spontaneous remissions (Jahnanshani 1990).

To date, no curative or disease-modifying treatments are available for cervical dystonia.

### Description of the intervention

Botulinum toxin 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). Botulinim toxin 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, botulinum toxin is endocytosed at the presynaptic membrane of 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 botulinum 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 botulinum toxin 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 botulinum toxin serotypes cleave specific SNARE proteins. Serotype A cleaves SNARE protein SNAP 25, located on the inner membrane of nerve cells (Pellizzari 1999).

Botulinum toxin is injected into the muscles thought to be involved in dystonia, with or without guidance by either electromyography (EMG) or ultrasound. As a general rule, the number of muscles injected are tailored to the severity of the case in question, and

the number of injection sites per muscle are determined by the mass of the muscle. Within roughly three months after injection of botulinum toxin into skeletal muscle, the nerve terminal resumes exocytosis, and the muscle returns to its baseline clinical function, showing a wearing-off response from the botulinum toxin injection (Jankovic 2004). Eventually, the muscle paralysis subsides; this is associated with the formation of new sprouts that are 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 botulinum toxin 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, or Azzalure, Ipsen Pharma, Boulogne Billancourt, France), incobotulinumtoxinA (Xeomin or Bocoture Merz GmbH, Frankfurt, Germany), and rimabotulinumtoxinB (Myobloc or 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 or 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 botulinum toxin 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 botulinum toxin 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 been further 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 botulinum toxin by way of retrograde axonal transport and penetration of the CNS (Antonucci 2008; Boroff 1975). However, botulinum toxin has not been shown to penetrate the blood-brain barrier in humans.

Until recently, SNARE proteins were considered the only target molecules of botulinum toxin. Thus, it was widely accepted that the therapeutic and toxic actions of botulinum toxin were exclusively mediated by SNARE cleavage preventing the release of synaptic neurotransmitters. However, recent studies have suggested that a number of botulinum toxin actions might not be mediated by SNARE cleavage, specifically regarding neuroexocytosis, cell cycle and apoptosis, neuritogenesis, and gene expression (Matak 2015). The existence of unknown botulinum toxin 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. BtA is considered first line therapy for cervical dystonia (Albanese 2013). BtB has also been shown to be efficacious, though with a different safety profile (Duarte 2016; Marques 2016). However, even in moderately severe dystonia, there is evidence that people attach a considerable expectation of harm due to botulinum toxin, the so called nocebo effect (Duarte 2018).

This is an update of a Cochrane Review that assessed the efficacy and safety of BtA compared to placebo in people with cervical dystonia. Since the release of the original review, three new trials have been published (Comella 2011; Poewe 2016; Truong 2010). Cochrane's criteria for evaluating studies' risk of bias and the certainty in evidence have also evolved and been updated. Therefore, the authors considered it important to update this review.

## OBJECTIVES

To compare the efficacy, safety, and tolerability of botulinum toxin type A (BtA) versus placebo in people with cervical dystonia.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs), blinded, single or multiple dose, parallel-designed, of any duration, assessing the efficacy or safety, or both, of botulinum toxin type A (BtA) treatment versus placebo, in people with cervical dystonia were eligible for inclusion in this review. We excluded non-parallel study designs, namely cross-over trials, due to uncertainty about whether this type of study design was appropriate to study people with cervical dystonia, as well as methodological concerns with regards to detection and performance bias.

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

#### 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 idiopathic cervical dystonia. We included trials enrolling participants with any form of cervical dystonia, with or without widespread dystonias. We included participants with prior exposure to BtA or botulinum toxin type B (BtB), or those taking concomitant medications, if they were on stable regimens.

#### Types of interventions

Intramuscular injections of BtA compared to placebo. We allowed all administration schedules and injection techniques, performed with or without guidance by either electromyography (EMG) or ultrasound.

#### Types of outcome measures

##### *Primary outcomes*

###### Cervical dystonia-specific improvement

Overall improvement on any validated symptomatic rating scale, such as Cervical Dystonia Severity Scale (CDSS), Tsui scale, Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), and TWSTRS severity and disability subscales, measured between weeks three and six.

#### Adverse events

The proportion of participants with any adverse event, measured at any point during study follow-up. For this outcome, we also evaluated adverse events of special interest, such as sore throat or dry mouth, neck weakness, dysphagia, injection site pain, voice change, 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, and 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.

#### Pain relief

As assessed with validated assessment tools such as Patient Assessment of Pain, TWSTRS pain subscale, and VAS for pain, measured between weeks three and six.

#### Health-related quality of life

Assessed with validated assessment tools, such as Short Form-36 (SF-36) Quality-of-Life questionnaire and Cervical Dystonia Impact Profile (CDIP)-58 scale, measured at any point during study follow-up.

#### Tolerability

We defined tolerability as the number of participants 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 the need for re-injection or waning of the effect.

## 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. We designed the search strategy 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 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. We ran the search for the current update 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 (searched July 2020);
- CENTRAL (2020, Issue 06), 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 of 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 our references 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**

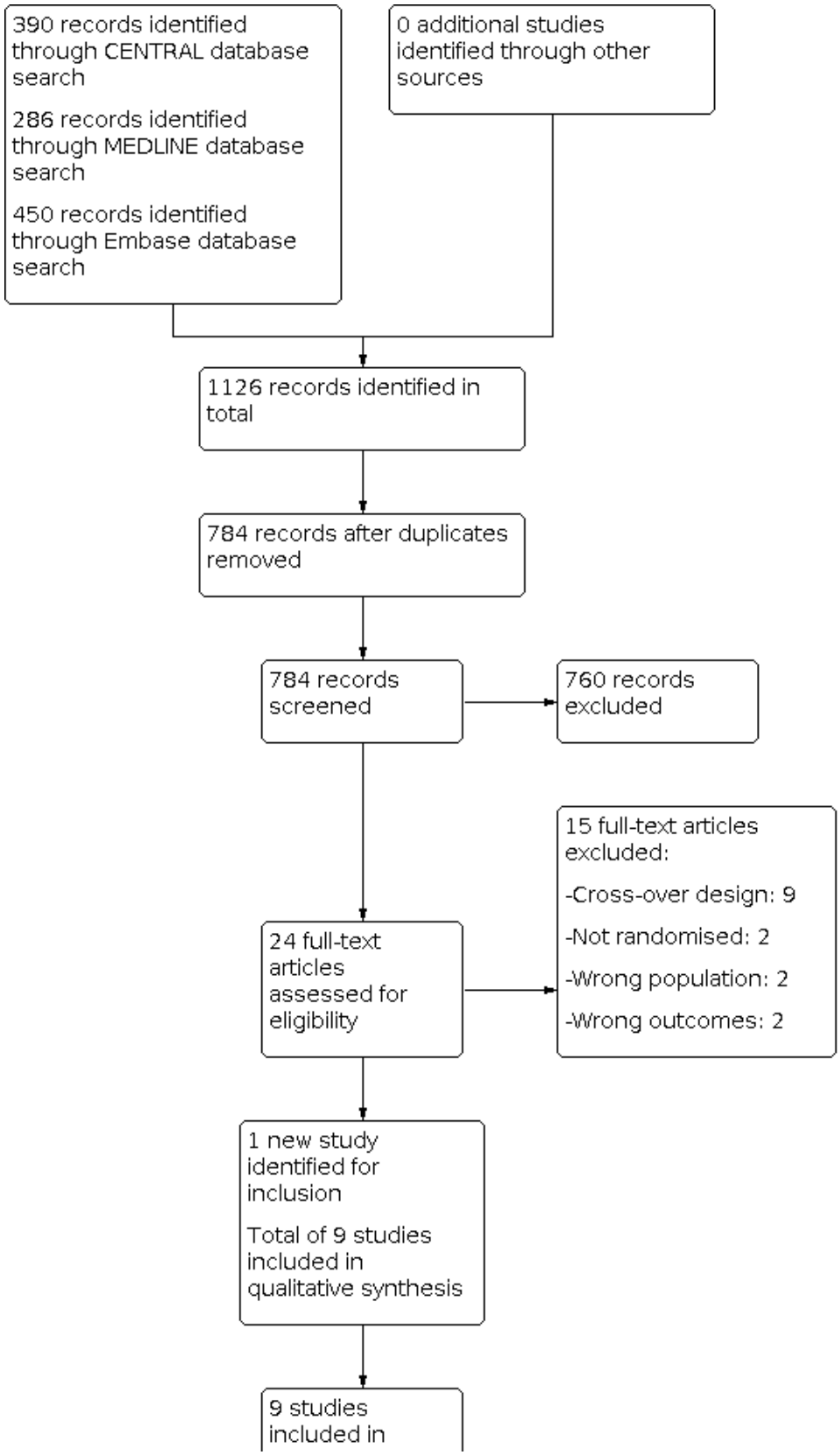
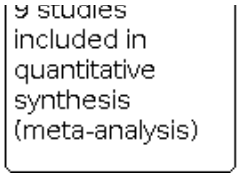


**Figure 1. (Continued)**




### Data extraction and management

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

- Participants: inclusion and exclusion criteria, demographics and clinical baseline characteristics, number and reasons for dropping out, exclusions and loss 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 number of 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 assessed the risk of bias of included studies according to the domains described in the Cochrane tool for assessing risk of bias, and classified the risk of bias for each domain as high, unclear, or low, and the overall assessment as high or low (Higgins 2011a). We assessed two further domains, which are described below: enriched population and independent funding. We used the following definitions for each domain in the 'Risk of bias' assessment.

- Random sequence generation (checking for possible selection bias). We assessed 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 assessed 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 assessed 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 assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed 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). Studies that were not double-blind were considered at high risk of bias.
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed 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 considered studies where outcome assessment was 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 assessed the methods used to deal with incomplete data as: low risk (< 10% of participants did not complete the study, trialist 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).

#### *Additional 'Risk of bias' items*

- Enriched population. Because the clinical effect of botulinum toxin treatment is easily perceived, participants naive to botulinum toxin are likely to recognise the presence or absence of beneficial clinical effects, or 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 opted to subdivide 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; the trial did not exclude any particular form of cervical dystonia including those associated with a poorer response to botulinum toxin (such as pure anterocollis and retrocollis).
  * 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 non-naive to botulinum toxin; explicit exclusion of people with forms of cervical dystonia associated with a poorer response to botulinum toxin.
- For-profit bias. In order to assess the study source of funding, we added this domain in place of the 'other bias' domain.
  * Low risk of bias: the trial appears to be free of industry sponsorship or other type of for-profit support that may introduce bias into trial design, conduct, or trial results.
  * Unclear risk of bias: the trial may or may not be free of for-profit bias, as 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 type of for-profit support.

### Measures of treatment effect

We compared disease symptoms at baseline to disease symptoms in weeks three to six post-injection in the BtA and placebo arms. We extracted continuous data whenever possible, pooled the data from the studies, where adequate, and used them for comparison. them for comparison.

#### *Dichotomous data*

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

#### *Continuous data*

We based 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. Where the MD was reported without individual group data, we used this to report the study results. If more than one study measured the same outcome using different validated tools, we calculated the standardised mean difference (SMD), namely Hedges' (adjusted) g, and 95% CI (Hedges 1985). For interpretation of effect sizes with SMDs, we used a rule of thumb to define a small effect (SMD = 0.2), a moderate effect (SMD = 0.5), or a large effect (SMD = 0.8; (Cohen 1988)). If necessary for comparison, we dichotomised 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

Whenever the included studies had multiple arms with different doses of botulinum toxin, we combined all groups to create a single pair-wise comparison, using the Review Manager 5 calculator, according to the methods suggested by Cochrane (Higgins 2011b; Review Manager 2014). We also would have opted to create a single, pair-wise comparison in cases when multiple treatment groups, using different interventions (e.g. onabotulinumtoxinA and abobotulinumtoxinA), were compared to the same comparator.

This method combines all relevant experimental intervention groups of the study into a single group, and all relevant control intervention groups into a single control group. This approach avoids the duplication of the control group, which would happen if multiple comparisons (e.g. BtA dose 1 versus placebo; BtA dose 2 versus placebo) were included in the meta-analysis, as well as the loss of information if one dose group is chosen over the others. If applicable, we plan to explore the effect of dose in subgroup analysis.

For dichotomous outcomes, we planned to sum both the sample sizes and the numbers of people with events across groups. For continuous outcomes, we planned to pool means and standard deviations in a meta-analysis (Higgins 2011b; Higgins 2011c).

### Dealing with missing data

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

As a first option, we used 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 data were not reported, or we were unable to extract them, we attempted to create a correlation coefficient, based on another study in the review, and then used this correlation coefficient to impute a change from baseline SD (Abrams 2005; Follmann 1992; Higgins 2011b).

If this failed, and there was at least one sufficiently large and similar study, we planned to use a method of single imputation (Furukawa 2006; Higgins 2011b).

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

If none of these methods proved successful, we planned to conduct a narrative synthesis for the data in question.

### Assessment of heterogeneity

We assessed whether studies were similar enough to allow pooling of data using meta-analysis. Where data were pooled using meta-analysis, we assessed the degree of heterogeneity by visual inspection of forest plots and by examining the $Chi^2$ test for heterogeneity (Deeks 2011). We quantified heterogeneity using the $I^2$ statistic (Higgins 2003). We considered an $I^2$ value of 50% or more to represent substantial levels of heterogeneity, but interpreted 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 included too few studies in this review, i.e. fewer than 10, to allow construction of a funnel plot (Sterne 2001), and formal testing of asymmetry, which may indicate publication bias (Peters 2006). Should enough studies be included in future updates of this review, we plan to undertake these analyses.

### Data synthesis

We performed the analyses with Review Manager 5 (Review Manager 2014), Stata version 15 (Stata), and Trial Sequential Analysis (TSA; Thorlund 2011; TSA 2011).

#### *Meta-analysis*

We based the decision whether or not 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 conducted data synthesis using a random-effects model.

We pooled effect measures by applying the Mantel-Haenszel method for dichotomous outcomes, and applied the inverse-variance or generic inverse-variance method for continuous outcomes. We had planned to pool time-to-event data using the generic inverse-variance method. We presented all results with 95% CI.

We calculated the number needed to treat for an additional beneficial outcome (NNTB) and for an additional harmful outcome (NNTH) from meta-analysis estimates, rather than treating data as if they came from a single trial, as the latter approach is more prone to bias, especially when there are important imbalances between groups within one or more trials in the meta-analysis (Altman 2002). However, caution 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 that could be combined into a meta-analysis, we undertook a narrative approach to result synthesis.

#### *Trial Sequential Analysis*

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

We calculated the required information size and computed the trial sequential monitoring boundaries, using the O'Brien-Fleming approach (O'Brien 1979). We based the required information size on the event proportion, or standard deviation in the control group; assumption of a plausible relative risk reduction (RRR) of 10%; a 5% risk of type I error; a 20% risk of type II error (power = 80%); and the observed heterogeneity of the meta-analysis (Jakobsen 2014; Wetterslev 2009).

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

As recommended by the GRADE Working Group methodology, two review authors independently assessed all of the outcomes in the following domains: study limitations, inconsistency, indirectness, imprecision, and publication bias (Schünemann 2011), In case of disagreement, the review authors attempted to reach consensus, consulting an independent third review author if necessary. For this purpose, we used the GRADEpro GDT software tool, which we then used to export a 'Summary of findings' table into the review text (GRADEpro GDT).

To ensure the consistency and reproducibility of GRADE judgements, we applied the following criteria to each critical outcome.

- 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, 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 criterion 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 where there was direct evidence of publication bias, or if estimates of effect were based on small scale, industry-sponsored studies, which raised a high index of suspicion of publication bias.

We applied 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 included 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. Version 3 was used for ease of interpretation (Carrasco-Labra 2016).

### Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses for the following areas, independently of the presence of significant heterogeneity.

- Different BtA formulations
- Different BtA doses, all defined arbitrarily: high (Botox or Xeomin > 200 U; Dysport = 1000 U), medium (Botox or Xeomin 100 U to 200 U; Dysport = 500 U), and low (Botox or Xeomin < 100 U; Dysport = 250 U)
- EMG-guided versus non-EMG-guided botulinum toxin injection

### Sensitivity analysis

We conducted sensitivity analyses for every study for which we applied imputation method.

## RESULTS

### Description of studies

We identified one new study for inclusion in this update: Lew 2018.

Overall, we included nine parallel-designed studies comparing botulinum toxin type A (BtA; different total treatment doses) with placebo in this update, enrolling a total of 1144 participants with cervical dystonia.

See also Characteristics of included studies.

### Results of the search

See flow diagram of study selection (Figure 1).

We ran the last electronic search in July 2020. The search returned 1126 records (390 through CENTRAL; 450 though MEDLINE; 286 through Embase), resulting in 784 records after removing all duplicates. After title and abstract screening, we assessed 24 full-text articles; we included nine for both the qualitative and quantitative syntheses.

We excluded nine trials for having a cross-over design; two because they were not randomised; two included the wrong population; and another two studied the wrong outcomes.

We did not retrieve any unpublished trials.

### Included studies

We listed details of the included studies in the 'Characteristics of included studies' table.

See Table 2 for a summary of the clinical characteristics of the included studies.

The nine included studies enrolled a total of 1144 adult participants, with a mean age of 52.8 years (range 18 to 82), 736 of whom were female (64%). Trial size varied from 55 to 233 participants. Eight studies were performed in a multicenter setting – four in North America (Charles 2012; Comella 2011; Lew 2018; Truong 2005), one in the USA and Russia (Truong 2010), and three in Europe (Poewe 1998; Poewe 2016; Wissel 2001). The three larger studies enrolled a total of 616 participants, accounting for 54% of the participants included in this review (Charles 2012; Comella 2011; Poewe 2016).

Participants' baseline characteristics differed between trials. The mean duration of cervical dystonia ranged from 4.8 years to 12.1 years, though the distribution was generally equivalent between treatment and placebo arms in each trial, exceeding a three-year difference in one study only (Greene 1990). One study did not report this information (Lew 2018). The overall disease impairment at baseline was moderate to severe in all trials, with scores ranging from 41.8 to 46.2 on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), 13.9 to 14.4 on the Tsui scale, and 9.2 to 9.3 on the Cervical Dystonia Severity Scale (CDSS).

Only two studies exclusively enrolled participants who had never been exposed to botulinum toxin (Greene 1990; Poewe 1998). For all other trials, between 61% and 100% of participants had received prior treatment with botulinum toxin, with time since last injection before study entry ranging from 10 weeks to 18 weeks. All but one small trial excluded clinical forms of cervical dystonia associated with a poorer response to botulinum toxin, such as pure anterocollis and retrocollis (Greene 1990). We deemed all other studies to be at high risk of bias for this domain. As a result, the population characteristics across studies did not allow us to conduct a subgroup analysis for people naive and non-naive to botulinum toxin.

The number of dropouts among trials varied from 3% to 6% at week eight (Comella 2011; Poewe 1998), to as high as 21% at week 10 (Charles 2012), and 58% at week 12 (Lew 2018). Two studies showed considerably higher proportions of dropouts, ranging from 54% as early as week 8, to 70% at week 12; in Truong 2005, reasons for dropouts were not reported by the trial authors; in Lew 2018, most study dropouts were related to participants being offered the opportunity to enter an open-label extension.

Overall, the number of dropouts was higher among participants allocated to placebo arms: 24% (74/289) of the participants allocated to placebo withdrew, compared to 11% (49/416) of participants allocated to BtA. In trials that reported the reasons for dropping out, lack of efficacy was one of the most frequent reasons given, accounting for half (45/217) of total dropouts in placebo arms, and for 23% (13/302) in BtA arms. Lew 2018 reported the most frequent dropout reason to be entering an open-label extension. In the intervention arms, 10% (5/273) reported adverse events as the reason they dropped out, compared to 0% (0/146) in the placebo arms.

#### *Study design and interventions*

Five trials used a fixed dose of 500 U of BtA formulation Dysport to compare with placebo (Poewe 1998; Poewe 2016; Truong 2005; Truong 2010; Wissel 2001; combined N = 515). In the same trial, Poewe 1998 further assessed low (250 U) and high (1000 U) doses of Dysport in two different arms (N = 37). One new study (N = 134) evaluated the same formulation of BtA up to 500 U, using a dilution factor of 500 U to 2 mL of dilution solution (Lew 2018). Two included studies compared BtA formulation Botox with placebo, with doses varying from 95 U to 360 U (Charles 2012; Greene 1990; combined N = 225). One study (N = 233) evaluating the BtA formulation Xeomin versus placebo used dosages of 120 U and 240 U (Comella 2011). All studies but two were designed to allow one single treatment session (Poewe 2016; Truong 2010).

Four studies gave the BtA injection without electromyography (EMG) guidance (Charles 2012; Greene 1990; Poewe 1998; Wissel

2001). For about half of the participants (N = 563), EMG guidance was left to the discretion of the investigator performing the injection (Comella 2011; Lew 2018; Truong 2005; Truong 2010).

Trial duration ranged from 8 weeks to 20 weeks post-injection. Most participants ended the trial between weeks 8 and 12, determined by the clinical need for reinjection, or dropping out. In one study, participants were allowed to enter an open-label extension, but no further information was provided (Lew 2018).

All studies except three, assessed efficacy and other primary outcomes using an intention-to-treat (ITT) analysis, which included all participants randomised to treatment (Charles 2012; Lew 2018; Poewe 1998). Four studies performed the safety assessment on a per-protocol (PP) population, which only included participants who had received a dose of study medication (Comella 2011; Greene 1990; Lew 2018; Truong 2010).

### Excluded studies

We listed all the excluded studies, together with reasons for their exclusion, in the 'Characteristics of excluded studies' table.

## Risk of bias in included studies

See Characteristics of included studies 'Risk of bias' table.

We evaluated the included studies using a modified version of the Cochrane 'Risk of bias' tool. See Figure 2 and Figure 3 for the 'Risk of bias' summary graphs. We based these assessments on the information available in the primary report.

**Figure 2. Risk of bias of included studies: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies**

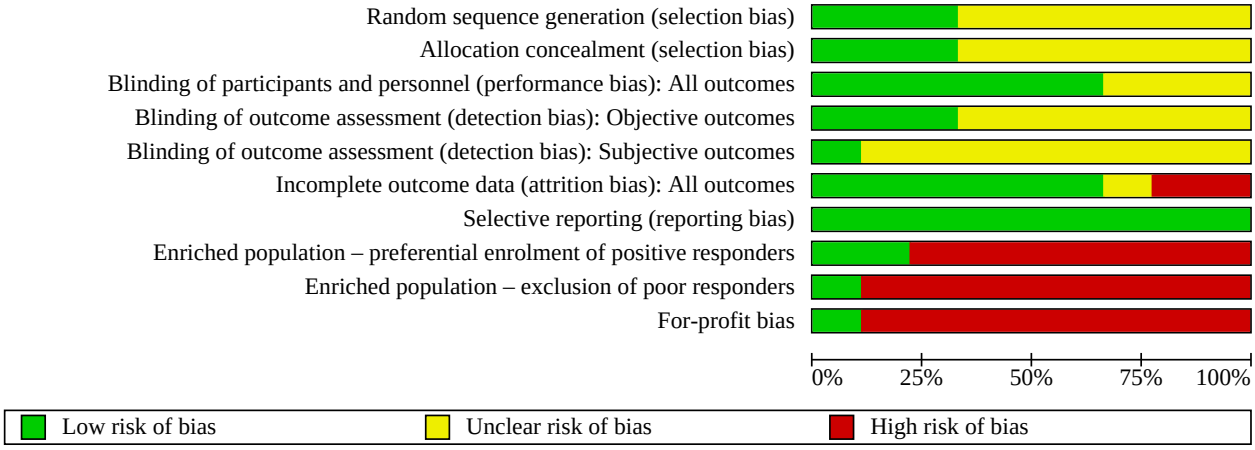
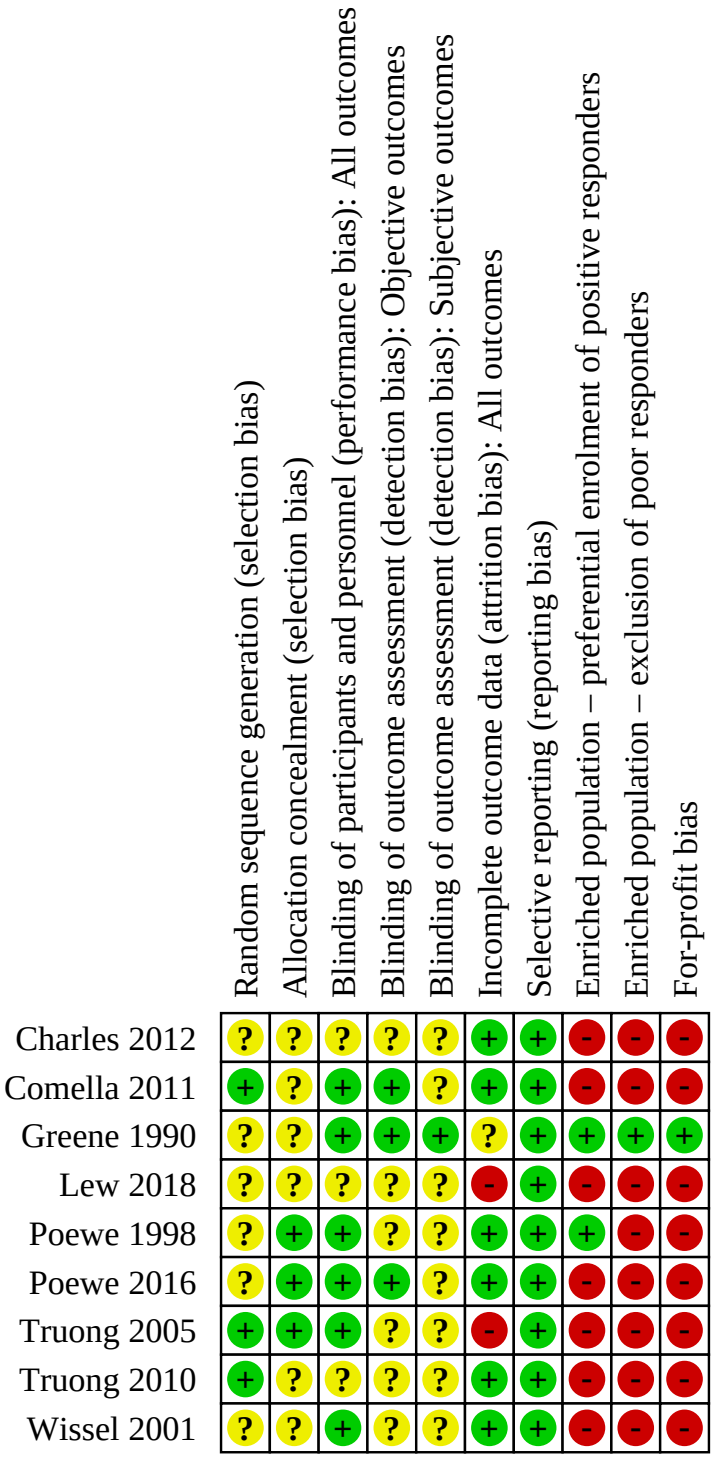


**Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study**



Overall, we did not consider any studies to be at low risk of bias across all domains. We considered three domains at high risk of bias: attrition bias, enriched population, and for-profit bias. It is noteworthy that all trials but one had a high risk of both for-profit bias and enriched population.

#### Allocation

Three studies clearly described the process of random sequence generation (Comella 2011; Truong 2005; Truong 2010); we assessed the other six studies to be at unclear risk of bias for this criterion. Poewe 1998, Poewe 2016, and Truong 2005 described an adequate allocation concealment process, and we rated them at a low risk of bias. All but one of the included trials reported a higher disease impairment at baseline in the control arm, although it is unclear whether these differences were either statistically or clinically relevant. This led us to assess the overall risk of selection bias across the included trials to be a serious cause for concern, despite the fact that overall, no one trial was uniquely responsible for this assessment.

#### Blinding

We judged the blinding of participants and personnel involved in the trial to be at a low risk of bias in six studies; three trials did not describe enough information to allow us to make a clear judgment (Charles 2012; Lew 2018; Truong 2010).

We considered that only Greene 1990 had adequately blinded participants and investigators measuring both objective and subjective outcomes. For the assessment of objective outcomes, we also judged Comella 2011 to be at low risk. We considered that the remaining studies were at an unclear risk of bias across this domain.

#### Incomplete outcome data

Six out of nine studies summarised the reasons for missing data and used appropriate statistical tools to deal with it, and we rated them at low risk of bias. Greene 1990 reported missing data across the study visits, so we assessed it as unclear risk of attrition bias. Truong 2005 and Lew 2018 reported a large number of dropouts in both intervention arms; we rated them at a high risk of attrition bias.

#### Selective reporting

We considered all studies to be at low risk for reporting bias.

#### Other potential sources of bias

##### *Enriched population*

Four studies preferentially enrolled participants known to have previously responded to BtA treatment; we judged them at high risk of bias (Charles 2012; Lew 2018; Poewe 2016; Truong 2010). All studies except one excluded people with forms of cervical dystonia known to have a poorer clinical response to BtA injection; we also considered them at a high risk of bias (Greene 1990).

##### *For-profit bias*

All trials but one declared funding or the supply of study vials from industry sources, and we rated them at a high risk of bias for funding and potential conflicts of interest (Greene 1990).

##### *Publication bias*

We intended to use funnel plots to explore publication bias. However, due to the small number of included studies, we considered the power of this analysis to be inadequate (Sterne 2011).

### Effects of interventions

See: **Summary of findings 1** Botulinum toxin type A compared to placebo for cervical dystonia

The key results of this review can be found in Summary of findings 1.

#### Preceding data analysis

See Dealing with missing data.

Poewe 1998, Poewe 2016, and Truong 2005 did not report standard deviations (SD) for the primary outcome, so, we imputed them from Wissel 2001, Truong 2010, and Truong 2010, respectively, since they used the same scale, time point, and error measurement to assess the same outcome.

Charles 2012 did not report the absolute numerical values for the primary outcome at week four, so, two review authors independently extracted these data from the graph provided in the report. Since the two review authors reported very similar values, we imputed these data (mean values from the two review authors) and used them for analysis.

Poewe 1998 and Comella 2011 presented data separately for each BtA dose, reporting sample sizes, means, and SD for each intervention group. In order to conduct pooled analyses, we combined the BtA groups, using a pooled SD formula for paired data.

#### Primary outcomes

##### *Cervical dystonia-specific improvement*

Following the initial injection of study medication, the included trials assessed the primary outcome at either week four (Charles 2012; Comella 2011; Lew 2018; Poewe 1998; Poewe 2016; Truong 2005; Truong 2010; Wissel 2001), or week six (Greene 1990). Most trials reported the primary efficacy outcome as the change from baseline, using validated scales: the CDSS (Charles 2012), the Tsui scale (Poewe 1998; Wissel 2001), and the TWSTRS (Comella 2011; Lew 2018; Poewe 2016; Truong 2005; Truong 2010). Greene 1990 did not report objective efficacy measurements. The CDSS uses a protractor and wall chart to rate the severity of the head's deviation. The Tsui scale (range, 0 to 25) grades severity of postural deviance, acknowledging the presence of tremor and the pattern of movements; it does not assess disability, pain, or other subjective symptoms. TWSTRS (range 0 to 85) is composed of three subscales that grade severity (range 0 to 35), disability (range 0 to 30), and pain (range 0 to 20). Tarsy 1997 demonstrated that after botulinum toxin therapy, score reduction rates from the Tsui and TWSTRS correlated with each other.

Eight trials (N = 962) contributed data for this outcome (Charles 2012; Comella 2011; Lew 2018; Poewe 1998; Poewe 2016; Truong 2005; Truong 2010; Wissel 2001).

Treatment with BtA resulted in a moderate to large improvement in cervical dystonia-specific symptoms at 4 weeks (standardised

mean difference (SMD) 0.71, 95% CI 0.55 to 0.87; $I^2$ = 26%; 8 trials, 962 participants; moderate-certainty evidence; Analysis 1.1).

Treatment with BtA resulted in an improvement at 4 weeks on the TWSTRS total score compared to placebo (mean difference (MD) 8.09 points, 95% CI 6.22 to 9.96; $I^2$ = 0%; 5 trials, 651 participants; Analysis 1.2). This represents an 18.6% improvement compared to the baseline clinical status (43.55 points combined baseline score), and reached the threshold for the minimal clinical important difference (Espay 2018).

Treatment with BtA resulted in an improvement at 4 weeks on the TWSTRS severity subscale (MD 3.13 points, 95% CI 2.15 to 4.11; $I^2$ = 0%; 3 trials, 429 participants; Analysis 1.3), and on the TWSTRS disability subscale (MD 2.52 points, 95% CI 1.72 to 3.31; $I^2$ = 23%; 3 trials, 429 participants; Analysis 1.4).

For the Trial Sequential Analysis (TSA), we could not use the results of the overall improvement, since these data were only available as SMD (Thorlund 2011). Thus, we used the data from trials that used the TWSTRS. To calculate the required information size, we assumed a baseline TWSTRS of 42 points and a SD of 10. Given these constraints, the cumulative evidence overcame the heterogeneity-adjusted required information size of 180 participants. We concluded that the cumulative evidence was adequately powered to demonstrate the 8.09 TWSTRS point difference at week four between BtA and placebo.

#### 1.1. Overall improvement with high versus medium versus low dose of BtA subgroup analysis

We carried out a subgroup analysis to assess overall improvement according to the BtA doses used. Considering the current evidence behind the potency equivalence between BtA formulations, we assigned arbitrary thresholds for high, medium, and low doses of BtA. One study reported a range of BtA doses that crossed our arbitrary dose classifications, therefore, we did not include it in this analysis (Charles 2012).

All three dosages were efficacious against placebo (high dose: SMD 0.92, 95% CI 0.63 to 1.21; $I^2$ = 29%; 3 trials, 322 participants; medium dose: SMD 0.76, 95% CI 0.59 to 0.94; $I^2$ = 0%; 6 trials, 545 participants; low dose: SMD 1.24, 95% CI 0.55 to 1.94; 1 trial, 39 participants). We did not find a distinction in efficacy between the subgroups (P = 0.31; Analysis 1.5).

#### 1.2. Overall improvement with Botox versus Dysport versus Xeomin subgroup analysis

We carried out a subgroup analysis to assess overall improvement according to BtA formulation.

All three formulation were efficacious against placebo (Botox: SMD 0.38, 95% CI 0.08 to 0.69; 1 trial, 170 participants; Dysport: SMD 0.75, 95% CI 0.58 to 0.93; $I^2$ = 0%; 6 trials, 559 participants; Xeomin: SMD 0.82, 95% CI 0.53 to 1.10; 1 trial, 233 participants). We did not find a distinction in efficacy between the subgroups (P = 0.08; Analysis 1.6).

#### 1.3 Overall improvement with EMG-guided versus non-EMG-guided injections subgroup analysis

We carried out a preplanned subgroup analysis to assess the comparative efficacy of BtA in trials that used EMG versus trials that did not use EMG.

Both techniques were efficacious against placebo (EMG-guided: SMD 0.72, 95% CI 0.56 to 0.88; $I^2$ = 0%; 5 trials, 651 participants); non-EMG-guided: SMD 0.79; 95% CI 0.27 to 1.31; $I^2$ = 75%; 3 trials, 311 participants). We did not find a distinction in efficacy between the subgroups (P = 0.79; Analysis 1.7). All five trials that used EMG-guided injections left the use of EMG to the discretion of the investigator (i.e. clinical judgement).

### *Adverse events*

Eight trials (N = 1085) contributed data for this outcome (Charles 2012; Comella 2011; Lew 2018; Poewe 1998; Poewe 2016; Truong 2005; Truong 2010; Wissel 2001). Adverse events were measured as the proportion of participants who experienced any adverse event during any point during follow-up. Adverse events related to BtA were reported by 51.2% of the participants in the BtA groups, compared to 43.8% of the participants in the placebo arms.

Treatment with BtA resulted in a 23% increase in the risk of adverse events compared with placebo (risk ratio (RR) 1.23; 95% CI 1.05 to 1.43; $I^2$ = 28%; 8 trials, 1085 participants; moderate-certainty evidence; Analysis 1.8). The number needed to treat for an additional harmful outcome (NNTH) with a single BtA treatment was 9 (95% CI 6 to 21).

To calculate the required information size with a TSA, we assumed a control event rate of 46%. Given this constraint, the cumulative evidence overcame the heterogeneity-adjusted required information size of 892 participants. We concluded that the cumulative evidence is adequately powered to demonstrate the 23% risk difference in adverse events between BtA and placebo.

#### 2.1 Adverse events with high versus medium versus low dose of BtA subgroup analysis

We carried out a subgroup analysis to assess the risk of adverse events according to the BtA dosages used. Considering the current evidence behind the potency equivalence between BtA formulations, we assigned arbitrary thresholds for low, medium, and high doses of BtA.

A low dose of BtA did not result in an increase in adverse events over placebo (RR 1.47, 95% CI 0.56 to 3.85; 3 trials, 326 participants; but there were more adverse events with a medium dose (RR 1.23, 95% CI 1.06 to 1.44; 6 trials, 664 participants), and a high dose (RR 1.79, 1.03 to 3.11; 1 trial, 39 participants; Analysis 1.9) over placebo.

The risk of adverse events between the subgroups of studies was not heterogeneous (P = 0.42; Analysis 1.9).

#### 2.2 Adverse events with Botox versus Dysport versus Xeomin subgroup analysis

We carried out a subgroup analysis to assess the risk of adverse events according to BtA formulation: Botox (Charles 2012); Dysport (Lew 2018; Poewe 1998; Poewe 2016; Truong 2005; Truong 2010; Wissel 2001); Xeomin (Comella 2011).

A dose of Botox did not result in an increase of adverse events over placebo (RR 1.01, 95% CI 0.78 to 1.30; 1 trial, 170 participants); nor did a dose of Xeomin (RR 1.22, 95% CI 0.92 to 1.62; 1 trial, 233 participants); but there were more adverse events following a dose of Dysport (RR 1.37, 95% CI 1.07 to 1.76; 6 trials, 549 participants; Analysis 1.10).

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The risk of adverse events between these subgroups of studies was not heterogenous (P = 0.23; Analysis 1.10).

#### 2.3 Adverse events with EMG-guided versus non-EMG-guided injections subgroup analysis

We carried out a subgroup analysis to assess the risk of adverse events in trials that used EMG versus trials that did not use EMG.

Non-EMG-guided injections did not results in an increase of adverse events (RR 1.43, 95% CI 0.82 to 2.50; 3 trials, 312 participants), but EMG-guides injections did (RR 1.21, 95% CI 1.06 to 1.38; 5 trials, 773 participants; Analysis 1.11). All five trials that used EMG-guided injections left the use of EMG to the discretion of the investigator.

The risk of adverse events between these subgroups of studies was not heterogenous (P = 0.56; Analysis 1.11).

#### 2.4 Adverse events of special interest

Treatment with BtA resulted in an increased risk for three adverse events of special interest: dysphagia (RR 3.19, 95% CI 1.79 to 5.70; $I^2$ = 0%; 9 trials, 1140 participants; moderate-certainty evidence; Analysis 1.12), diffuse weakness or tiredness (RR 1.80, 95% CI 1.10 to 2.95; $I^2$ = 0%; 7 trials, 956 participants; moderate-certainty evidence; Analysis 1.13), and neck weakness (RR 3.40, 95% CI 1.19 to 9.71; $I^2$ = 15%; 5 trials, 410 participants; Analysis 1.14). The NNTH with a single BtA treatment for dysphagia was 51 (95% CI 44 to 76); for diffuse weakness or tiredness, it was 36 (95% CI 27 to 114); and for neck weakness it was 47 (95% CI 38 to 146).

Treatment with BtA was did not result in an increased risk for the remaining adverse events that were reported in the included trials included: voice changes or hoarseness (RR 1.83, 95% CI 0.37 to 8.95; $I^2$ = 26%; 2 trials, 154 participants; Analysis 1.15); sore throat or dry mouth (RR 1.66, 95% CI 0.78 to 3.51; $I^2$ = 5%; 3 trials, 222 participants; Analysis 1.16); vertigo or dizziness (RR 1.47, 95% CI 0.38 to 5.73; $I^2$ = 0%; 2 trials, 154 participants; Analysis 1.17); malaise or upper respiratory infection (RR 1.35, 95% CI 0.69 to 2.65; $I^2$ = 39%; 8 trials, 1085 participants; Analysis 1.18); injection site pain (RR 1.38, 95% CI 0.91 to 2.09; $I^2$ = 0%; 8 trials, 970 participants; Analysis 1.19); and headache (RR 1.12, 95% CI 0.64 to 1.97; $I^2$ = 0%; 7 trials, 839 participants; Analysis 1.20).

### Secondary outcomes

#### *Subjective evaluation of clinical status*

The included trials assessed subjective evaluation of overall improvement by both physicians and participants between weeks three and six after BtA injection. They used six scales to evaluate the amount of improvement: the Patient Evaluation of Global Response (PEGR), the Global Assessment of Change (GAS), the visual analogue scale (VAS), the Clinical Global Rating, the Clinical Global Impression of Change (CGIC), and the Patient Global Impression of Change (PGIC). The PERG and GAS are similar scales, ranging from -4 (very marked worsening) to +4 (complete resolution of cervical dystonia symptoms). VAS (range 0 mm to 100 mm) assesses the change from baseline in symptom severity, where 0 mm indicates much worse, 50 mm = no change, and 100 mm = symptom-free. The Clinical Global Rating measures six grades of efficacy (excellent, good, moderate, slight improvement, no change, condition worse), and four grades of adverse events (none, mild, moderate, extreme). The Clinical Global Impression of Change measures seven grades of efficacy (very much improved, much improved, improved, neutral, worse, much worse, very much worse). The Patient Global Impression of Change measures seven grades of efficacy (very much improved, much improved, improved, neutral, worse, much worse, very much worse).

The trials measured subjective assessments using these validated scales as the change from baseline to weeks 3 to 6.

We excluded data from three studies in the meta-analysis for this outcome. Greene 1990 reported no data for the control group, Poewe 2016 reported a change from baseline for both study groups but did not report a measure of dispersion, and Truong 2010 did not report the change from baseline.

#### 3.1. Subjective assessment by clinicians

Treatment with BtA resulted in an increased likelihood of clinical improvement compared to placebo, assessed by physicians between weeks 4 and 20 after drug injection (RR 1.88, CI 1.55 to 2.28; $I^2$ = 4; (5 trials, 675 participants); high-certainty evidence; Analysis 1.21). We calculated the number needed to treat for an additional beneficial outcome (NNTB) as 5 (95% CI 4 to 7) with a single BtA treatment session.

#### 3.2. Subjective assessment by participants

Treatment with BtA resulted in an increased likelihood of clinical improvement compared to placebo, assessed by the participants between weeks 4 and 20 after drug injection (RR 2.19, CI 1.78 to 2.70; $I^2$ = 0%; 6 trials, 755; high-certainty evidence; Analysis 1.22). We calculated an NNTB of 6 (95% CI 5 to 7) with a single BtA treatment session.

Two trials (N = 153) considered only those participants reporting more than a half of improvement from baseline, and therefore, these pooled results may underestimate the likelihood of participants reporting a subjective benefit with BtA treatment (Poewe 1998; Truong 2005).

#### *Pain relief*

Six trials contributed data to this outcome (Charles 2012; Comella 2011; Greene 1990; Truong 2005; Truong 2010; Wissel 2001). They measured pain relief with validated pain scales as the change from baseline to weeks three to six.

Participants reported that treatment with BtA provided moderate pain relief at weeks four to six (SMD 0.50, 95% CI 0.35 to 0.65; $I^2$ = 0%; 6 trials, 722 participants; moderate-certainty evidence; Analysis 1.26).

Participants reported that treatment with BtA resulted more pain relief than placebo (MD 2.11 TWSTRS points, 95% CI 1.38 to 2.83; $I^2$ = 0%; 3 trials, 429 participants; moderate-certainty evidence; Analysis 1.27).

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

Three studies assessed the impact of BtA on quality of life (Poewe 2016; Truong 2005; Truong 2010).

Poewe 2016 (N = 213) used the Cervical Dystonia Impact Profile (CDIP)-58 scale, including eight subscales: head and neck symptoms, pain and discomfort, sleep, upper limb activities,

walking, annoyance, mood and psychosocial functioning. They reported an improvement in total CDIP-58 score (49.3 in BtA versus 59.4 in placebo; P < 0.0001), and in all eight CDIP-58 subscales (P < 0.0003).

Truong 2005 (odds ratio (OR) 1.60; P = 0.011; N = 80) and Truong 2010 (MD 10.10, 95% CI 2.95 to 17.25; P = 0.018; 116 participants) reported an improvement from baseline to week eight in the physical function domain of the SF-36 for the BtA group over placebo. They did not report improved social functioning when compared to placebo (Truong 2005: OR 0.30, 95% CI -0.23 to 0.82; P = 0.265; Truong 2010: MD 6.90, 95% CI -2.31 to 16.11; P = 0.160).

#### *Tolerability*

Adverse drug reactions (ADRs) can be caused by the intervention (i.e. type A, type B ADRs, or both), or can be classified as such due to lack of efficacy of the treatment (i.e. failure of therapy, a type F ADR; Edwards 2000). Either cause can lead to dropping out of the trial.

BtA treatment resulted in a decreased likelihood of dropping out for any reason (RR 0.48, 95% CI 0.32 to 0.73; $I^2$ = 24%; 5 trials, 705 participants; high-certainty; Analysis 1.30).

BtA treatment resulted in a decreased likelihood of dropping out of trials due to lack of efficacy (RR 0.30, 95% CI 0.17 to 0.53; $I^2$ = 0%; 3 trials, 519 participants; high-certainty evidence; Analysis 1.31).

The results were inconclusive between BtA and placebo for dropouts due to adverse events (RR 2.51; 95% CI 0.42 to 14.94; $I^2$ = 0%; 3 trials, 419 participants; high-certainty evidence; Analysis 1.32).

#### *Duration of effect*

We did not pool results for this outcome due to the lack of combinable data. Only two trials assessed multiple BtA treatment sessions, though neither compared BtA treatment with placebo. Five studies assessed the duration of effect on participants who showed some level of response to the assigned study treatment, either BtA or placebo.

Lew 2018 reported the proportion of responders to the allocated intervention, defined as ≥ 30% reduction in TWSTRS total score, at two and four weeks. At two weeks, there were 27.9% (95% CI 18.8 to 38.6) responders in the BtA arm and 11.4% (95% CI 3.8 to 24.6) in the placebo arm. At four weeks, there were 41.9% (95% CI 31.3 to 53.0) responders in the BtA arm and 11.1% (95% CI 3.7 to 24.1) in the placebo arm.

Poewe 1998 reported a dose-dependent duration of effect. Participants requested re-injection at week eight in 39% of those who received high doses, 50% of those who received a medium or low dose, and 94% of participants treated with placebo.

Poewe 2016 evaluated response to BtA over five treatment cycles. They reported that the duration of treatment effect for treatment responders was more than 85 days from treatment cycles 2 to 5, regardless of the dose used.

Truong 2005 reported a mean duration of effect of 22.8 weeks (SD 12.5 weeks; range 9 to 46 weeks) until symptoms came back.

Truong 2010 reported a mean time to re-treatment of 14.4 weeks (range 4 to 30 weeks).

## DISCUSSION

### Summary of main results

This updated review included nine randomised, parallel-designed trials, which enrolled 1144 people with cervical dystonia, 74% of whom had been previously treated with botulinum toxin for their condition.

As seen in Summary of findings 1, in comparison to placebo, botulinum toxin type A (BtA) was likely to be more efficacious in reducing cervical dystonia-specific overall impairment and associated pain. Treatment with BtA also increased the likelihood that participants and clinicians would detect any form of improvement. Uncertainty remains over the effect of BtA on other domains of people's quality of life, such as social functioning, and on the duration of treatment effect.

However, treatment with BtA increased the risk of experiencing an adverse event. In particular, BtA increased in the risk of three specific adverse events of special interest: dysphagia, diffuse weakness or tiredness, and neck weakness. No included study reported fatalities or serious adverse events related to BtA treatment. Finally, treatment with BtA slightly decreased the risk of dropping out of the trials. Data for special subpopulations, such as children and pregnant women, were not available.

We found low to moderate statistical heterogeneity ($I^2$ < 40%) for most efficacy and safety outcome estimates.

#### BtA doses

All doses were efficacious against placebo, but we found no clear evidence of a dose-response gradient. However, these trials were not dose-response studies. They were not adequately powered to assess this question, and we based this conclusion on arbitrarily defined dose subgroup analyses.

#### BtA formulations

Although none of the trials was designed or powered to evaluate the comparative utility of the three most widely used formulations of BtA (Botox (onabotulinumtoxinA), Dysport (abobotulinumtoxinA), and Xeomin (incobotulinumtoxinA)), we did not find divergences between these subgroups for overall efficacy or safety.

#### Use of electromyography (EMG)

None of the trials was designed to evaluate the comparative utility of an injection technique with or without EMG. As most trials allowed for EMG use according to the investigator's criteria, and these data were not presented, we cannot determine whether or not the use of EMG had an impact on efficacy or safety.

#### Duration of effect

Results from the few studies that addressed the duration of clinical effect of a treatment cycle were inconclusive, with time to re-treatment ranging greatly, from 1 to 11 months. We could not adequately evaluate long-term duration of effect, as all trials but two evaluated only a single treatment session.

### Overall completeness and applicability of evidence

All included trials addressed the primary research question directly, using similar and validated assessment tools. However, they did not fully report data for all outcomes, and in some cases, we could not pool results or compare them across studies. This limited the amount of data available, and consequently, the confidence in overall conclusions for under-reported outcomes.

The participants included in the trials were not fully representative of the overall population of people with cervical dystonia. The effects of population enrichment, and the moderate overall disease impairment (as assessed by the baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores) preclude definite conclusions concerning all people with this condition. The proportion of participants with any adverse event was high in both the BtA and placebo arms, as is common in movement disorders research, a large nocebo effect which may mask safety conclusions (Duarte 2018; Rato 2018; Rato 2019; Silva 2017).

Four noteworthy factors challenge the implementation of the evidence in this review. First, there was a considerably heterogeneous regional distribution, with most trials conducted in North America and Europe. Differences in clinical practice, training of experts, and local guidelines in other regions of the world may present an obstacle to the application of the evidence. Second, sample size across included trials was relatively small and subgroup analyses addressing clinically relevant questions for the main outcomes may have been underpowered. More studies are needed to provide robust evidence for these questions. Third, the use of enriched populations in clinical trials limits applicability of results into clinical practice, as complex and potentially poorer responders, such as pure anterior or retrocollis, are usually excluded from these trials, further complicating issues of generalisation. Fourth, it is common for people with cervical dystonia to be taking concomitant medications for their condition, such as muscle relaxants and benzodiazepines. Reasonably, participants are required to be on a stable dose of these medications for many weeks prior to entering the trial, to avoid confounding factors. As a result, little is known about the impact of these drugs on the efficacy and safety of BtA treatment.

### Quality of the evidence

See Characteristics of included studies, 'Risk of bias' tables, 'Risk of bias' summary tables (Figure 2; Figure 3), and Summary of findings 1.

We considered all included trials but one to be at a high risk for both for-profit bias and for having an enriched population. Only three of the included studies adequately described the randomisation or allocation methods, or both, while we assessed the remaining trials as unclear risk of bias for these items. We considered most studies to be appropriately blinded in general. However, only a single trial provided a satisfactory description of blinding of an objective outcome assessment, and we considered all but one possibly biased for a subjective outcome assessment, as studies predominantly enrolled participants with previous exposure to botulinum toxin. This represents a major methodological limitation that may have resulted in a biased assessment of the intervention effect, particularly with subjective outcomes, such as pain assessment, subjective assessment by participants and clinicians, and quality of life assessments, which are highly susceptible to biased estimations.

We could not compare some outcomes across studies, as some studies did not report relevant data. We were unable to impute values for missing data due to imbalances between baseline characteristics of the participants, and incomplete description of the variables, further reducing the amount of combinable data, and therefore our confidence in the results.

The included trials each enrolled between 55 and 233 participants, and although individually, some of these trials were underpowered, the pooling of the trials permitted an adequate sample size for the primary efficacy outcome.

For duration of effect, only 3 studies contributed with data and in a heterogeneous way, limiting both our ability to assess this outcome and our confidence in the evidence available.

As seen in Summary of findings 1, there is moderate certainty in the evidence that a single treatment session of BtA improves overall cervical dystonia-specific impairment in certain types of cervical dystonia, and pain. There is moderate certainty in the evidence supporting the higher occurrence of any adverse event with BtA. There is high certainty in the evidence that participants reported feeling better in the subjective evaluation of clinical status. Finally, there is high certainty in the evidence that treatment with BtA increases the likelihood of participants staying in the trials.

### 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 have extensively contacted other experts in this field, and US and European trials in this area are well known.

An additional bias was that we were unable to obtain data for all outcomes in the included trials. A further limitation of this review is the small number of participants contributing data to each outcome, although Trial Sequential Analysis showed that both the primary efficacy and safety outcomes were adequately powered to demonstrate the effects that we observed.

### Agreements and disagreements with other studies or reviews

Overall, the results of this updated review are in agreement with the conclusions of earlier versions (Costa 2005; Castelão 2017). The current clinical practice guidelines of the American Academy of Neurology and the European Academy of Neurology state that BtA is "established as safe and effective for cervical dystonia treatment" (Simpson 2016), and that it is considered an "effective and safe treatment for cervical dystonia" (Albanese 2011). We now conclude that no claims can be made regarding a clear dose-response relationship for efficacy outcomes.

## AUTHORS' CONCLUSIONS

### Implications for practice

In this updated Cochrane Review, we found that a single treatment session of botulinum toxin type A (BtA) is effective and well-tolerated in the treatment of moderately impaired adults with certain types of cervical dystonia. The clinical benefit includes moderate to large improvements in severity, disability, and pain. The benefit is also meaningful when subjectively assessed by participants. The evidence is less robust regarding health-related quality of life improvements. Adverse events are frequent, but are not commonly associated with discontinuing treatment. In fact, since dropouts were less frequent in the BtA group, we can assume that people with cervical dystonia find the risk-benefit profile of BtA to be favourable. Dysphagia, diffuse weakness or tiredness, and neck weakness are the most frequent treatment-related adverse events of special interest. We are moderately certain about the conclusions based on the evidence.

The available evidence does not allow us to draw conclusions on the existence of a clear dose-benefit response, support or refute the routine use of electromyography (EMG)-guided BtA injections, or to determine the comparative risk-benefit profiles of the different BtA formulations available.

We can draw no conclusions for people with pure retrocollis or anterocollis, as they were predominantly excluded in the clinical trials.

### Implications for research

We had access to published research data from trials of BtA versus placebo, in adults with certain types of cervical dystonia. The net benefit of a single BtA injection in the treatment of cervical dystonia was not clearly established in the published trials, making it difficult to determine which, and how many resources should be invested in future research. Essentially, the clinical benefit and utility of BtA is not in doubt, although the magnitude of this benefit, as with other movement disorders, is liable to vary in a real-world setting (Duarte 2018; Rodrigues 2019).

Nonetheless, further studies are needed to establish the relative effectiveness of different doses of BtA, assessing efficacy, safety, duration of effect, and quality of life across regimens. They should consider repeated BtA treatment sessions, and assess these factors under conditions more closely resembling clinical practice (pragmatic clinical trials). Because therapy typically requires optimising a dose for each person, rather than administering a fixed dose of botulinum toxin, such a line of research would be important to support physicians' management of doses, and allow a more solid and safe individualisation of treatment. Also to be determined is the added value, if any, of guidance methods (e.g. EMG) for injecting botulinum toxin into the cervical muscles.

Future research concerning 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). Research is required to establish such a parameter for the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), currently the most widely used and disseminated clinical scale in the field. We are aware of an effort to create a new clinical scale in dystonia - the Comprehensive Cervical Dystonia Rating Scale, which will include a revision of the TWSTRS, to be named TWSTRS-2, with plans in the works to validate a minimal clinically important change (Comella 2015).

It is currently uncertain whether or not the clinical effectiveness of botulinum toxin decays over 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 systematic review, we were faced with the fact that there is no defined core outcome set in cervical dystonia research, as there are for other areas (Tugwell 2007). To promote research in this field, and to support the clinical effectiveness of botulinum toxin, it would be relevant to define a set of core outcome measures, and include it in future research, via well-established methodology, to determine the inclusion of participant-reported outcomes (Macefield 2014).

Given the high degree of certainty in the results, and the fact that most of the outcomes are adequately-powered and provide robust evidence of efficacy, future efforts to update this review may not be justified, unless Cochrane methodology changes or some of the research suggestions are published.

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# REFERENCES

## References to studies included in this review

**Charles 2012** *{published data only}*10.1097/WNF.0b013e31826538c7

Brashear A, Truong D, Charles D, Comella C, Hauser RA, Tsui J. A randomized double-blind, placebo-controlled study of intramuscular botox for the treatment of cervical dystonia (CD). *Movement Disorders* 1998;**13**(Suppl 2):276 (P4.243).

* Charles D, Brashear A, Hauser RA, Li HI, Boo LM, Brin MF, CD 140 Study Group. Efficacy, tolerability, and immunogenicity of onabotulinumtoxinA in a randomized, double-blind, placebo-controlled trial for cervical dystonia. *Clinical Neuropharmacology* 2012;**35**(5):208-14.

Hauser RA, Comella C, Brashear A, Truong D, Charles PD, Tsui J. A randomized, multicenter, placebo-controlled study of original botox (botulinum toxin type A) purified neurotoxin complex for the treatment of cervical dystonia. *Movement Disorders* 2000;**15**(Suppl 2):30.

**Comella 2011** *{published data only}*

* Comella CL, Jankovic J, Truong DD, Hanschmann A, Grafeon S, on behalf of the US Xeomin Cervical Dystonia Study Group. Efficacy and safety of incobotulinumtoxinA (NT 201, XEOMIN®, botulinumneurotoxin type A, without accessory proteins) in patients with cervical dystonia. *Journal of the Neurological Sciences* 2011;**308**(1-2):103-9. [DOI: 10.1016/j.jns.2011.05.041.]

Coulonn J-M. Incobotulinumtoxin A (Xeomin) injected with flexible intervals is a well-tolerated long-term treatment of cervical dystonia. *Annals of Physical and Rehabilitation Medicine* 2013;**56**:e398.

Evidente VG, Brashear A, Comella CL, Fernandez H, Grafe S, LeDoux MS, et al. IncobotulinumtoxinA (Xeomin; botulinumneurotoxin type A, free from accessory proteins): flexibility of dosing and injection intervals in cervical dystonia. *PM&R* 2011;**3**(10S1):S215 (P131).

Evidente VG, Truong D, Jankovic J, Comella CL, Grafe S, Hanschmann A. IncobotulinumtoxinA (Xeomin®) injected for blepharospasm or cervical dystonia according to patient needs is well tolerated. *Journal of the Neurological Sciences* 2014;**346**(1-2):116-20. [DOI: 10.1016/j.jns.2014.08.004] [MEDLINE: 25186131]

Fernandez H, Truong D, Asmus F, Hanschmann A, LeDoux M. IncobotulinumtoxinA (Xeomin®) remains well tolerated across flexible inter-injection intervals of 6-20 weeks in the treatment of cervical dystonia. *Neurology* 2012;**78**(Meeting Abstracts 1):P01.219.

Fernandez HH, Evidente VG, Truong D, Brodsky M, Hanschmann A, Comella CL, et al. Long-term treatment of blepharospasm and cervical dystonia: incobotulinum toxin A is well tolerated when injected at flexible intervals based on patient needs. *Journal of the Neurological Sciences* 2013;**333**:109-51 (P1070).

Fernandez HH, Pappert EJ, Comella CL, Evidente VG, Truong DD, Verma A, et al. Efficacy and safety of incobotulinumtoxinA in subjects previously treated with botulinum toxin versus toxin-naïve subjects with cervical dystonia. *Tremor and Other Hyperkinetic Movements* 2013;**3**:1-9.

Grafe S, Comella C, Hanschmann A, Jankovic J, Truong D. Efficacy and safety of NT 201 (botulinum neurotoxin free from complexing proteins) in cervical dystonia. *PM&R* 2010;**2**(9S):S29 (P49).

Singer C, Pappert E, Hanschmann A, Fernandez H. IncobotulinumtoxinA (NT 201, Xeomin) administered at flexible intervals of 6-20 weeks in subjects with cervical dystonia. *Movement Disorders* 2012;**27**(Suppl 1):S365 (P1105).

Truong D, Fernandez H, Grafe S. IncobotulinumtoxinA (NT-201) injections are safe and effective in adult subjects with cervical dystonia across dosing intervals in a repeated dose-study. *Movement Disorders* 2011;**26**(Suppl 2):S211 (P625).

**Greene 1990** *{published data only}*

Greene P, Kang U, Fahn S, Brin M, Moskowitz C, Flaster E. Double-blind, placebo-controlled study of botulinum toxin injection for torticollis. *Neurology* 1988;**38**(Suppl 1):244.

* Greene P, Kang U, Fahn S, Brin M, Moskowitz C, Flaster E. Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. *Neurology* 1990;**40**(8):1213-8.

**Lew 2018** *{published data only}*

* Lew MF, Brashear A, Dashtipour K, Isaacson S, Hauser RA, Maisonobe P, et al. A 500 U/2 mL dilution ofabobotulinumtoxinA vs. placebo: randomized study in cervical dystonia. *International Journal of Neuroscience* 2018;**128**(7):619-26. [DOI: 10.1080/00207454.2017.1406935]

**Poewe 1998** *{published data only}*

Poewe W, Brans J, Kessler K, Kanovsky P, Odergren T, Aramideh M, et al. Dysport for cervical dystonia. *Movement Disorders* 2000;**15**(Suppl 2):7.

* Poewe W, Deuschl G, Nebe A, Feifel E, Wissel J, Benecke R, et al. What is the optimal dose of botulinum toxin A in the treatment of cervical dystonia? Results of a double blind, placebo controlled, dose ranging study using Dysport. German Dystonia Study Group. *Journal of Neurology, Neurosurgery and Psychiatry* 1998;**64**(1):13-7.

**Poewe 2016** *{published data only}*10.1002/mds.26760

Poewe W, Burbaud P, Castelnovo G, Jost WH, Ceballos-Baumann AO, Banach M, et al. Efficacy and safety of abobotulinumtoxinA liquid formulation in cervical dystonia: a randomized-controlled trial. Movement Disorders 21 September 2016 [Epub ahead of print]. [DOI: 10.1002/mds.26760]

**Truong 2005** *{published data only}*

Coleman CM, Chang SF, Copley-Merriman C, Hubble J, Masaquel C. Health-related quality of life improvements with

Dysport in cervical dystonia. *PM&R* 2011;**3 Suppl 1**(10):S190 (P41).

Hauser RA, Truong D, Hubble J, Coleman C, Beffy JL, Chang S, et al. AbobotulinumtoxinA (Dysport) dosing in cervical dystonia: an exploratory analysis of two large open-label extension studies. *Journal of Neural Transmission* 2013;**120**(2):299-307. [DOI: 10.1007/s00702-012-0872-1] [PMID: 22878514]

Jen M, Kurth H, Iheanacho I, Dinet J, Gabriel S, Wasiak R, et al. Improvement of SF-36 scores in cervical dystonia patients – is there a treatment effect when evaluating subscales? *Basal Ganglia* 2014;**126**:1-6.

* Truong D, Duane DD, Jankovic J, Singer C, Seeberger LC, Comella CL, et al. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: results of the first US randomized, double-blind, placebo-controlled study. *Movement Disorders* 2005;**20**(7):783-91.

Truong DD, Duane DD, Jankovic J, Singer C, Comella CL. The efficacy and safety of Dysport (botulinumtype A toxin) in cervical dystonia: results of the first US study. *Movement Disorders* 2002;**17**(Suppl 5):S306 (P1007).

**Truong 2010** *{published data only}*

Mordin M, Masaquel C, Abbott C, Copley-Merriman C. Factors affecting the health-related quality of life of patients with cervical dystonia and impact of treatment with abobotulinumtoxinA (Dysport): results from a randomised, double-blind, placebo-controlled study. *BMJ Open* 2014;**4**(10):e005150. [DOI: 10.1136/bmjopen-2014-005150] [PMID: 25324317]

* Truong D, Brodsky M, Lew M, Brashear A, Jankovic J, Molho E, et al, Global Dysport Cervical Dystonia Study Group. Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia. *Parkinsonism & Related Disorders* 2010;**16**(5):316-23. [DOI: 10.1016/j.parkreldis.2010.03.002] [MEDLINE: 20359934]

**Wissel 2001** *{published data only}*

Kanovsky P, Ruzicka E, Jech R, Roth J, Schnider P, Auff E, et al. Standardized dose of 500 Mu of Dysport for cervical dystonia: results of a prospective, randomized, double-blind, placebo-controlled study. *Movement Disorders* 2000;**15**(Suppl 2):31.

Poewe W, Brans J, Kessler K, Kanovsky P, Odergren T, Aramideh M, et al. Dysport for cervical dystonia. *Movement Disorders* 2000;**15**(Suppl 2):7.

* Wissel J, Kanovsky P, Ruzicka E, Bares M, Hortova H, Streitova H et al. Efficacy and safety of a standardised 500 unit dose of Dysport (clostridium botulinum toxin type A haemaglutinin complex) in a heterogeneous cervical dystonia population: results of a prospective, multicentre, randomised, double-blind, placebo-controlled, parallel group study. *Journal of Neurology* 2001;**248**(12):1073-8.

## References to studies excluded from this review

**Blackie 1990** *{published data only}*

* Blackie JD, Lees AJ. Botulinum toxin treatment in spasmodic torticollis. *Journal of Neurology, Neurosurgery and Psychiatry* 1990;**53**(8):640-3.

**Buchman 1994** *{published data only}*

Buchman AS, Comella CL, Stebbins GT, Weinstein SL. Determining a dose-effect curve for botulinum toxin in the sternocleidomastoid muscle in cervical dystonia. *Clinical Neuropharmacology* 1994;**17**(2):188-95.

**Gelb 1989** *{published data only}*

Gelb DJ, Arbor A, Don M, Yoshimura RKO, Lowenstein DH, Aminoff MJ. Change in pattern of muscle activity following botulinum toxin injections for torticollis. *Neurology* 1989;**39**(Suppl 1):320.

Gelb DJ, Lowenstein DH, Aminoff MJ. Botulinum toxin in the treatment of spasmodic torticollis. *Neurology* 1988;**38**(Suppl 2):244.

* Gelb DJ, Lowenstein DH, Aminoff MJ. Controlled trial of botulinum toxin injections in the treatment of spasmodic torticollis. *Neurology* 1989;**39**(1):80-4.

**Koller 1990** *{published data only}*

* Koller W, Vetere-Overfield B, Gray C, Dubinsky R. Failure of fixed-dose, fixed muscle injection of botulinum toxin in torticollis. *Clinical Neuropharmacology* 1990;**13**(4):355-8.

**Lange 1991** *{published data only}*

Lange DJ, Rubin M, Greene PE, Kang J, Moskowitz CB, Brin MF, et al. Distant effects of locally injected botulinum toxin: a double-blind study of single fiber EMG changes. *Muscle and Nerve* 1991;**14**:672-5.

**Lorentz 1991** *{published data only}*

Lorentz IT, Subramaniam SS, Yiannikas C. Treatment of idiopathic spasmodic torticollis with botulinum toxin A: a double-blind study on twenty-three patients. *Movement Disorders* 1991;**6**(2):145-50.

**Lu 1995** *{published data only}*

Lu CS, Chen RS, Tsai CH. Double-blind, placebo-controlled study of botulinum toxin injections in the treatment of cervical dystonia. *Journal of the Formosan Medical Association* 1995;**94**(4):189-92.

**Maurri 1990** *{published data only}*

Maurri S, Brogelli S. Botulinum toxin therapy for blepharospasm, hemifacial spasm and spasmodic torticollis: clinical studies with a follow-up of 40 months. *Movement Disorders* 1990;**5**(Suppl 1):73 (P262).

**Moore 1991** *{published data only}*

* Moore AP, Blumhardt LD. A double blind trial of botulinum toxin 'A' in torticollis, with one year follow-up. *Journal of Neurology, Neurosurgery and Psychiatry* 1991;**54**(9):813-6.

Moore AP, Blumhardt LD. Double blind study of botulinum toxin A in torticollis. *Journal of Neurology* 1991;**54**(9):813-6.

**Ostergaard 1994** *{published data only}*

Ostergaard L, Fuglsang-Frederiksen A, Werdelin L, Sjo O, Winkel H. Quantitative EMG in botulinum toxin treatment of cervical dystonia. A double-blind, placebo-controlled study. *Electroencephalography and Clinical Neurophysiology* 1994;**93**(6):434-9.

**Perlmutter 1989** *{published data only}*

Perlmutter JS, Tempel LW, Burde R. Double-blind, placebo-controlled, crossover trial of botulinum-A toxin for torticollis. *Neurology* 1989;**39**(Suppl 1):352.

**Relja 1993** *{published data only}*

* Relja M, Petravic D. Botulinum toxin type A injections for cervical dystonia: a double-blind, placebo controlled study. *The Canadian Journal of Neurological Sciences* 1993;**20**(Suppl 4):S185.

**Tsui 1986** *{published data only}*

Tsui JK, Eisen A, Stoessl AJ, Calne S, Calne DB. Double-blind study of botulinum toxin in spasmodic torticollis. *Lancet* 1996;**2**(2):245-7.

**Tsui 1988** *{published data only}*

Tsui J, Eisen A, Calne DB. Botulinum toxin in spasmodic torticollis. In: Stanley Fahn et al, editors(s). Advances in Neurology. New York: Raven Press, 1988:593-7.

**Yoshimura 1990** *{published data only}*

Yoshimura D, Aminoff M, Gelb D. Long term follow-up of patients treated with botulinum toxin for spasmodic torticollis. *Movement Disorders* 1990;**5**(Suppl 1):75 (P268).

## Additional references

**Abrams 2005**

Abrams KR, Gillies CL, Lambert PC. Meta-analysis of heterogeneously reported trials assessing change from baseline. *Statistics in Medicine* 2005;**24**:3823-44.

**Albanese 2011**

Albanese A, Asmus F, Bhatia KP, Elia AE, Elibol B, Filippini G, et al. EFNS guidelines on diagnosis and treatment of primary dystonias. *European Journal of Neurology* 2011;**18**:5-18.

**Albanese 2013**

Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, et al. Phenomenology and classification of dystonia: a consensus update. *Movement Disorders* 2013;**28**(7):863-73.

**Altman 2002**

Altman DG, Deeks JJ. Meta-analysis, Simpson's paradox, and the number needed to treat. *BMC Medical Research Methodology* 2002;**2**(1):3.

**Antonucci 2008**

Antonucci F, Rossi C, Gianfranceschi L, Rossetto O, Caleo M. Long-distance retrograde effects of botulinum neurotoxin. *Journal of Neuroscience* 2008;**28**:3689–96.

**Balint 2015**

Balint B, Bhatia KP. Isolated and combined dystonia syndromes – an update on new genes and their phenotypes. *European Journal of Neurology* 2015;**22**(4):610-7.

**Balshem 2011**

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(4):401-6.

**Boroff 1975**

Boroff DA, Chen GS. On the question of permeability of the blood–brain barrier to botulinum toxin. *International Archives of Allergy and Applied Immunology* 1975;**48**:495–504.

**Brożek 2006**

Brożek JL, Guyatt GH, Schünemann HJ. How a well-grounded minimal important difference can enhance transparency of labelling claims and improve interpretation of a patient reported outcome measure. *Health and Quality of Life Outcomes* 2006;**4**:69.

**Carpenter 2013**

Carpenter J, Kenward M. Multiple Imputation and its Application. 1st edition. Chichester: John Wiley & Sons, Lda, 2013.

**Carrasco-Labra 2016**

Carrasco-Labra A, Brignardello-Petersen R, Santesso N, Neumann I, Mustafa RA, Mbuagbaw L, et al. Improving GRADE evidence tables part 1: a randomized trial shows improved understanding of content in summary of findings tables with a new format. *Journal of clinical epidemiology* 2016;**74**:7-18. [PMID: 26791430]

**Chan 1991**

Chan J, Brin MF, Fanh S. Idiopathic cervical dystonia: clinical characteristics. *Movement Disorders* 1991;**6**:119-26.

**Cohen 1988**

Cohen J. Statistical Power Analysis in the Behavioral Sciences. 2nd edition. Hillsdale (NJ): Lawrence Erlbaum Associates, Inc, 1988.

**Comella 2015**

Comella CL, Fox SH, Bhatia KP, Perlmutter JS, Jinnah HA, Zurowski M, et al. Development of the comprehensive cervical dystonia rating scale: methodology. *Movement Disorders* 2015;**2**(2):135-41.

**Corbett 2014**

Corbett MS, Higgins JP, Woolacott NF. Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. *Research Synthesis Methods* 2014;**5**(1):79-85.

**de Paiva 1999**

de Paiva A, Meunier FA, Molgó J, Aoki KR, Dolly JO. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proceedings of the National Academy of Sciences of the United States of America* 1999;**96**:3200–5.

**Deeks 2011**

Deeks JJ, Higgins JPT, Altman DG, editor(s). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.training.cochrane.org/handbooks.

**Defazio 2013**

Defazio G, Jankovic J, Giel JL, Papapetropoulos S. Descriptive epidemiology of cervical dystonia. *Tremor and Other Hyperkinetic Movements* 2013;**3**:tre-03-193-4374-2. [DOI: 10.7916/D80C4TGJ]

**Duarte 2016**

Duarte GS, Castelão M, Rodrigues FB, Marques RE, Ferreira J, Sampaio C, et al. Botulinum toxin type A versus botulinum toxin type B for cervical dystonia. *Cochrane Database of Systematic Reviews* 2016, Issue 10. Art. No: CD004314. [DOI: 10.1002/14651858.CD004314.pub3]

**Duarte 2018**

Duarte GD, Rodrigues FB, Ferreira JJ, Costa J. Adverse events with botulinum toxin treatment in cervical dystonia: How much should we blame placebo? *Parkinsonism & Related Disorders* 2018;**56**:16-9. [DOI: 10.1016/j.parkreldis.2018.06.017]

**Duchen 1971**

Duchen LW. An electron microscopic study of the changes induced by botulinum toxin in the motor end-plates of slow and fast skeletal muscle fibres of the mouse. *Journal of the Neurological Sciences* 1971;**14**:47-60.

**Edwards 2000**

Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;**356**(9237):1255-9.

**ESDE 2000**

Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group. A prevalence study of primary dystonia in eight European countries. *Journal of Neurology* 2000;**247**:787-92.

**Espay 2018**

Espay AJ, Trosch R, Suarez G, Johnson J, Marchese D, Comella C. Minimal clinically important change in the Toronto Western Spasmodic Torticollis Rating Scale. *Parkinsonism & Related Disorders* 2018;**52**:94-7. [PMID: 29530726]

**Filippi 1993**

Filippi GM, Errico P, Santarelli R, Bagolini B, Manni E. Botulinum A toxin effects on rat jaw muscle spindles. *Acta Oto-laryngologica* 1993;**113**:400–4.

**Follmann 1992**

Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *Journal of Clinical Epidemiology* 1992;**45**:769-73.

**Foltz 1959**

Foltz EL, Knopp LM, Ward AA. Experimental spasmodic torticollis. *Journal of Neurosurgery* 1959;**16**:55-72.

**Frevert 2010**

Frevert J, Dressler D. Complexing proteins in botulinum toxin type A drugs: a help or a hindrance? *Biologics: Targets & Therapy* 2010;**4**:325-32.

**Furukawa 2006**

Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *Journal of Clinical Epidemiology* 2006;**59**(1):7-10.

**GRADEpro GDT [Computer program]**

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version assessed 3 January 2017. Hamilton (ON): McMaster University (developed by Evidence Prime). Available at gradepro.org.

**Guyatt 2011**

Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence-imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283-93.

**Hallett 1998**

Hallett M. The neurophysiology of dystonia. *Archives of Neurology* 1998;**55**(5):601-3.

**Hedges 1985**

Hedges LV, Olkin I. Statistical Methods for Meta-Analysis. San Diego, California: Academic Press, Inc, 1985.

**Higgins 2003**

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

**Higgins 2011a**

Higgins JPT, Altman DG, Sterne JAC, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.training.cochrane.org/handbooks.

**Higgins 2011b**

Higgins JPT, Deeks JJ, Altman DG, editor(s). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S, editor(s), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.training.cochrane.org/handbooks.

**Higgins 2011c**

Higgins JPT, Deeks JJ, editor(s). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S, editor(s), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.training.cochrane.org/handbooks.

**Holland 1981**

Holland RL, Brown MC. Nerve growth in botulinum toxin poisoned muscles. *Neuroscience* 1981;**6**:1167–79.

**Imberger 2016**

Imberger G, Thorlund K, Gluud C, Wetterslev J. False-positive findings in Cochrane meta-analyses with and without application of Trial Sequential Analysis: an empirical review. *BMJ Open* 2016;**6**(8):e011890.

**Jahnanshani 1990**

Jahnanshani M, Marion M-H, Marsden CD. Natural history of adult-onset idiopathic torticollis. *Archives of Neurology* 1990;**47**:548-52.

**Jakobsen 2014**

Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Medical Research Methodology* 2014;**14**(1):120.

**Jankovic 2004**

Jankovic J. Botulinum toxin in clinical practice. *Journal of Neurology, Neurosurgery, and Psychiatry* 2004;**75**:951–7.

**Jankovic 2006**

Jankovic J, Tsui J, Bergeron C. Prevalence of cervical dystonia and spasmodic torticollis in the United States general population. *Parkinsonism & Related Disorders* 2007;**13**(7):411–6.

**Juzans 1996**

Juzans P, Comella J, Molgo J, Faille L, Angaut-Petit D. Nerve terminal sprouting in botulinum type-A treated mouse levator auris longus muscle. *Neuromuscular Disorders: NMD* 1996;**6**(3):177-85.

**Liberati 2009**

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**:e1000100.

**Lundh 2017**

Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No: MR000033. [DOI: 10.1002/14651858.MR000033.pub3]

**Macefield 2014**

Macefield RC, Jacobs M, Korfage IJ, Nicklin J, Whistance RN, Brookes ST, et al. Developing core outcomes sets: methods for identifying and including patient-reported outcomes (PROs). *Trials* 2014;**15**:49.

**Marques 2016**

Marques RE, Duarte GS, Rodrigues FB, Castelão M, Ferreira J, Sampaio C, et al. Botulinum toxin type B for cervical dystonia. *Cochrane Database of Systematic Reviews* 2016, Issue 5. Art. No: CD004315. [DOI: 10.1002/14651858.CD004315.pub3] [PMID: 27176573]

**Matak 2014**

Matak I, Lacković Z. Botulinum toxin A, brain and pain. *Progress in Neurobiology* 2014;**119-120**:39–59.

**Matak 2015**

Matak I, Lacković Z. Botulinum neurotoxin type A: actions beyond SNAP-25? *Toxicology* 2015;**335**:79-84.

**O'Brien 1979**

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;**35**:549-56.

**Palomar 2012**

Palomar FJ, Mir P. Neurophysiological changes after intramuscular injection of botulinum toxin. *Clinical Neurophysiology* 2012;**123**(23):54–60.

**Pellizzari 1999**

Pellizzari R, Rossetto O, Schiavo G, Montecucco C. Tetanus and botulinum neurotoxins: mechanism of action and therapeutic uses. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 1999;**354**:259–68.

**Peters 2006**

Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 2006;**295**(6):676-80.

**Rato 2018**

Rato ML, Duarte GS, Mestre T, de Carvalho M, Ferreira JJ. Strong nocebo effect in amyotrophic lateral sclerosis trials might mask conclusions. *Lancet Neurology* 2018;**17**(10):842. [DOI: 10.1016/S1474-4422(18)30310-7]

**Rato 2019**

Rato ML, Duarte GS, Ferreira AN, Alves M, Mainoli B, Teodoro T, et al. Nocebo response in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism & Related Disorders* 2019;**65**:13-9. [DOI: 10.1016/j.parkreldis.2019.04.015]

**Review Manager 2014 [Computer program]**

Nordic Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Centre, The Cochrane Collaboration, 2014.

**Rodrigues 2019**

Rodrigues FB, Duarte GS, Prescott D, Ferreira J, Costa J. Deep brain stimulation for dystonia. *Cochrane Database of Systematic Reviews* 2019, Issue 1. Art. No: CD012405. [DOI: 10.1002/14651858.CD012405.pub2]

**Rosales 1996**

Rosales RL, Arimura K, Takenaka S, Osame M. Extrafusal and intrafusal muscle effects in experimental botulinum toxin-A injection. *Muscle & Nerve* 1996;**19**:488–96.

**Rosales 2010**

Rosales RL, Dressler D. On muscle spindles, dystonia and botulinum toxin. *European Journal of Neurology* 2010;**17**:71–80.

**Rubin 1991**

Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Statistics in Medicine* 1991;**10**:585–98.

**Schünemann 2011**

Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S, editor(s), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.training.cochrane.org/handbooks.

**Silva 2017**

Silva MA, Duarte GS, Camara R, Rodrigues FB, Fernandes RM, Abreu D, et al. Placebo and nocebo responses in restless legs syndrome: a systematic review and meta-analysis. *Neurology* 2017;**88**(23):2216-24. [DOI: 10.1212/WNL.0000000000004004]

**Simpson 2004**

Simpson LL. Identification of the major steps in botulinum toxin action. *Annual Review of Pharmacology and Toxicology* 2004;**44**:167-93.

**Simpson 2016**

Simpson DM, Hallett M, Ashman EJ, Comella CL, Green MW, Gronseth GS, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2016;**10**:1818-26.

**Smeeth 1999**

Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analysis – sometimes informative, usually misleading. *BMJ* 1999;**318**(7197):1548-51.

**Stata [Computer program]**

Stata Statistical Software: release 14. StataCorp, Version 14. College Station, TX, USA: StataCorp, 2017. Available at www.stata.com.

**Steeves 2012**

Steeves TD, Day L, Dykeman J, Jette N, Pringsheim T. The prevalence of primary dystonia: a systematic review and meta-analysis. *Movement Disorders* 2012;**27**(14):1789-96.

**Sterne 2001**

Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *Journal of Clinical Epidemiology* 2001;**54**(10):1046-55.

**Sterne 2011**

Sterne JAC, Egger M, Moher D, editor(s). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Intervention. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.training.cochrane.org/handbooks.

**Tarsy 1997**

Tarsy D. Comparison of clinical rating scales in treatment of cervical dystonia with botulinum toxin. *Movement Disorders* 1997;**12**(1):100-2.

**Tarsy 2006**

Tarsy D, Simon DK. Dystonia. *New England Journal of Medicine* 2006;**355**:818-29.

**Thorlund 2011**

Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). ctu.dk/tsa/files/tsa˙manual.pdf 2011.

**TSA 2011 [Computer program]**

Copenhagen Trial Unit Trial Sequential Analysis. Version 0.9 Beta. Copenhagen Trial Unit, Version accessed 3 January 2017. Copenhagen: Copenhagen Trial Unit, 2011. Available at www.ctu.dk/tsa/downloads.aspx.

**Tugwell 2007**

Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. *Trials* 2007;**8**:38.

**Walker 2014**

Walker TJ, Dayan SH. Comparison and overview of currently available neurotoxins. *Journal of Clinical and Aesthetic Dermatology* 2014;**7**(2):31-9.

**Wetterslev 2008**

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial Sequential Analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**:64-75.

**Wetterslev 2009**

Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Medical Research Methodology* 2009;**9**:86.

**Wiebe 2006**

Wiebe N, Vandermeer B, Platt RW, Klassen TP, Moher D, Barrowman NJ. A systematic review identifies a lack of standardization in methods for handling missing variance data. *Journal of Clinical Epidemiology* 2006;**59**(4):342-53.

**Zoons 2012**

Zoons E, Dijkgraaf MG, Dijk JM, Van Schaik IN, Tijssen MA. Botulinum toxin as treatment for focal dystonia: a systematic review of the pharmaco-therapeutic and pharmaco-economic value. *Journal of Neurology* 2012;**259**(12):2519-26.

## References to other published versions of this review

**Castelão 2017**

Castelão M, Marques RE, Duarte GS, Rodrigues FB, Ferreira J, Sampaio C, et al. Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database of Systematic Reviews* 2017, Issue 12. Art. No: CD003633. [DOI: 10.1002/14651858.CD003633.pub3]

**Costa 2000**

Costa J, Ferreira JJ, Sampaio C. Botulinum toxin type A for the treatment of cervical dystonia: a systematic review. *Movement Disorders* 2000;**15**(Suppl 3):29.

**Costa 2005**

Costa J, Espírito-Santo C, Borges A, Ferreira JJ, Coelho M, Moore P, et al. Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No: CD003633. [DOI: 10.1002/14651858.CD003633.pub2]

**Ferreira 1999**

Ferreira JJ, Costa J, Sampaio C. Botulinum toxin type A for the treatment of cervical dystonia: a systematic review. *European Journal of Neurology* 1999;**6**(Suppl 3):76.

* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Charles 2012

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised, double-blind, parallel design<br><br>**Randomisation:** carried out in blocks of four; method not described<br><br>**Setting:** multicentre (22 centres in the USA, 1 in Canada)<br><br>**Duration:** 10 weeks |
| Participants | 170 participants enrolled (BtA group = 88; placebo group = 82)<br><br>**% Female:** BtA: 70%; placebo: 80%<br><br>**Mean age, range:** BtA: 55 years; placebo: 55 years<br><br>**Mean CD duration:** BtA: 11.2 years; placebo: 9.1 years<br><br>**Mean CD severity (SD; CDSS):** BtA: 9.2 (4.8); placebo: 9.3 (4.2)<br><br>**Inclusion criteria:**<br><br>• 21 to 75 years of age<br>• idiopathic CD with a minimum score of 4 on the CDSS<br>• ≥ 2 previous successful treatments with ≤ 360 U of Botox administered at 12- to 16-week intervals<br><br>**Exclusion criteria:**<br><br>• previous treatment with onabotulinumtoxinA for any other indication<br>• pure anterocollis or isolated head shift<br>• pregnancy<br>• profound atrophy of cervical musculature<br>• medical conditions or treatments known to be contraindicated for the injection of onabotulinumtoxinA |
| Interventions | **BtA:** Botox (onabotulinumtoxinA); 25 ng of neurotoxin complex protein per 100 U, diluted with 1 mL sterile solution<br><br>**Placebo:** 0.5 mg of human serum albumin and 0.9 mg of sodium chloride<br><br>**Study drug preparation:** BtA provided in vials by Allergan |

**Charles 2012** *(Continued)*

| | |
|---|---|
| | **Muscles injected:** the doses and muscles injected were determined by the physician based on clinical assessment<br><br>**EMG guidance:** no<br><br>**BtA dose per participant:** maximum: 360 U; mean (range): 236 U (91 U to 360 U) |
| Outcomes | **Primary outcomes:**<br><br>• CDSS (range, 0 to 54) at week 4<br>• Physician GAS (range, -4 to +4; -4 = very marked worsening, +4 = complete remission) at week 6<br><br>**Secondary outcomes:**<br><br>• Functional disability (range, 0 to 4; 0 = no disability, 4 = extreme disability)<br>• Range of cervical motion<br>• Participant assessment of pain (5-point scale for both frequency and intensity)<br>• Frequency of pain (range, 0 to 4; 0 = never, 4 = constant)<br>• Intensity of pain (range, 0 to 4; 0 = none, 4 = very severe)<br>• Participant GAS (range, -4 to +4; -4 = very marked worsening, +4 = complete remission)<br>• Adverse events<br>• Time to treatment failure<br>• Plasma neutralising antibodies |
| Notes | This was a 2-period clinical trial consisting of a 10-week open-label period. followed by a 10-week double-blind period, with up to 6 weeks between periods. Participants who successfully completed the open phase (i.e. responded to BtA and were compliant with the study protocol) were enrolled in the blinded phase. 214 participants were enrolled in phase I, 170 of whom continued into phase II. We only considered the results of the blinded phase in this review.<br><br>**Study dropouts, reasons:**<br><br>BtA: n = 11 (13%): lack of efficacy = 8, unrelated reasons = 3<br><br>Placebo: n = 24 (29%); lack of efficacy = 19, unrelated reasons = 5 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: method of randomisation not specified |
| Allocation concealment (selection bias) | Unclear risk | Comment: method of concealment not specified |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Comment: blinding not specified although study described as double-blind |
| Blinding of outcome assessment (detection bias)<br>Objective outcomes | Unclear risk | Comment: blinding not specified although study described as double-blind |
| Blinding of outcome assessment (detection bias)<br>Subjective outcomes | Unclear risk | Comment: blinding not specified although study described as double-blind |

**Charles 2012** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Comment: post-randomisation exclusions were described as related to lack of efficacy or administrative reasons |
| Selective reporting (reporting bias) | Low risk | Comment: the expected outcomes that are usually evaluated in intervention trials for this condition were reported in this study |
| Enriched population – preferential enrolment of positive responders | High risk | Comment: to enrol in the study, participants must have had at least 2 previous successful treatments with ≤ 360 U of Botox administered at 12- to 16-week intervals. Also, all participants enrolled in phase II were compliant to treatment during phase I trial. |
| Enriched population – exclusion of poor responders | High risk | Quote: "Pure anterocollis and isolated head shift was exclusionary" |
| For-profit bias | High risk | The study was supported by Allergan. |

**Comella 2011**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised, double-blind, parallel design<br>**Randomisation:** block-wise randomisation using a software-generated code<br>**Setting:** multicentre (37 centres in the USA)<br>**Duration:** 8 weeks, follow-up to 20 weeks |
| Participants | 233 participants enrolled (BtA 120 U group = 78; BtA 240 U group = 81; placebo group = 74)<br>**% Female:** BtA 120 U: 51%; BtA 240 U: 54%; placebo: 49%<br>**Mean age (SD):** BtA 120 U: 52.8 years (11.5); BtA 240 U: 53.2 years (12.2); placebo: 52.4 years (10.8)<br>**Mean CD duration, SD:** BtA 120 U: 9.3 years (8.4); BtA 240 U: 9.7 years (9.0); placebo: 10.8 years (9.0)<br>**Mean CD severity (SD; TWSTRS total):** BtA 120 U: 42.6 (9.7); BtA 240 U: 42.1 (9.3); placebo: 41.8 (7.9)<br>**Inclusion criteria:**<br>• 18 to 75 years of age<br>• primary CD with predominantly rotational form<br>• TWSTRS total score ≥ 20<br>**Exclusion criteria:**<br>• predominant anterocollis or retrocollis<br>• prior CD surgery<br>• previous treatment with Bt injections in the last 10 weeks<br>• concomitant treatment with phenol, alcohol injections or local anaesthetics in the affected area<br>• intrathecal baclofen in the last 2 weeks<br>• parenteral use of tubocurarines, barbiturates, aminoglycosides or aminoquinolones<br>Other medications for focal dystonia must be on a stable dose for at least 3 months |
| Interventions | **BtA:** Xeomin (incobotulinumtoxinA); 120 U or 240 U, diluted in 4.8 mL |

**Comella 2011** *(Continued)*

| | |
|---|---|
| | **Placebo:** reconstitution of powder with 0.9% NaCl diluted in 4.8 mL<br><br>**Study drug preparation:** vials and providers not mentioned<br><br>**Muscles injected:** the number of injection sites per muscle and the volume injected into each muscle were determined at the discretion of the investigator<br><br>**EMG guidance:** left to the discretion of the investigator<br><br>**BtA dose per participant:** 120 U or 240 U |
| Outcomes | **Primary outcomes:**<br><br>• TWSTRS total (range, 0 to 85) at week 4<br><br>**Secondary outcomes:**<br><br>• TWSTRS total and TWSTRS subscales at weeks 4, 8, and final visit<br>• PEGR (range, -4 to +4; -4 = marked worsening, +4 = complete remission)<br>• IGAE (4-point scale; poor, moderate, good, very good)<br>• Adverse events |
| Notes | **Study dropouts (at week 8), reasons:**<br><br>BtA 120 U: n = 3 (4%); adverse events = 1, consent withdrawal = 1, lost to F/U = 1<br><br>BtA 240 U: n = 5 (6%); adverse events = 2, consent withdrawal = 1, lost to F/U = 1, unrelated reasons = 1<br><br>Placebo: n = 6 (8%); lack of efficacy = 3, consent withdrawal = 1, lost to F/U = 1, unrelated reasons = 1 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was performed using RANCODE version 3.6 (IDV, Gauting). Block-wise randomization by previous treatment with botulinum toxin ensured a balanced treatment assignment for each center for pretreated and treatment-naïve patients" |
| Allocation concealment (selection bias) | Unclear risk | Comment: method of concealment not specified |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Subjects, investigators, medical staff, (…) data managers and monitors were blind to subjects' treatment group" |
| Blinding of outcome assessment (detection bias)<br>Objective outcomes | Low risk | Quote: "Subjects, investigators, medical staff, biostatisticians responsible for data analysis, data managers and monitors were blind to subjects' treatment group" |
| Blinding of outcome assessment (detection bias)<br>Subjective outcomes | Unclear risk | Comment: although placebo was identical to intervention, the fact that most of the participants had previously been treated with Bt could have led to a degree of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Quote: "Missing subject data were provided and their absence was regarded according to an ITT protocol"<br><br>Comment: post-randomisation exclusions were low and roughly distributed evenly between groups (BtA 120 U group = 3; BtA 240 U group = 5; placebo group = 6). The reasons for exclusions were described. |

**Comella 2011** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | Comment: the outcomes mentioned in the study protocol matched the outcomes reported in the study. |
| Enriched population – preferential enrolment of positive responders | High risk | Quote: "A total of 233 subjects were randomised (...) Of these, 143 were previously treated with botulinum toxin" |
| Enriched population – exclusion of poor responders | High risk | Quote: "Subjects were excluded if they had (…) predominant anterocollis or retrocollis" |
| For-profit bias | High risk | Comment: study funded by Merz Pharmaceuticals GmbH, Frankfurt |

**Greene 1990**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Randomised, double-blind, parallel design<br>**Randomisation:** stratified by CD classification; method not described<br>**Setting:** single-centre (USA)<br>**Duration:** 12 weeks |
| Participants | 55 participants enrolled (BtA group = 28; placebo group = 27)<br>**% Female:** BtA: 61%; placebo: 67%<br>**Mean age:** BtA: 46.8 years; placebo: 52.6 years<br>**Mean CD duration:** BtA: 6.6 years; placebo: 9.8 years<br>**CD severity:** BtA: 7% mild, 71% moderate, 21% severe; placebo: 11% mild, 48% moderate, 41% severe<br>**Inclusion criteria:**<br>• Idiopathic CD non-responder to at least 2 drug trials including at least 1 trial of anticholinergics<br>**Exclusion criteria:**<br>• Known or suspected cause for CD<br>• prior thalamotomy or peripheral surgery<br>• previous treatment with Bt |
| Interventions | **BtA:** Botox (onabotulinumtoxinA); diluted in saline solution to a concentration of 25 U per 1 mL<br>**Placebo:** saline solution<br>**Study drug preparation:** BtA provided in vials by Smith-Kettlewell Eye Research Institute (USA)<br>**Muscles injected: t**he doses, muscles, and number of injected sites per muscle were determined by the physician based on clinical assessment and classification of CD<br>**EMG guidance:** no<br>**BtA dose per participant:** rotational torticollis and torticollis plus retrocollis – 150 U; head tilt – 165 U |
| Outcomes | **Primary outcomes:** |

**Greene 1990** *(Continued)*

- Patient Subjective Assessment of Change - 3 scales: Res Scale (results of injection: marked, moderate, slight improvement, no change, slight and definitely worse); Cap Scale (functional capability; 0% = completely disabled, 100% = fully functional); Pain scale (0% = no difference, 100% = complete relief)

**Secondary outcomes:**

- Columbia Torticollis Rating Scale (objective video records rating)
- Time course of benefit
- Adverse events

| Notes | **Study dropouts, reasons:**<br>BtA: n = 3 (11%); adverse events = 1, unrelated reasons = 2<br>Placebo: n = 0 |
|---|---|

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "They were divided into 3 cells (A, pure rotational torticollis; B, torticollis plus retrocollis; and C, head tilt with or without torticollis and retrocollis). In order to ensure reasonable balance of Botox and placebo injections in each cell, randomization was stratified by cell type, which was completed for blocks of 4 sequentially enrolled patients in each cell type"<br>Comment: insufficient information about the method of randomisation to permit judgement of low or high risk |
| Allocation concealment (selection bias) | Unclear risk | Comment: method of concealment not specified |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "The blinded physicians then injected them with Botox or saline, using syringes filled by the unblinded physicians according to the protocol" |
| Blinding of outcome assessment (detection bias)<br>Objective outcomes | Low risk | Quote: "Two blinded physicians gave the injections, determined the degree of head turning and disability, and videotaped the patients; but they did not examine the strength or size of the neck muscles, so that the presence of muscle atrophy would not identify patients receiving active injection. Videotapes of each patient visit were rated by the 2 blinded observers independently" |
| Blinding of outcome assessment (detection bias)<br>Subjective outcomes | Low risk | Quote: "Patients previously treated with Botox were excluded from the trial" |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Comment: the study authors stated that some data were lost, accounting for up to 13% of total data, and it is unclear whether this had an impact on the overall results. |
| Selective reporting (reporting bias) | Low risk | Comment: the expected outcomes that are usually evaluated in intervention trials for this condition were reported in this study. |
| Enriched population – preferential enrolment of positive responders | Low risk | Comment: participants who had previously received Botox injections were excluded. |

**Greene 1990** *(Continued)*

| | | |
|---|---|---|
| Enriched population – exclusion of poor responders | Low risk | Comment: exclusion criteria did not include forms of dystonia known to have poorer response to treatment |
| For-profit bias | Low risk | Study drug was provided by Dr. A. Scott, from Smith-Kettlewell Eye Research Institute (USA). |

**Lew 2018**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised, double-blind, parallel design<br><br>**Randomisation:** stratified by onabotulinumtoxinA (onaBtaA) exposure; method not described<br><br>**Setting:** multicentre (43 centres in the USA)<br><br>**Duration:** 12 weeks |
| Participants | 134 participants enrolled (BtA 500 U group = 89; placebo group = 45)<br><br>**% Female:** all groups: 65%<br><br>**Mean age, SD:** all groups: 57 years (11.3)<br><br>**Mean CD duration, SD:** not specified<br><br>**CD severity (TWSTRS total):** BtA 500 U: 42.4; placebo: 42.5<br><br>**Inclusion criteria:**<br><br>• adults (> 18 years)<br>• idiopathic CD with a duration of at least nine months<br>• TWSTRS total score ≥ 20<br>• TWSTRS severity score ≥ 10<br>• onaBtA naive or non-naive if receiving a total dose of 100 U to 200 U, and ≤ 60 U in the sternocleidomastoid since the last cycle, a satisfactory treatment responses to the last two cycles within the past 18 months, and not receiving onaBtA for at least 12 weeks. Any other formulation was allowed prior to the last two cycles.<br><br>**Exclusion criteria:**<br><br>• Pure retrocollis or pure anterocollis<br>• Lack of response to previous Bt treatment<br>• Weight under 43.09 kg<br>• Previous phenol injections in the neck muscles and myotomy or other surgeries for CD |
| Interventions | **BtA:** Dysport (abobotulinumtoxinA); vials of 500 U, diluted with 2 mL sterile solution<br><br>**Placebo:** not described<br><br>**Study drug preparation:** BtA provided in vials by Ipsen Biopharmaceuticals<br><br>**Muscles injected:** up to 2 mL of the study drug or placebo was injected into each participant (in a minimum of two clinically affected muscles)<br><br>**EMG guidance:** at the investigator preference<br><br>**BtA dose per participant:** 500 U for onaBtA-naive participants, and 250 U to 500 U if non-naive (2.5:1 conversion ratio). For the sternocleidomastoid, the limit was 150 U |

**Lew 2018** *(Continued)*

| | |
|---|---|
| Outcomes | **Primary outcomes:**<br>• TWSTRS total (range, 0 to 85) at week 4<br>**Secondary outcomes:**<br>• TWSTRS total (range, 0 to 85) at week 2<br>• Clinical Global Impression of Change (CGIC, 7-point Likert scale) in CD at week 2<br>• TWSTRS responders (30% reduction in TWSTRS total) at week 2<br>• CGIC (7-point Likert scale) in CD at week 4<br>• TWSTRS responders (30% reduction in TWSTRS total) at week 4<br>• Cervical Dystonia Impact Profile-58 (CDIP-58) total score at week 4<br>• CDIP-58 total score at week 2<br>• Adverse events |
| Notes | **Study dropouts, reasons:**<br>BtA 500 U: n = 32 (36%); lost to F/U = 2, adverse events = 1, participant decision = 1, sponsor decision = 1, withdrew consent = 1, entered OLE phase = 25<br>Placebo: n = 24 (53%); lost to F/U = 0, entered OLE phase = 22 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: method of randomisation not specified |
| Allocation concealment (selection bias) | Unclear risk | Comment: method of concealment not specified |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Comment: method of blinding not specified |
| Blinding of outcome assessment (detection bias)<br>Objective outcomes | Unclear risk | Comment: method of blinding not specified |
| Blinding of outcome assessment (detection bias)<br>Subjective outcomes | Unclear risk | Comment: method of blinding not specified |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Fifty-six subjects (32 aboBoNT-A, 24 placebo) withdrew" |
| Selective reporting (reporting bias) | Low risk | Comment: the expected outcomes that are usually evaluated in intervention trials for this condition were reported in this study. |
| Enriched population – preferential enrolment of positive responders | High risk | "Quote: "Exclusion criteria included (...) lack of response to previous botulinum neurotoxin treatment" |
| Enriched population – exclusion of poor responders | High risk | Quote: "Exclusion criteria included pure retro- or anterocollis," |

**Lew 2018** *(Continued)*

| | | |
|---|---|---|
| For-profit bias | High risk | Quote: "This study was funded by Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ. Ipsen was involved in the study design; collection, analysis, and interpretation of data; writing the article; and in the decision to submit the article for publication." |

**Poewe 1998**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised, double-blind, parallel design<br><br>**Randomisation:** not described<br><br>**Setting:** multicentre (Germany and Austria)<br><br>**Duration:** 8 weeks |
| Participants | 75 participants enrolled (BtA 250 U group = 19; BtA 500 U group = 18; BtA 1000 U group = 18; placebo group = 20).<br><br>**% Female:** all groups: 48%<br><br>**Mean age, SD:** all groups: 47 years (11.5)<br><br>**Mean CD duration, SD:** all groups: 7.4 years (6.7)<br><br>**CD severity (Tsui modified scale):** BtA 250 U: 14.3; BtA 500 U: 13.1; BtA 1000 U: 14.5; placebo: 14.4<br><br>**Inclusion criteria:**<br><br>• Rotational CD with hyperactivity clinically confined to one splenius capitis muscle and the contralateral sternocleidomastoid muscle<br>• previously untreated with Bt<br><br>**Exclusion criteria:**<br><br>• not mentioned |
| Interventions | **BtA:** Dysport (abobotulinumtoxinA); vials of 500 U, diluted with 1 mL sterile solution<br><br>**Placebo:** 0.125 mg of human serum albumin and 2.5 mg of lactose, diluted with 1 mL sterile solution<br><br>**Study drug preparation:** BtA provided in vials by Speywood Pharmaceuticals<br><br>**Muscles injected:** a total of 2.5 mL of the study drug or placebo was injected into each participant (0.75 mL into 2 sites in the sternocleidomastoid muscle, and 1.75 mL into 2 sites in the splenius capitis muscle)<br><br>**EMG guidance:** no<br><br>**BtA dose per participant:** 250 U, 500 U, or 1000 U |
| Outcomes | **Primary outcomes:**<br><br>• Modified Tsui Scale score<br><br>**Secondary outcomes:**<br><br>• Physician Global Assessment of Improvement (5-point scale: worse, no improvement, improvement < 50%, improvement > 50%, remission) |

**Poewe 1998** *(Continued)*

- Patient Global Assessment of Improvement (5-point scale: worse, no improvement, improvement < 50%, improvement > 50%, remission)
- Assessment of Swallowing Difficulties (5-point scale: none, mild, moderate, severe, swallowing not possible)
- Adverse events
- Clinical Global Rating (taking into account efficacy and safety)
- Need for retreatment

| | |
|---|---|
| Notes | **Study dropouts, reasons:**<br>BtA 250 U: n = 0<br>BtA 500 U: n = 2 (11%); lost to F/U = 2<br>BtA 1000 U: n = 0<br>Placebo: n = 0 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Patients were randomly assigned to receive treatment with placebo or total dose of 250, 500, or 1000 Dysport units of botulinum toxin type A in a double blind prospective study design"<br>Comment: insufficient information about the sequence generation process to permit judgement of low risk or high risk |
| Allocation concealment (selection bias) | Low risk | Comment: sequentially numbered drug containers of identical appearance |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Patients were randomly assigned to receive treatment with placebo or total dose of 250, 500, or 1000 Dysport units of botulinum toxin type A in a double blind prospective study design"<br>Quote: "All three vials were identical in appearance" |
| Blinding of outcome assessment (detection bias)<br>Objective outcomes | Unclear risk | Comment: insufficient information to permit judgement of low risk or high risk |
| Blinding of outcome assessment (detection bias)<br>Subjective outcomes | Unclear risk | Comment: insufficient information to permit judgement of low risk or high risk |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Quote: "One patient in the 500 unit group was lost to follow-up and had to be excluded from results analysis. A further case of 500 unit group had missed one follow-up visit and was excluded from efficacy analysis but included in analysis of adverse events"<br>Comment: reasons for missing outcome data unlikely to be related to true outcome |
| Selective reporting (reporting bias) | Low risk | Comment: the expected outcomes that are usually evaluated in intervention trials for this condition were reported in this study. |

**Poewe 1998** *(Continued)*

| | | |
|---|---|---|
| Enriched population – preferential enrolment of positive responders | Low risk | Comment: all participants were previously untreated with botulinum toxin type A |
| Enriched population – exclusion of poor responders | High risk | Quote: "Seventy five patients (...) with rotational torticollis and hyperactivity clinically confined to one splenius capitis and the contralateral sternomastoid muscles" |
| For-profit bias | High risk | Quote: "Toxin and placebo preparations was supplied by Speywood Pharmaceuticals Ltd" |

**Poewe 2016**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised, double-blind, parallel design<br><br>**Randomisation:** not adequately described<br><br>**Setting:** multicentre (61 centres in 11 countries)<br><br>**Duration:** 12 weeks |
| Participants | 369 participants enrolled overall<br><br>213 participants enrolled with data contributing to the current review (BtA group = 159; placebo group = 54)<br><br>**% Female:** BtA: 64%; placebo: 63%<br><br>**Mean age:** BtA: 49 years; placebo: 50 years<br><br>**Mean CD duration:** BtA: 7 years; placebo: 6 years<br><br>**Mean CD severity (SD; TWSTRS total):** BtA: 46 (9); placebo: 47 (9)<br><br>**Inclusion criteria:**<br><br>• ≥ 18 years old<br>• diagnosed with CD ≥ 18 months before trial enrolment<br>• untreated with BtA or BtB in the prior 14 weeks<br>• TWSTRS total score at baseline ≥ 30 with subscale scores for severity ≥ 15, disability ≥ 3, and pain ≥ 2<br><br>**Exclusion criteria:**<br><br>• known hypersensitivity to BtA, BtB, or related compounds or components in the study drug formulations<br>• diagnosis of isolated anterocollis or retrocollis<br>• previous poor response to BtA<br>• previous need for ≥ 300 U of onabotulinumtoxinA injected into the neck muscles, ≥ 12,500 U of BtB, or ≥1000 U of abobotulinumtoxinA<br>• requirement for injections at body sites other than the neck<br>• swallowing or respiratory abnormalities<br>• defective neuromuscular transmission or persistent neuromuscular weakness or any condition interfering with TWSTRS scoring<br>• body weight < 45.4 kg<br>• previous phenol or alcohol injections into the neck muscles |

**Poewe 2016** *(Continued)*

- previous myotomy or denervation surgery to the neck or shoulder region
- limited passive range of motion in the neck region
- pregnancy

| | |
|---|---|
| Interventions | **BtA:** Dysport (abobotulinumtoxinA)<br><br>**Placebo:** supplied in a 1 mL prefilled syringe indistinguishable from the active products<br><br>**Study drug preparation:** provided as a freeze-dried powder containing 500 U of BtA haemagglutinin complex, together with 125 µg of human albumin and 2.5 mg of lactose. The powder was reconstituted with 1.1 mL sodium chloride for injection, using a glass syringe<br><br>**Muscles injected:** administered into 2 to 4 neck muscles (levator scapulae, trapezius, sternocleidomastoid, splenius capitis, scalenus (medius and anterior), semispinalis capitis, or longissimus capitis) in a single dose session, according to the physician's clinical judgment of the individual's pattern of dystonic activity<br><br>**EMG guidance:** left to the discretion of the investigator<br><br>**BtA dose per patient:** 500 U |
| Outcomes | **Primary outcome:**<br><br>• TWSTRS total score at week 4<br><br>**Secondary outcomes:**<br><br>• TWSTRS total and TWSTRS subscales at weeks 4 and 8<br>• Investigator's and participant's VAS on symptoms<br>• Investigator's overall treatment success<br>• VAS for pain at week 4<br>• CD Impact Profile-58 score at week 4<br>• Adverse events |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Insufficient information about the sequence generation process to permit judgement of low or high risk |
| Allocation concealment (selection bias) | Low risk | Participants and investigators enrolling participants could not foresee assignment |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "To maintain blinding, all study treatments were identical in appearance and smell. All injections during the double-blind phase were prepared by dedicated and trained site personnel who were independent from investigators and had no contact with the investigators performing study assessment or the trial patients" |
| Blinding of outcome assessment (detection bias)<br>Objective outcomes | Low risk | Quote: "To maintain blinding, all study treatments were identical in appearance and smell. All injections during the double-blind phase were prepared by dedicated and trained site personnel who were independent from investigators and had no contact with the investigators performing study assessment or the trial patients" |
| Blinding of outcome assessment (detection bias) | Unclear risk | Included a considerable proportion (>60%) of non-naive participants, meaning they may have been able to foresee group allocation |

**Poewe 2016** *(Continued)*
Subjective outcomes

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Reasons for missing outcome data unlikely to be related to true outcome |
| Selective reporting (reporting bias) | Low risk | The study protocol was not available, but it is clear that the published report includes all expected outcomes |
| Enriched population – preferential enrolment of positive responders | High risk | Inclusion of a considerable proportion(>60%) of non-naive participants, meaning they may have been able to foresee group allocation |
| Enriched population – exclusion of poor responders | High risk | Exclusion of nonresponsive phenotypes |
| For-profit bias | High risk | Quote: "This study was sponsored by Ipsen" |

**Truong 2005**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised, double-blind, parallel design<br>**Randomisation:** block-wise randomisation using a software-generated code, stratification by centre<br>**Setting:** multicentre (16 centres in USA)<br>**Duration:** 4 weeks, follow-up to 20 weeks |
| Participants | 80 participants enrolled (BtA group = 37; placebo group = 43)<br>**% Female:** BtA: 62%; placebo: 63%<br>**Mean age (SD):** BtA: 53.4 years (11.6); placebo: 53.6 years (12.1)<br>**Mean CD duration, SD:** BtA: 7.1 years (7.1); placebo: 5.7 years (5.2)<br>**Mean CD severity (SD; TWSTRS total):** BtA: 45.1 (8.7); placebo: 46.2 (9.4)<br>**Inclusion criteria:**<br>• ≥ 18 months since cervical dystonia diagnosis<br>• TWSTRS total score ≥ 30<br>• de novo, or previously treated with Bt ≥ 16 weeks prior to enrolment<br>**Exclusion criteria:**<br>• suspected secondary non-responsiveness<br>• prior CD surgery or phenol injections<br>• participants believed to require a Botox dose < 80 U or > 250 U<br>• pure retrocollis forms<br>Medications, such as muscle relaxants and benzodiazepines must have been at a stable dose for ≥ 6 weeks |
| Interventions | **BtA:** Dysport (abobotulinumtoxinA); 500 U<br>**Placebo:** 0.125 mg of human serum albumin and 2.5 mg of lactose |

**Truong 2005** *(Continued)*

| | |
|---|---|
| | **Study drug preparation:** BtA provided in vials by Ipsen Ltd<br><br>**Muscles injected: t**he doses and number of injection sites per muscle were determined at the discretion of the investigator.<br><br>**EMG guidance:** left to the discretion of the investigator<br><br>**BtA dose per participant:** 500 U |
| Outcomes | **Primary outcome:**<br><br>• TWSTRS total and TWSTRS subscales at week 4<br><br>**Secondary outcomes:**<br><br>• TWSTRS total and TWSTRS subscales at weeks 8 and 12<br>• Participant assessment of pain using a VAS (range, 0 to 100; 0 mm = least possible pain, 100 mm = worst possible pain)<br>• Investigator assessment of change using a VAS (range, 0 to 100; 0 mm = much worse, 50 mm = no change, 100 mm = symptom-free)<br>• Participant assessment of change using a VAS (range, 0 to 100; 0 mm = much worse, 50 mm = no change, 100 mm = symptom-free)<br>• Adverse events<br>• Plasma neutralising antibodies |
| Notes | Participants who showed no benefit at week 4 were terminated from the study. Those who had evidence of response at week 4 continued in the study until additional injections were needed.<br><br>**Study dropouts (at week 4), reasons:**<br><br>BtA: n = 15 (41%), reasons not described<br><br>Placebo: n = 27 (63%), reasons not described |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was in blocks of four and was stratified by center and according to whether or not the patient had been treated previously with botulinum toxin"<br><br>Quote: "All patients were randomly assigned to treatment using a randomization code generated before the study" |
| Allocation concealment (selection bias) | Low risk | Quote: "Dysport was provided in a clear glass vial as a freeze-dried white pellet (…). Placebo was provided in identical clear glass vials (…)" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Placebo was provided in identical clear glass vials (…). Study medication was supplied in individual patient boxes, containing one vial of either Dysport or placebo. Subjects, investigators, medical staff, (…) data managers and monitors were blind to subjects' treatment group" |
| Blinding of outcome assessment (detection bias)<br>Objective outcomes | Unclear risk | Quote: "Whenever possible, an investigator or research nurse, other than the one performing the TWSTRS assessment, who was blind to treatment condition performed the assessment for adverse events. All sites were asked to achieve as much consistency as possible with respect to assessors"<br><br>Comment: insufficient information to permit judgement of low risk or high risk |

**Truong 2005** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) Subjective outcomes | Unclear risk | Quote: "At each post-treatment visit, patients and investigators independently assessed the change from baseline"<br><br>Comment: insufficient information to permit judgement of low risk or high risk. Although placebo was identical to intervention, the fact that most of the participants had previously been treated with Botox could have led to a degree of bias. |
| Incomplete outcome data (attrition bias) All outcomes | High risk | Comment: post-randomisation exclusions at week 4 were high in both intervention arms, though this difference was asymmetrical, with more dropouts from the placebo arm |
| Selective reporting (reporting bias) | Low risk | Comment: the outcomes mentioned in the study protocol matched the outcomes reported in the study |
| Enriched population – preferential enrolment of positive responders | High risk | Comment: out of the 80 participants enrolled, 21 were BtA-naive (i.e. haven't been treated previously with BtA) |
| Enriched population – exclusion of poor responders | High risk | Quote: "Patients with pure retrocollis were not permitted to participate" |
| For-profit bias | High risk | Comment: study funded by Beauford Ipsen |

**Truong 2010**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised, double-blind, parallel design<br><br>**Randomisation:** pre-generated randomisation code<br><br>**Setting:** multicentre (16 centres in USA, 4 in Russia)<br><br>**Duration:** 12 weeks |
| Participants | 116 participants enrolled (BtA group = 55; placebo group = 61)<br><br>**% Female:** BtA: 67%; placebo: 62%<br><br>**Mean age, SD:** BtA: 51.9 (13.4); placebo: 53.9 (12.5)<br><br>**Mean CD duration, SD:** BtA: 12.0 years (8.8); placebo: 11.8 years (8.8)<br><br>**Mean CD severity (SD; TWSTRS total):** BtA: 43.8 (8.0); placebo: 45.8 (8.8)<br><br>**Inclusion criteria:**<br><br>• reported symptoms for ≥ 18 months<br>• TWSTRS total score ≥ 30, TWSTRS severity subscale score ≥ 15, and TWSTRS disability subscale score ≥ 3<br>• previously untreated with Bt, or previously treated with Bt with a minimum interval of 16 weeks since the last injection, or returned to pre-treatment status<br><br>**Exclusion criteria:**<br><br>• pure anterocollis or retrocollis<br>• apparent symptom remission at screening<br>• previous poor response to Bt |

**Truong 2010** *(Continued)*

- current treatment with BtB due to lack of efficacy of BtA or the presence of neutralising antibodies to BtA
- myasthenia gravis, other disease of the neuromuscular junction, or symptoms that could interfere with TWSTRS scoring
- use of muscle relaxants and benzodiazepines if not on a stable dosage for 6 weeks prior to study treatment
- known hypersensitivity to Bt or related compounds; total body weight < 100 lbs (45.4 kg)
- pregnant or lactating
- previous phenol injections to the neck muscles, myotomy or denervation surgery involving the neck or shoulder region
- cervical contracture that limited passive range of motion

| | |
|---|---|
| Interventions | **BtA:** Dysport (abobotulinumtoxinA)<br><br>**Placebo:** not described<br><br>**Study drug preparation:** BtA provided in vials by Ipsen<br><br>**Muscles injected:** the doses and number of injection sites per muscle were determined at the discretion of the investigator<br><br>**EMG guidance:** left to the discretion of the investigator<br><br>**BtA dose per participant:** 500 U |
| Outcomes | **Primary outcome:**<br><br>• TWSTRS total score at week 4<br><br>**Secondary outcomes:**<br><br>• TWSTRS total and subtotal scores at weeks 8 and 12<br>• Investigator assessment of symptom severity using a VAS, participant Assessment of Symptom Severity using a VAS<br>• Pain VAS scores<br>• Short Form-36 quality-of-life questionnaire scores<br>• Investigator assessment of overall treatment success (Global Assessment of Efficacy ratings of better or much better, and a Global Safety Assessment of moderate or better)<br>• Adverse events<br>• Plasma neutralising antibodies |
| Notes | **Study dropouts, reasons:**<br><br>BtA: n = 10 (18%); lack of efficacy = 5, consent withdrawal = 2, lost to F/U = 1, unrelated reasons = 2<br><br>Placebo: n = 23 (38%); lack of efficacy = 23 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "In the double-blind treatment phase, patients were randomised using a pre-generated randomization code to receive intramuscular injection of either 500 units Dysport or placebo (1:1)" |
| Allocation concealment (selection bias) | Unclear risk | Comment: method of concealment not specified |

**Truong 2010** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Comment: blinding not specified, although study described as double-blind |
| Blinding of outcome assessment (detection bias)<br>Objective outcomes | Unclear risk | Comment: blinding not specified, although study described as double-blind |
| Blinding of outcome assessment (detection bias)<br>Subjective outcomes | Unclear risk | Comment: blinding not specified, although study described as double-blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Quote: "Efficacy variables were assessed using intention-to-treat (ITT) analysis"<br>Quote: "Safety assessments were based on the safety population, which included all patients who received at least one dose of study medication" |
| Selective reporting (reporting bias) | Low risk | Comment: the expected outcomes that are usually evaluated in intervention trials for this condition were reported in this study. |
| Enriched population – preferential enrolment of positive responders | High risk | Quote: "Patients were excluded if they had a (...) previous poor response to BoNT-A or BoNT-B treatments; current treatment with BoNT-B due to lack of efficacy of BoNT-A, or the presence of neutralising antibodies to BoNT-A" |
| Enriched population – exclusion of poor responders | High risk | Quote: "Patients were excluded if they had a diagnosis of pure anterocollis or retrocollis" |
| For-profit bias | High risk | Quote: "This study was supported by the Ipsen Group. Editorial assistance for the preparation of this manuscript was provided by Ogilvy Healthworld Medical Education; funding was provided by Ipsen Limited, Slough, UK" |

**Wissel 2001**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised, double-blind, parallel design<br>**Randomisation:** method not described<br>**Setting:** multicentre (Austria and Czech Republic)<br>**Duration:** 4 weeks, follow-up to 16 weeks |
| Participants | 68 participants enrolled (BtA group = 35; placebo group = 33)<br>**% Female:** BtA: 46%; placebo: 56%<br>**Mean age, SD:** BtA: 45.8 years (13.2); placebo: 49.7 years (9.6)<br>**Mean CD duration,SD:** BtA: 6.5 years (8.0); placebo: 4.8 years (4.4)<br>**Mean CD severity (SD; Tsui scale):** BtA: 11.1 (1.7); placebo: 11.5 (1.8)<br>**Inclusion criteria:**<br>• moderate or severe CD (Tsui score ≥ 9) |

**Wissel 2001** *(Continued)*

| | |
|---|---|
| | **Exclusion criteria:**<br>• pure anterocollis<br>• treatment with BtA in the last 12 weeks<br>• last BtA dose > 750 U (Dysport) or < 250 U (Dysport)<br>• lack of response to previous BtA treatments<br>• complex pattern of CD requiring EMG assistance or injection of > 3 muscles |
| Interventions | **BtA:** Dysport (abobotulinumtoxinA); 500 U, diluted with 1 mL 0.9% saline solution<br>**Placebo:** 0.125 mg of human serum albumin and 2.5 mg of lactose, diluted with 1 mL 0.9% saline solution<br>**Study drug preparation:** BtA and placebo provided in vials by Ipsen<br>**Muscles injected:** based on clinical assessment, 2 or 3 muscles were selected for injection: sternocleidomastoid (100 U to 200 U), splenius capitis (250 U to 350 U), trapezius (100 U to 200 U), and levator scapulae (100 U to 200 U). Each muscle was injected in 2 sites<br>**EMG guidance:** no<br>**BtA dose per participant:** 500 U |
| Outcomes | **Primary outcome:**<br>• Tsui Scale score<br>**Secondary outcomes:**<br>• Pain Assessment (4-point scale: none, mild, moderate, severe)<br>• Physician Global Assessment of Change (5-point scale: worse, no improvement, improvement < 50%, improvement > 50%, symptom free)<br>• Patient Global Assessment of Change (5-point scale: worse, no improvement, improvement < 50%, improvement > 50%, symptom free)<br>• Clinical Global Assessment (taking into account efficacy and safety)<br>• Adverse effects |
| Notes | Participants were withdrawn from the study if they were considered non-responders at week 4. Participants with an ongoing response at weeks 4 and 8 continued until re-treatment was required.<br>**Study dropouts (at week 4), reasons:**<br>BtA: n = 0<br>Placebo: n = 0 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Patients were randomly assigned to receive either placebo or 500 units of Dysport"<br>Comment: insufficient information about the method of randomisation to permit judgement of low risk or high risk |
| Allocation concealment (selection bias) | Unclear risk | Comment: insufficient information to permit judgement of low risk or high risk |

**Wissel 2001** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Blinded study medication was supplied (...) as identical vials containing either Dysport (...) or placebo" |
| Blinding of outcome assessment (detection bias)<br>Objective outcomes | Unclear risk | Comment: insufficient information to permit judgement of low or high risk |
| Blinding of outcome assessment (detection bias)<br>Subjective outcomes | Unclear risk | Comment: although placebo was identical to intervention, the fact that a large proportion (>60%) of the participants had previously been treated with Bt could have led to a degree of bias. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Quote: "In order to remove the bias created by the withdrawal of the majority of placebo patients at week 4, a last observation carried forward technique was used for the week 8 analyses" |
| Selective reporting (reporting bias) | Low risk | Comment: the expected outcomes that are usually evaluated in intervention trials for this condition were reported in this study. |
| Enriched population – preferential enrolment of positive responders | High risk | Comment: out of the 68 participants enrolled, 47 had received BtA injections previously |
| Enriched population – exclusion of poor responders | High risk | Quote: "Patients with pure anterocollis were excluded" |
| For-profit bias | High risk | Quote: "Blinded study medication was supplied by Ipsen Ltd" |

Bt: botulinum toxin
BtA: botulinum toxin type A
CD: cervical dystonia
CDSS: Cervical Dystonia Severity Scale
F/U: follow-up
GAS: Global Assessment Scale
IGAE: Investigator Global Assessment of Efficacy
OLE: open-label extension
PEGR: Patient Evaluation of Global Response
TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale
VAS: visual analogue scale

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

| Study | Reason for exclusion |
|---|---|
| Blackie 1990 | Cross-over design |
| Buchman 1994 | The primary outcome was not clinical; pharmacokinetic study |
| Gelb 1989 | Cross-over design |
| Koller 1990 | Cross-over design |
| Lange 1991 | This study recruited part of the same population as Greene 1990; the primary outcome was not clinical |

| Study | Reason for exclusion |
|---|---|
| Lorentz 1991 | Cross-over design |
| Lu 1995 | Cross-over design |
| Maurri 1990 | Not randomised |
| Moore 1991 | Cross-over design |
| Ostergaard 1994 | Cross-over design |
| Perlmutter 1989 | Cross-over design |
| Relja 1993 | Not randomised |
| Tsui 1986 | Cross-over design |
| Tsui 1988 | The primary outcome was not clinical |
| Yoshimura 1990 | This study recruited part of the same population as Gelb 1989 |

## DATA AND ANALYSES

### Comparison 1. Botulinum toxin type A (BtA) versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 Cervical dystonia-specific improvement | 8 | 962 | Std. Mean Difference (IV, Random, 95% CI) | 0.71 [0.55, 0.87] |
| 1.2 Cervical dystonia-specific improvement: TWSTRS subgroup analysis | 5 | 651 | Mean Difference (IV, Random, 95% CI) | 8.09 [6.22, 9.96] |
| 1.3 Cervical dystonia-specific severity: assessed with TWSTRS subscale | 3 | 429 | Mean Difference (IV, Random, 95% CI) | 3.13 [2.15, 4.11] |
| 1.4 Cervical dystonia-specific disability: assessed with TWSTRS subscale | 3 | 429 | Mean Difference (IV, Random, 95% CI) | 2.52 [1.72, 3.31] |
| 1.5 Cervical dystonia-specific improvement: doses subgroup analysis | 7 | 906 | Std. Mean Difference (IV, Random, 95% CI) | 0.83 [0.69, 0.97] |
| 1.5.1 Low dose | 1 | 39 | Std. Mean Difference (IV, Random, 95% CI) | 1.24 [0.55, 1.94] |
| 1.5.2 Medium dose | 6 | 545 | Std. Mean Difference (IV, Random, 95% CI) | 0.76 [0.59, 0.94] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.5.3 High dose | 3 | 322 | Std. Mean Difference (IV, Random, 95% CI) | 0.92 [0.63, 1.21] |
| 1.6 Cervical dystonia-specific improvement: Botox A formulation subgroup analysis | 8 | 962 | Std. Mean Difference (IV, Random, 95% CI) | 0.71 [0.55, 0.87] |
| 1.6.1 Botox | 1 | 170 | Std. Mean Difference (IV, Random, 95% CI) | 0.38 [0.08, 0.69] |
| 1.6.2 Dysport | 6 | 559 | Std. Mean Difference (IV, Random, 95% CI) | 0.75 [0.58, 0.93] |
| 1.6.3 Xeomin | 1 | 233 | Std. Mean Difference (IV, Random, 95% CI) | 0.82 [0.53, 1.10] |
| 1.7 Cervical dystonia-specific improvement: EMG-guided versus non-EMG-guided subgroup analysis | 8 | 962 | Std. Mean Difference (IV, Random, 95% CI) | 0.71 [0.55, 0.87] |
| 1.7.1 EMG-guided injection | 5 | 651 | Std. Mean Difference (IV, Random, 95% CI) | 0.72 [0.56, 0.88] |
| 1.7.2 Non-EMG-guided injection | 3 | 311 | Std. Mean Difference (IV, Random, 95% CI) | 0.79 [0.27, 1.31] |
| 1.8 Adverse events | 8 | 1085 | Risk Ratio (M-H, Random, 95% CI) | 1.23 [1.05, 1.43] |
| 1.9 Adverse events: doses subgroup analysis | 7 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.9.1 Low dose | 1 | 39 | Risk Ratio (M-H, Random, 95% CI) | 1.47 [0.56, 3.85] |
| 1.9.2 Medium dose | 6 | 664 | Risk Ratio (M-H, Random, 95% CI) | 1.23 [1.06, 1.44] |
| 1.9.3 High dose | 3 | 326 | Risk Ratio (M-H, Random, 95% CI) | 1.79 [1.03, 3.11] |
| 1.10 Adverse events: Botox A formulation subgroup analysis | 8 | 1085 | Risk Ratio (M-H, Random, 95% CI) | 1.23 [1.05, 1.43] |
| 1.10.1 Botox | 1 | 170 | Risk Ratio (M-H, Random, 95% CI) | 1.01 [0.78, 1.30] |
| 1.10.2 Dysport | 6 | 682 | Risk Ratio (M-H, Random, 95% CI) | 1.37 [1.07, 1.76] |
| 1.10.3 Xeomin | 1 | 233 | Risk Ratio (M-H, Random, 95% CI) | 1.22 [0.92, 1.62] |
| 1.11 Adverse events: EMG-guided vs non-EMG-guided subgroup analysis | 8 | 1085 | Risk Ratio (M-H, Random, 95% CI) | 1.23 [1.05, 1.43] |
| 1.11.1 EMG-guided injection | 5 | 773 | Risk Ratio (M-H, Random, 95% CI) | 1.21 [1.06, 1.38] |
| 1.11.2 Non-EMG-guided injection | 3 | 312 | Risk Ratio (M-H, Random, 95% CI) | 1.43 [0.82, 2.50] |
| 1.12 Dysphagia | 9 | 1140 | Risk Ratio (M-H, Random, 95% CI) | 3.19 [1.79, 5.70] |
| 1.13 Diffuse weakness, tiredness | 7 | 956 | Risk Ratio (M-H, Random, 95% CI) | 1.80 [1.10, 2.95] |
| 1.14 Neck weakness | 5 | 410 | Risk Ratio (M-H, Random, 95% CI) | 3.40 [1.19, 9.71] |

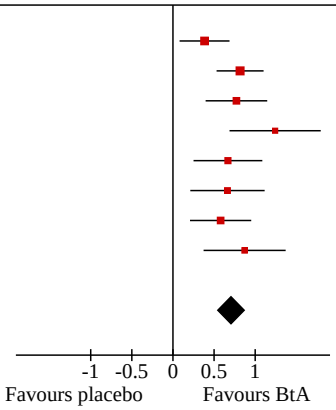
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.15 Voice change, hoarseness | 2 | 154 | Risk Ratio (M-H, Random, 95% CI) | 1.83 [0.37, 8.95] |
| 1.16 Sore throat, dry mouth | 3 | 222 | Risk Ratio (M-H, Random, 95% CI) | 1.66 [0.78, 3.51] |
| 1.17 Vertigo, dizziness | 2 | 154 | Risk Ratio (M-H, Random, 95% CI) | 1.47 [0.38, 5.73] |
| 1.18 Malaise, upper respiratory infection | 8 | 1085 | Risk Ratio (M-H, Random, 95% CI) | 1.35 [0.69, 2.65] |
| 1.19 Local pain (injection site) | 8 | 970 | Risk Ratio (M-H, Random, 95% CI) | 1.38 [0.91, 2.09] |
| 1.20 Headache | 7 | 839 | Risk Ratio (M-H, Random, 95% CI) | 1.12 [0.64, 1.97] |
| 1.21 Any improvement by subjective clinician assessment | 5 | 675 | Risk Ratio (M-H, Random, 95% CI) | 1.88 [1.55, 2.28] |
| 1.22 Any improvement by subjective participant assessment | 6 | 755 | Risk Ratio (M-H, Random, 95% CI) | 2.19 [1.78, 2.70] |
| 1.23 Any improvement by subjective participant assessment: doses subgroup analysis | 4 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.23.1 Low dose | 1 | 39 | Risk Ratio (M-H, Random, 95% CI) | 1.58 [0.30, 8.43] |
| 1.23.2 Medium dose | 4 | 336 | Risk Ratio (M-H, Random, 95% CI) | 2.44 [1.82, 3.25] |
| 1.23.3 High dose | 2 | 193 | Risk Ratio (M-H, Random, 95% CI) | 3.39 [2.16, 5.33] |
| 1.24 Any improvement by subjective participant assessment: Botox A formulation subgroup analysis | 5 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.24.1 Botox | 1 | 170 | Risk Ratio (M-H, Random, 95% CI) | 1.99 [1.34, 2.94] |
| 1.24.2 Dysport | 3 | 221 | Risk Ratio (M-H, Random, 95% CI) | 2.13 [1.49, 3.04] |
| 1.24.3 Xeomin | 1 | 233 | Risk Ratio (M-H, Random, 95% CI) | 3.23 [2.03, 5.14] |
| 1.25 Any improvement by subjective participant assessment: EMG guided vs non-EMG-guided subgroup analysis | 5 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.25.1 EMG-guided injection | 2 | 313 | Risk Ratio (M-H, Random, 95% CI) | 2.97 [1.99, 4.43] |
| 1.25.2 Non-EMG-guided injection | 3 | 311 | Risk Ratio (M-H, Random, 95% CI) | 2.03 [1.53, 2.69] |
| 1.26 Cervical dystonia-specific pain | 6 | | Std. Mean Difference (IV, Random, 95% CI) | 0.50 [0.35, 0.65] |
| 1.27 Cervical dystonia-specific pain: TWSTRS pain subscale subgroup analysis | 3 | | Mean Difference (IV, Random, 95% CI) | 2.11 [1.38, 2.83] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.28 Cervical dystonia-specific pain: Botox A formulation subgroup analysis | 6 | | Std. Mean Difference (IV, Random, 95% CI) | 0.50 [0.35, 0.65] |
| 1.28.1 Botox | 2 | | Std. Mean Difference (IV, Random, 95% CI) | 0.51 [0.01, 1.02] |
| 1.28.2 Dysport | 3 | | Std. Mean Difference (IV, Random, 95% CI) | 0.52 [0.28, 0.77] |
| 1.28.3 Xeomin | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.55 [0.27, 0.83] |
| 1.29 Cervical dystonia-specific pain: EMG-guided vs non-EMG-guided subgroup analysis | 6 | 654 | Std. Mean Difference (IV, Random, 95% CI) | 0.50 [0.35, 0.65] |
| 1.29.1 EMG-guided injection | 3 | 429 | Std. Mean Difference (IV, Random, 95% CI) | 0.53 [0.33, 0.73] |
| 1.29.2 Non-EMG-guided injection | 3 | 225 | Std. Mean Difference (IV, Random, 95% CI) | 0.50 [0.20, 0.80] |
| 1.30 Tolerability: dropouts | 5 | 705 | Risk Ratio (IV, Random, 95% CI) | 0.48 [0.32, 0.73] |
| 1.31 Tolerability: dropouts due to lack of efficacy subgroup analysis | 3 | 519 | Risk Ratio (IV, Random, 95% CI) | 0.30 [0.17, 0.53] |
| 1.32 Tolerability: dropouts due to adverse events subgroup analysis | 3 | 419 | Risk Ratio (IV, Random, 95% CI) | 2.51 [0.42, 14.94] |

## Analysis 1.1. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 1: Cervical dystonia-specific improvement

| Study or Subgroup | SMD | SE | BtA Total | Placebo Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Charles 2012 (1) | 0.3843 | 0.1549 | 88 | 82 | 17.6% | 0.38 [0.08 , 0.69] |
| Comella 2011 (2) | 0.8163 | 0.1458 | 159 | 74 | 19.0% | 0.82 [0.53 , 1.10] |
| Lew 2018 (3) | 0.7719 | 0.1911 | 84 | 45 | 13.2% | 0.77 [0.40 , 1.15] |
| Poewe 1998 (4) | 1.2425 | 0.2829 | 53 | 20 | 7.1% | 1.24 [0.69 , 1.80] |
| Poewe 2016 (5) | 0.6686 | 0.2134 | 46 | 47 | 11.2% | 0.67 [0.25 , 1.09] |
| Truong 2005 (5) | 0.663 | 0.2306 | 37 | 43 | 10.0% | 0.66 [0.21 , 1.11] |
| Truong 2010 (3) | 0.5797 | 0.1899 | 55 | 61 | 13.4% | 0.58 [0.21 , 0.95] |
| Wissel 2001 (6) | 0.8715 | 0.2546 | 35 | 33 | 8.5% | 0.87 [0.37 , 1.37] |
| **Total (95% CI)** | | | **557** | **405** | **100.0%** | **0.71 [0.55 , 0.87]** |

Heterogeneity: Tau² = 0.01; Chi² = 9.51, df = 7 (P = 0.22); I² = 26%
Test for overall effect: Z = 8.64 (P < 0.00001)
Test for subgroup differences: Not applicable

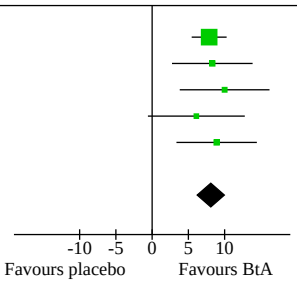



**Footnotes**
(1) CDSS, week 4, mean and SD obtained from graph
(2) TWSTRS, week 4, combined groups method
(3) TWSTRS, week 4
(4) Tsui (computed from baseline value and % of change), week 4, appropriated SD from Wissel 2001
(5) TWSTRS, week 4, appropriated SD from Truong 2010
(6) Tsui, week 4, pooled SD

## Analysis 1.2. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 2: Cervical dystonia-specific improvement: TWSTRS subgroup analysis

| Study or Subgroup | BtA Mean | BtA SD | BtA Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Comella 2011 (1) | 10.066 | 11.2176 | 159 | 2.2 | 7.3 | 74 | 60.3% | 7.87 [5.46 , 10.28] |
| Lew 2018 (1) | 10.8 | 14.8324 | 84 | 2.5 | 15.6205 | 45 | 11.3% | 8.30 [2.74 , 13.86] |
| Poewe 2016 (2) | 15 | 14.8324 | 46 | 5 | 15.6205 | 47 | 9.1% | 10.00 [3.81 , 16.19] |
| Truong 2005 (2) | 9.9 | 14.8324 | 37 | 3.8 | 15.6205 | 43 | 7.8% | 6.10 [-0.58 , 12.78] |
| Truong 2010 (1) | 15.6 | 14.8324 | 55 | 6.7 | 15.6205 | 61 | 11.4% | 8.90 [3.36 , 14.44] |
| **Total (95% CI)** | | | **381** | | | **270** | **100.0%** | **8.09 [6.22 , 9.96]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 4 (P = 0.93); I² = 0%
Test for overall effect: Z = 8.47 (P < 0.00001)
Test for subgroup differences: Not applicable

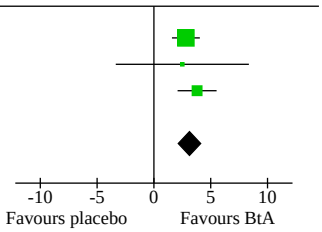



**Footnotes**
(1) week 4
(2) appropriated SD from Truong 2010 (same scale and week 4)

## Analysis 1.3. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 3: Cervical dystonia-specific severity: assessed with TWSTRS subscale

| Study or Subgroup | BtA Mean | BtA SD | BtA Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Comella 2011 | 4.7151 | 5.2804 | 159 | 1.9 | 4 | 74 | 64.3% | 2.82 [1.59 , 4.04] |
| Truong 2005 (1) | 4.6 | 4.002 | 37 | 2.1 | 19.118 | 43 | 2.8% | 2.50 [-3.36 , 8.36] |
| Truong 2010 | 6.2 | 5.4 | 55 | 2.4 | 3.8 | 61 | 32.8% | 3.80 [2.08 , 5.52] |
| **Total (95% CI)** | | | **251** | | | **178** | **100.0%** | **3.13 [2.15 , 4.11]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 6.24 (P < 0.00001)
Test for subgroup differences: Not applicable

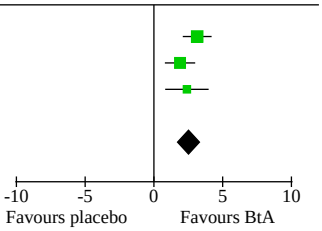



**Footnotes**
(1) TWSTRS, week 4, appropriated SD from Truong 2010 (same scale, measurement error, and week 4)

## Analysis 1.4. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 4: Cervical dystonia-specific disability: assessed with TWSTRS subscale

| Study or Subgroup | BtA Mean | BtA SD | BtA Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Comella 2011 | 3.1472 | 4.5377 | 159 | 0 | 3.4 | 74 | 40.7% | 3.15 [2.10 , 4.19] |
| Truong 2005 (1) | 2.5 | 3.15 | 37 | 0.6 | 1.44 | 43 | 37.8% | 1.90 [0.80 , 3.00] |
| Truong 2010 | 3.9 | 4.9 | 55 | 1.5 | 3.6 | 61 | 21.4% | 2.40 [0.82 , 3.98] |
| **Total (95% CI)** | | | **251** | | | **178** | **100.0%** | **2.52 [1.72 , 3.31]** |

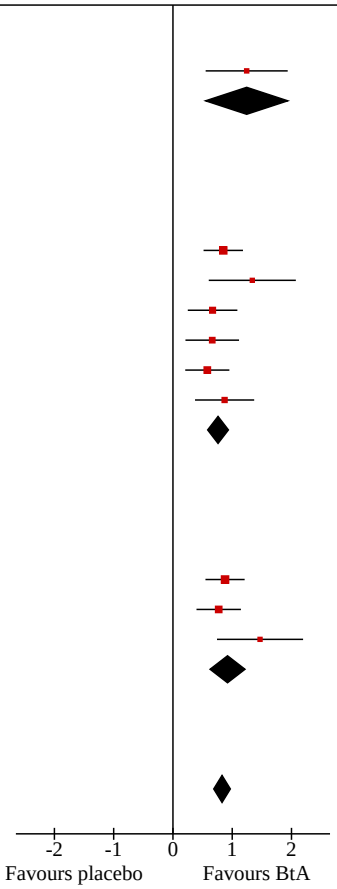
Heterogeneity: Tau² = 0.12; Chi² = 2.61, df = 2 (P = 0.27); I² = 23%
Test for overall effect: Z = 6.20 (P < 0.00001)
Test for subgroup differences: Not applicable




**Footnotes**
(1) appropriated SD from Truong 2010

## Analysis 1.5. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 5: Cervical dystonia-specific improvement: doses subgroup analysis

| Study or Subgroup | SMD | SE | BtA Total | Placebo Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.5.1 Low dose** | | | | | | |
| Poewe 1998 (1) | 1.2439 | 0.3531 | 19 | 20 | 4.0% | 1.24 [0.55 , 1.94] |
| **Subtotal (95% CI)** | | | **19** | **20** | **4.0%** | **1.24 [0.55 , 1.94]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 3.52 (P = 0.0004) | | | | | | |
| **1.5.2 Medium dose** | | | | | | |
| Comella 2011 (2) | 0.8489 | 0.1696 | 78 | 74 | 16.9% | 0.85 [0.52 , 1.18] |
| Poewe 1998 (1) | 1.3387 | 0.3748 | 16 | 20 | 3.6% | 1.34 [0.60 , 2.07] |
| Poewe 2016 (3) | 0.6686 | 0.2134 | 46 | 47 | 10.8% | 0.67 [0.25 , 1.09] |
| Truong 2005 (3) | 0.663 | 0.2306 | 37 | 43 | 9.3% | 0.66 [0.21 , 1.11] |
| Truong 2010 (2) | 0.5797 | 0.1899 | 55 | 61 | 13.6% | 0.58 [0.21 , 0.95] |
| Wissel 2001 (4) | 0.8715 | 0.2546 | 35 | 33 | 7.7% | 0.87 [0.37 , 1.37] |
| **Subtotal (95% CI)** | | | **267** | **278** | **61.8%** | **0.76 [0.59 , 0.94]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.11$, df = 5 (P = 0.53); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 8.53 (P < 0.00001) | | | | | | |
| **1.5.3 High dose** | | | | | | |
| Comella 2011 (2) | 0.879 | 0.1686 | 81 | 74 | 17.1% | 0.88 [0.55 , 1.21] |
| Lew 2018 (2) | 0.7719 | 0.1911 | 84 | 45 | 13.4% | 0.77 [0.40 , 1.15] |
| Poewe 1998 (1) | 1.4694 | 0.3705 | 18 | 20 | 3.7% | 1.47 [0.74 , 2.20] |
| **Subtotal (95% CI)** | | | **183** | **139** | **34.1%** | **0.92 [0.63 , 1.21]** |
| Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 2.83$, df = 2 (P = 0.24); $I^2 = 29\%$ | | | | | | |
| Test for overall effect: Z = 6.14 (P < 0.00001) | | | | | | |
| **Total (95% CI)** | | | **469** | **437** | **100.0%** | **0.83 [0.69 , 0.97]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.24$, df = 9 (P = 0.42); $I^2 = 3\%$ | | | | | | |
| Test for overall effect: Z = 11.62 (P < 0.00001) | | | | | | |
| Test for subgroup differences: $Chi^2 = 2.33$, df = 2 (P = 0.31), $I^2 = 14.3\%$ | | | | | | |

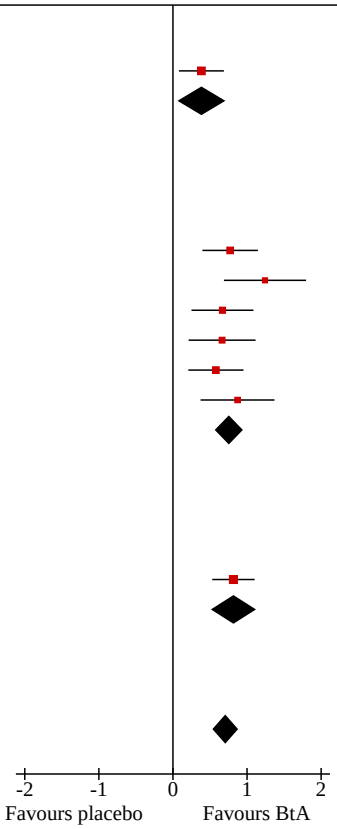



**Footnotes**

(1) Tsui (computed from baseline value and % of change), week 4, appropriated SD from Wissel 2001
(2) TWSTRS
(3) TWSTRS, week 4, appropriated SD from Truong 2010
(4) Tsui, week 4, pooled SD

## Analysis 1.6. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 6: Cervical dystonia-specific improvement: Botox A formulation subgroup analysis

| Study or Subgroup | SMD | SE | Placebo Total | BtA Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.6.1 Botox** | | | | | | |
| Charles 2012 (1) | 0.3843 | 0.1549 | 88 | 82 | 17.6% | 0.38 [0.08 , 0.69] |
| **Subtotal (95% CI)** | | | **88** | **82** | **17.6%** | **0.38 [0.08 , 0.69]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.48 (P = 0.01) | | | | | | |
| **1.6.2 Dysport** | | | | | | |
| Lew 2018 (2) | 0.7719 | 0.1911 | 84 | 45 | 13.2% | 0.77 [0.40 , 1.15] |
| Poewe 1998 (3) | 1.2425 | 0.2829 | 53 | 20 | 7.1% | 1.24 [0.69 , 1.80] |
| Poewe 2016 (4) | 0.6686 | 0.2134 | 46 | 47 | 11.2% | 0.67 [0.25 , 1.09] |
| Truong 2005 (4) | 0.663 | 0.2306 | 37 | 43 | 10.0% | 0.66 [0.21 , 1.11] |
| Truong 2010 (2) | 0.5797 | 0.1899 | 55 | 61 | 13.4% | 0.58 [0.21 , 0.95] |
| Wissel 2001 (5) | 0.8715 | 0.2546 | 35 | 33 | 8.5% | 0.87 [0.37 , 1.37] |
| **Subtotal (95% CI)** | | | **310** | **249** | **63.4%** | **0.75 [0.58 , 0.93]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.36$, df = 5 (P = 0.50); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 8.39 (P < 0.00001) | | | | | | |
| **1.6.3 Xeomin** | | | | | | |
| Comella 2011 (6) | 0.8163 | 0.1458 | 159 | 74 | 19.0% | 0.82 [0.53 , 1.10] |
| **Subtotal (95% CI)** | | | **159** | **74** | **19.0%** | **0.82 [0.53 , 1.10]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 5.60 (P < 0.00001) | | | | | | |
| **Total (95% CI)** | | | **557** | **405** | **100.0%** | **0.71 [0.55 , 0.87]** |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.51$, df = 7 (P = 0.22); $I^2 = 26\%$ | | | | | | |
| Test for overall effect: Z = 8.64 (P < 0.00001) | | | | | | |
| Test for subgroup differences: $Chi^2 = 5.14$, df = 2 (P = 0.08), $I^2 = 61.1\%$ | | | | | | |

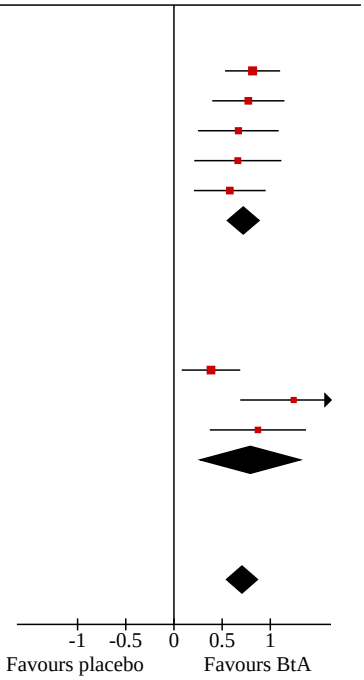



**Footnotes**

(1) CDSS, week 4, mean and SD obtained from graph
(2) TWSTRS, week 4
(3) Tsui (computed from baseline value and % of change), week 4, appropriated SD from Wissel 2001
(4) TWSTRS, week 4, appropriated SD from Truong 2010
(5) Tsui, week 4, pooled SD
(6) TWSTRS, week 4, combined groups method

## Analysis 1.7. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 7: Cervical dystonia-specific improvement: EMG-guided versus non-EMG-guided subgroup analysis

| Study or Subgroup | SMD | SE | Placebo Total | BtA Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.7.1 EMG-guided injection** | | | | | | |
| Comella 2011 (1) | 0.8163 | 0.1458 | 159 | 74 | 19.0% | 0.82 [0.53 , 1.10] |
| Lew 2018 (2) | 0.7719 | 0.1911 | 84 | 45 | 13.2% | 0.77 [0.40 , 1.15] |
| Poewe 2016 (3) | 0.6686 | 0.2134 | 46 | 47 | 11.2% | 0.67 [0.25 , 1.09] |
| Truong 2005 (3) | 0.663 | 0.2306 | 37 | 43 | 10.0% | 0.66 [0.21 , 1.11] |
| Truong 2010 (2) | 0.5797 | 0.1899 | 55 | 61 | 13.4% | 0.58 [0.21 , 0.95] |
| **Subtotal (95% CI)** | | | **381** | **270** | **66.8%** | **0.72 [0.56 , 0.88]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.17, df = 4 (P = 0.88); I² = 0% | | | | | | |
| Test for overall effect: Z = 8.60 (P < 0.00001) | | | | | | |
| **1.7.2 Non-EMG-guided injection** | | | | | | |
| Charles 2012 (4) | 0.3843 | 0.1549 | 88 | 82 | 17.6% | 0.38 [0.08 , 0.69] |
| Poewe 1998 (5) | 1.2425 | 0.2829 | 53 | 20 | 7.1% | 1.24 [0.69 , 1.80] |
| Wissel 2001 (6) | 0.8715 | 0.2546 | 35 | 33 | 8.5% | 0.87 [0.37 , 1.37] |
| **Subtotal (95% CI)** | | | **176** | **135** | **33.2%** | **0.79 [0.27 , 1.31]** |
| Heterogeneity: Tau² = 0.16; Chi² = 8.08, df = 2 (P = 0.02); I² = 75% | | | | | | |
| Test for overall effect: Z = 3.00 (P = 0.003) | | | | | | |
| **Total (95% CI)** | | | **557** | **405** | **100.0%** | **0.71 [0.55 , 0.87]** |
| Heterogeneity: Tau² = 0.01; Chi² = 9.51, df = 7 (P = 0.22); I² = 26% | | | | | | |
| Test for overall effect: Z = 8.64 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0% | | | | | | |

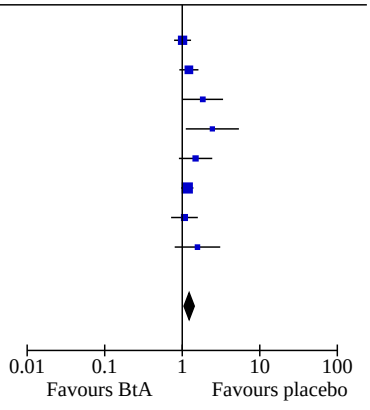



**Footnotes**

(1) TWSTRS, week 4, combined groups method
(2) TWSTRS, week 4
(3) TWSTRS, week 4, appropriated SD from Truong 2010
(4) CDSS, week 4, mean and SD obtained from graph
(5) Tsui (computed from baseline value and % of change), week 4, appropriated SD from Wissel 2001
(6) Tsui, week 4, pooled SD

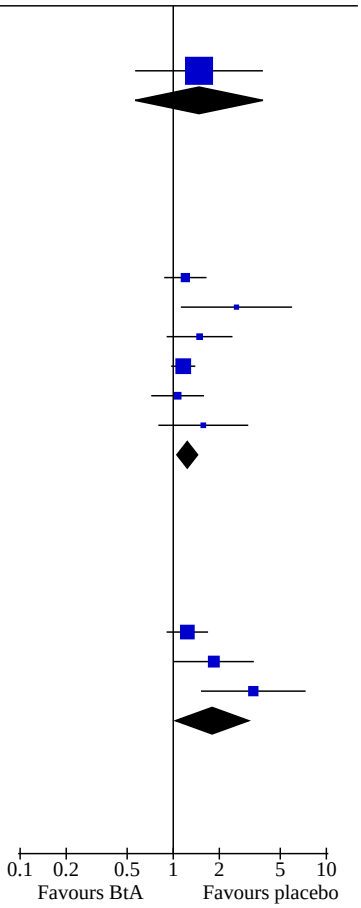
## Analysis 1.8. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 8: Adverse events

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Charles 2012 | 52 | 88 | 48 | 82 | 20.7% | 1.01 [0.78 , 1.30] |
| Comella 2011 | 89 | 159 | 34 | 74 | 18.0% | 1.22 [0.92 , 1.62] |
| Lew 2018 | 36 | 88 | 10 | 45 | 5.6% | 1.84 [1.01 , 3.36] |
| Poewe 1998 | 33 | 54 | 5 | 20 | 3.4% | 2.44 [1.11 , 5.38] |
| Poewe 2016 | 59 | 156 | 14 | 55 | 7.9% | 1.49 [0.91 , 2.44] |
| Truong 2005 | 34 | 37 | 34 | 43 | 28.6% | 1.16 [0.97 , 1.39] |
| Truong 2010 | 26 | 55 | 27 | 61 | 11.2% | 1.07 [0.72 , 1.59] |
| Wissel 2001 | 15 | 35 | 9 | 33 | 4.6% | 1.57 [0.80 , 3.09] |
| **Total (95% CI)** | | **672** | | **413** | **100.0%** | **1.23 [1.05 , 1.43]** |
| Total events: | 344 | | 181 | | | |
| Heterogeneity: Tau² = 0.01; Chi² = 9.74, df = 7 (P = 0.20); I² = 28% | | | | | | |
| Test for overall effect: Z = 2.64 (P = 0.008) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



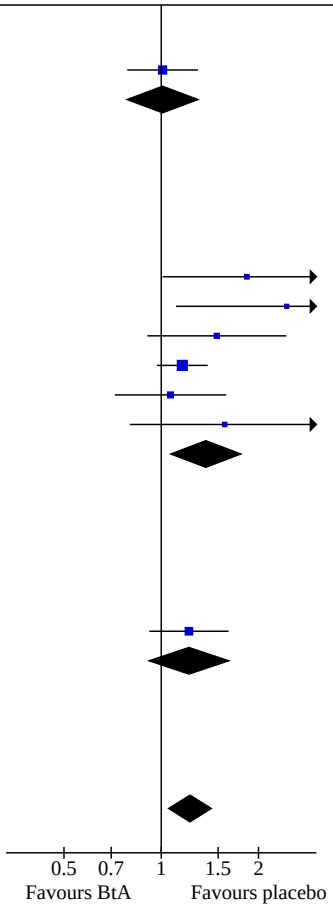
## Analysis 1.9. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 9: Adverse events: doses subgroup analysis

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.9.1 Low dose** | | | | | | |
| Poewe 1998 | 7 | 19 | 5 | 20 | 100.0% | 1.47 [0.56 , 3.85] |
| **Subtotal (95% CI)** | | **19** | | **20** | **100.0%** | **1.47 [0.56 , 3.85]** |
| Total events: | 7 | | 5 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.79 (P = 0.43) | | | | | | |
| **1.9.2 Medium dose** | | | | | | |
| Comella 2011 | 43 | 78 | 34 | 74 | 20.4% | 1.20 [0.87 , 1.65] |
| Poewe 1998 | 11 | 17 | 5 | 20 | 3.4% | 2.59 [1.12 , 5.97] |
| Poewe 2016 | 59 | 156 | 14 | 55 | 9.2% | 1.49 [0.91 , 2.44] |
| Truong 2005 | 34 | 37 | 34 | 43 | 47.9% | 1.16 [0.97 , 1.39] |
| Truong 2010 | 26 | 55 | 27 | 61 | 13.9% | 1.07 [0.72 , 1.59] |
| Wissel 2001 | 15 | 35 | 9 | 33 | 5.1% | 1.57 [0.80 , 3.09] |
| **Subtotal (95% CI)** | | **378** | | **286** | **100.0%** | **1.23 [1.06 , 1.44]** |
| Total events: | 188 | | 123 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 5.62, df = 5 (P = 0.35); I² = 11% | | | | | | |
| Test for overall effect: Z = 2.64 (P = 0.008) | | | | | | |
| **1.9.3 High dose** | | | | | | |
| Comella 2011 | 46 | 81 | 34 | 74 | 43.5% | 1.24 [0.91 , 1.69] |
| Lew 2018 | 36 | 88 | 10 | 45 | 31.6% | 1.84 [1.01 , 3.36] |
| Poewe 1998 | 15 | 18 | 5 | 20 | 24.9% | 3.33 [1.52 , 7.32] |
| **Subtotal (95% CI)** | | **187** | | **139** | **100.0%** | **1.79 [1.03 , 3.11]** |
| Total events: | 97 | | 49 | | | |
| Heterogeneity: Tau² = 0.16; Chi² = 6.05, df = 2 (P = 0.05); I² = 67% | | | | | | |
| Test for overall effect: Z = 2.08 (P = 0.04) | | | | | | |
| Test for subgroup differences: Chi² = 1.73, df = 2 (P = 0.42), I² = 0% | | | | | | |



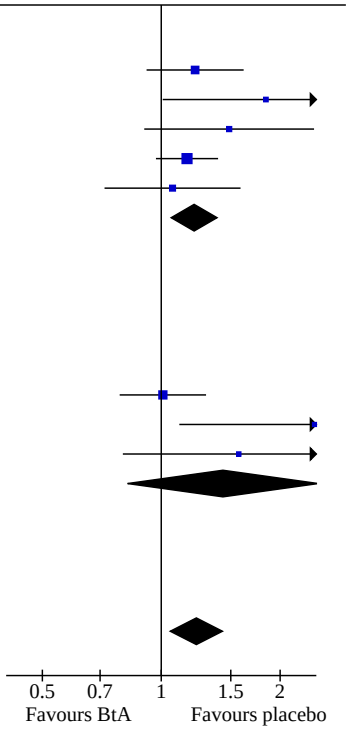
## Analysis 1.10. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 10: Adverse events: Botox A formulation subgroup analysis

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.10.1 Botox** | | | | | | |
| Charles 2012 | 52 | 88 | 48 | 82 | 20.7% | 1.01 [0.78 , 1.30] |
| **Subtotal (95% CI)** | | **88** | | **82** | **20.7%** | **1.01 [0.78 , 1.30]** |
| Total events: | 52 | | 48 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.07 (P = 0.94) | | | | | | |
| **1.10.2 Dysport** | | | | | | |
| Lew 2018 | 36 | 88 | 10 | 45 | 5.6% | 1.84 [1.01 , 3.36] |
| Poewe 1998 | 33 | 54 | 5 | 20 | 3.4% | 2.44 [1.11 , 5.38] |
| Poewe 2016 | 59 | 156 | 14 | 55 | 7.9% | 1.49 [0.91 , 2.44] |
| Truong 2005 | 34 | 37 | 34 | 43 | 28.6% | 1.16 [0.97 , 1.39] |
| Truong 2010 | 26 | 55 | 27 | 61 | 11.2% | 1.07 [0.72 , 1.59] |
| Wissel 2001 | 15 | 35 | 9 | 33 | 4.6% | 1.57 [0.80 , 3.09] |
| **Subtotal (95% CI)** | | **425** | | **257** | **61.3%** | **1.37 [1.07 , 1.76]** |
| Total events: | 203 | | 99 | | | |
| Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 8.96$, df = 5 (P = 0.11); $I^2 = 44\%$ | | | | | | |
| Test for overall effect: Z = 2.50 (P = 0.01) | | | | | | |
| **1.10.3 Xeomin** | | | | | | |
| Comella 2011 | 89 | 159 | 34 | 74 | 18.0% | 1.22 [0.92 , 1.62] |
| **Subtotal (95% CI)** | | **159** | | **74** | **18.0%** | **1.22 [0.92 , 1.62]** |
| Total events: | 89 | | 34 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.37 (P = 0.17) | | | | | | |
| **Total (95% CI)** | | **672** | | **413** | **100.0%** | **1.23 [1.05 , 1.43]** |
| Total events: | 344 | | 181 | | | |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.74$, df = 7 (P = 0.20); $I^2 = 28\%$ | | | | | | |
| Test for overall effect: Z = 2.64 (P = 0.008) | | | | | | |
| Test for subgroup differences: $Chi^2 = 2.95$, df = 2 (P = 0.23), $I^2 = 32.2\%$ | | | | | | |



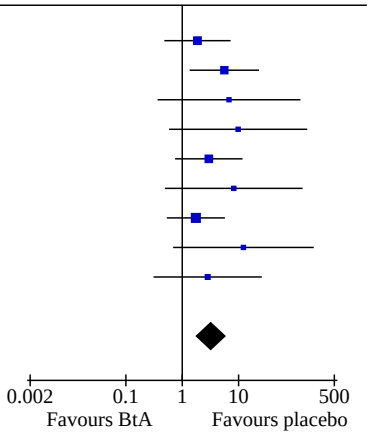
## Analysis 1.11. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 11: Adverse events: EMG-guided vs non-EMG-guided subgroup analysis

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.11.1 EMG-guided injection** | | | | | | |
| Comella 2011 | 89 | 159 | 34 | 74 | 18.0% | 1.22 [0.92 , 1.62] |
| Lew 2018 | 36 | 88 | 10 | 45 | 5.6% | 1.84 [1.01 , 3.36] |
| Poewe 2016 | 59 | 156 | 14 | 55 | 7.9% | 1.49 [0.91 , 2.44] |
| Truong 2005 | 34 | 37 | 34 | 43 | 28.6% | 1.16 [0.97 , 1.39] |
| Truong 2010 | 26 | 55 | 27 | 61 | 11.2% | 1.07 [0.72 , 1.59] |
| **Subtotal (95% CI)** | | **495** | | **278** | **71.3%** | **1.21 [1.06 , 1.38]** |
| Total events: | 244 | | 119 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 3.72, df = 4 (P = 0.45); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.82 (P = 0.005) | | | | | | |
| **1.11.2 Non-EMG-guided injection** | | | | | | |
| Charles 2012 | 52 | 88 | 48 | 82 | 20.7% | 1.01 [0.78 , 1.30] |
| Poewe 1998 | 33 | 54 | 5 | 20 | 3.4% | 2.44 [1.11 , 5.38] |
| Wissel 2001 | 15 | 35 | 9 | 33 | 4.6% | 1.57 [0.80 , 3.09] |
| **Subtotal (95% CI)** | | **177** | | **135** | **28.7%** | **1.43 [0.82 , 2.50]** |
| Total events: | 100 | | 62 | | | |
| Heterogeneity: Tau² = 0.16; Chi² = 5.95, df = 2 (P = 0.05); I² = 66% | | | | | | |
| Test for overall effect: Z = 1.27 (P = 0.20) | | | | | | |
| **Total (95% CI)** | | **672** | | **413** | **100.0%** | **1.23 [1.05 , 1.43]** |
| Total events: | 344 | | 181 | | | |
| Heterogeneity: Tau² = 0.01; Chi² = 9.74, df = 7 (P = 0.20); I² = 28% | | | | | | |
| Test for overall effect: Z = 2.64 (P = 0.008) | | | | | | |
| Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.56), I² = 0% | | | | | | |




## Analysis 1.12. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 12: Dysphagia

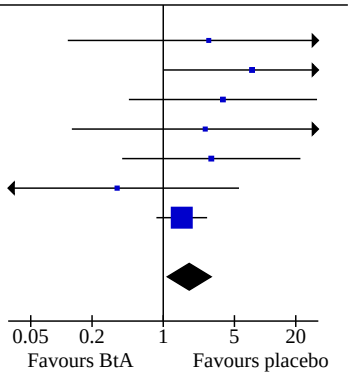
| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Charles 2012 | 6 | 88 | 3 | 82 | 18.4% | 1.86 [0.48 , 7.21] |
| Comella 2011 | 24 | 159 | 2 | 74 | 16.8% | 5.58 [1.36 , 23.01] |
| Greene 1990 | 3 | 28 | 0 | 27 | 3.9% | 6.76 [0.37 , 124.98] |
| Lew 2018 | 9 | 88 | 0 | 45 | 4.2% | 9.82 [0.58 , 164.99] |
| Poewe 1998 | 16 | 54 | 2 | 20 | 17.7% | 2.96 [0.75 , 11.75] |
| Poewe 2016 | 11 | 156 | 0 | 55 | 4.2% | 8.20 [0.49 , 136.94] |
| Truong 2005 | 6 | 37 | 4 | 43 | 23.9% | 1.74 [0.53 , 5.71] |
| Truong 2010 | 5 | 55 | 0 | 61 | 4.1% | 12.18 [0.69 , 215.31] |
| Wissel 2001 | 3 | 35 | 1 | 33 | 6.9% | 2.83 [0.31 , 25.85] |
| **Total (95% CI)** | | **700** | | **440** | **100.0%** | **3.19 [1.79 , 5.70]** |
| Total events: | 83 | | 12 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 4.74, df = 8 (P = 0.79); I² = 0% | | | | | | |
| Test for overall effect: Z = 3.93 (P < 0.0001) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



### Analysis 1.13. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 13: Diffuse weakness, tiredness

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Charles 2012 | 1 | 88 | 0 | 82 | 2.4% | 2.80 [0.12 , 67.72] |
| Comella 2011 | 16 | 159 | 1 | 74 | 6.1% | 7.45 [1.01 , 55.10] |
| Greene 1990 | 4 | 28 | 1 | 27 | 5.4% | 3.86 [0.46 , 32.35] |
| Lew 2018 | 2 | 88 | 0 | 45 | 2.7% | 2.58 [0.13 , 52.71] |
| Poewe 1998 | 8 | 54 | 1 | 20 | 6.0% | 2.96 [0.40 , 22.21] |
| Poewe 2016 | 1 | 156 | 1 | 55 | 3.2% | 0.35 [0.02 , 5.54] |
| Truong 2005 | 17 | 37 | 13 | 43 | 74.2% | 1.52 [0.86 , 2.70] |
| **Total (95% CI)** | | **610** | | **346** | **100.0%** | **1.80 [1.10 , 2.95]** |
| Total events: | 49 | | 17 | | | |

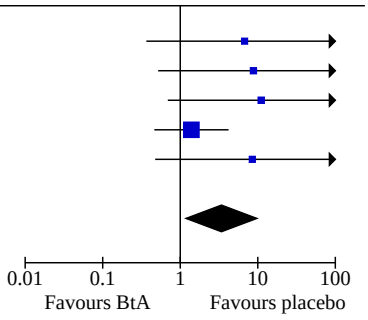
Heterogeneity: Tau² = 0.00; Chi² = 5.05, df = 6 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.33 (P = 0.02)
Test for subgroup differences: Not applicable




### Analysis 1.14. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 14: Neck weakness

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Greene 1990 | 3 | 28 | 0 | 27 | 11.7% | 6.76 [0.37 , 124.98] |
| Lew 2018 | 8 | 88 | 0 | 45 | 12.3% | 8.79 [0.52 , 148.87] |
| Poewe 1998 | 14 | 54 | 0 | 20 | 12.8% | 11.07 [0.69 , 177.41] |
| Truong 2005 | 6 | 37 | 5 | 43 | 51.3% | 1.39 [0.46 , 4.20] |
| Wissel 2001 | 4 | 35 | 0 | 33 | 11.9% | 8.50 [0.48 , 152.01] |
| **Total (95% CI)** | | **242** | | **168** | **100.0%** | **3.40 [1.19 , 9.71]** |
| Total events: | 35 | | 5 | | | |

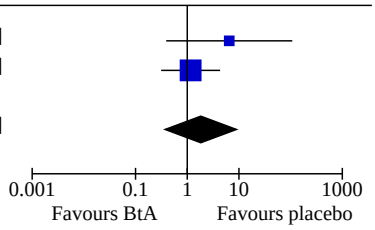
Heterogeneity: Tau² = 0.24; Chi² = 4.70, df = 4 (P = 0.32); I² = 15%
Test for overall effect: Z = 2.28 (P = 0.02)
Test for subgroup differences: Not applicable




### Analysis 1.15. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 15: Voice change, hoarseness

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Poewe 1998 | 8 | 54 | 0 | 20 | 26.3% | 6.49 [0.39 , 107.54] |
| Truong 2005 | 4 | 37 | 4 | 43 | 73.7% | 1.16 [0.31 , 4.33] |
| **Total (95% CI)** | | **91** | | **63** | **100.0%** | **1.83 [0.37 , 8.95]** |
| Total events: | 12 | | 4 | | | |

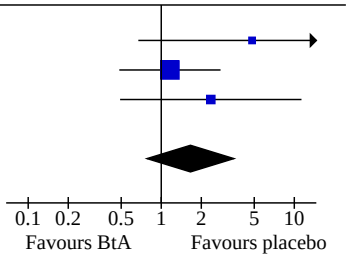
Heterogeneity: Tau² = 0.44; Chi² = 1.35, df = 1 (P = 0.24); I² = 26%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



### Analysis 1.16. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 16: Sore throat, dry mouth

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Poewe 1998 | 13 | 54 | 1 | 20 | 14.1% | 4.81 [0.67 , 34.46] |
| Truong 2005 | 8 | 37 | 8 | 43 | 64.0% | 1.16 [0.48 , 2.79] |
| Wissel 2001 | 5 | 35 | 2 | 33 | 21.9% | 2.36 [0.49 , 11.32] |
| **Total (95% CI)** | | **126** | | **96** | **100.0%** | **1.66 [0.78 , 3.51]** |
| Total events: | 26 | | 11 | | | |

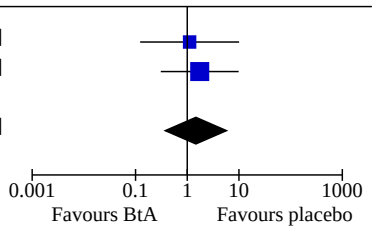
Heterogeneity: Tau² = 0.03; Chi² = 2.11, df = 2 (P = 0.35); I² = 5%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable




### Analysis 1.17. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 17: Vertigo, dizziness

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Poewe 1998 | 3 | 54 | 1 | 20 | 38.2% | 1.11 [0.12 , 10.07] |
| Truong 2005 | 3 | 37 | 2 | 43 | 61.8% | 1.74 [0.31 , 9.88] |
| **Total (95% CI)** | | **91** | | **63** | **100.0%** | **1.47 [0.38 , 5.73]** |
| Total events: | 6 | | 3 | | | |

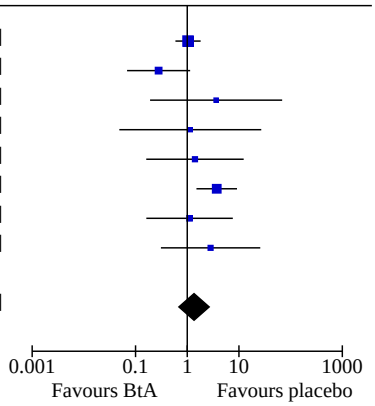
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable




### Analysis 1.18. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 18: Malaise, upper respiratory infection

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Charles 2012 | 20 | 88 | 18 | 82 | 30.1% | 1.04 [0.59 , 1.81] |
| Comella 2011 | 3 | 159 | 5 | 74 | 14.3% | 0.28 [0.07 , 1.14] |
| Lew 2018 | 3 | 88 | 0 | 45 | 4.6% | 3.62 [0.19 , 68.56] |
| Poewe 1998 | 1 | 54 | 0 | 20 | 4.1% | 1.15 [0.05 , 27.02] |
| Poewe 2016 | 4 | 156 | 1 | 55 | 7.7% | 1.41 [0.16 , 12.35] |
| Truong 2005 | 16 | 37 | 5 | 43 | 22.6% | 3.72 [1.51 , 9.17] |
| Truong 2010 | 2 | 55 | 2 | 61 | 9.2% | 1.11 [0.16 , 7.61] |
| Wissel 2001 | 3 | 35 | 1 | 33 | 7.4% | 2.83 [0.31 , 25.85] |
| **Total (95% CI)** | | **672** | | **413** | **100.0%** | **1.35 [0.69 , 2.65]** |
| Total events: | 52 | | 32 | | | |

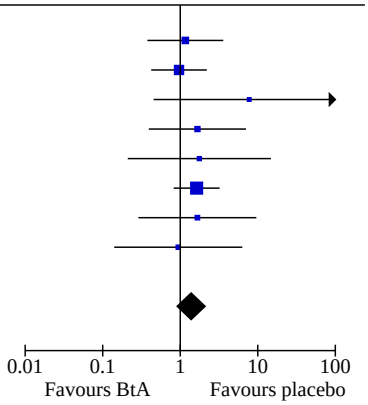
Heterogeneity: Tau² = 0.31; Chi² = 11.45, df = 7 (P = 0.12); I² = 39%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable



### Analysis 1.19. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 19: Local pain (injection site)

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Comella 2011 | 10 | 159 | 4 | 74 | 13.5% | 1.16 [0.38 , 3.59] |
| Greene 1990 | 8 | 28 | 8 | 27 | 25.2% | 0.96 [0.42 , 2.20] |
| Lew 2018 | 7 | 88 | 0 | 45 | 2.1% | 7.75 [0.45 , 132.76] |
| Poewe 1998 | 9 | 54 | 2 | 20 | 8.2% | 1.67 [0.39 , 7.06] |
| Poewe 2016 | 5 | 156 | 1 | 55 | 3.8% | 1.76 [0.21 , 14.76] |
| Truong 2005 | 14 | 37 | 10 | 43 | 36.8% | 1.63 [0.82 , 3.22] |
| Truong 2010 | 3 | 55 | 2 | 61 | 5.6% | 1.66 [0.29 , 9.59] |
| Wissel 2001 | 2 | 35 | 2 | 33 | 4.7% | 0.94 [0.14 , 6.31] |
| **Total (95% CI)** | | **612** | | **358** | **100.0%** | **1.38 [0.91 , 2.09]** |
| Total events: | 58 | | 29 | | | |

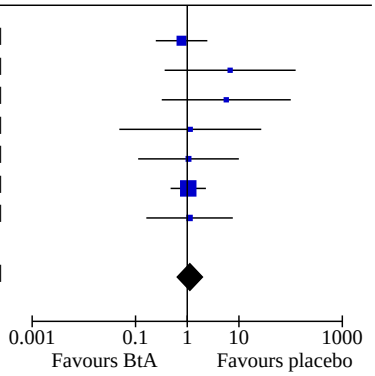
Heterogeneity: Tau² = 0.00; Chi² = 2.86, df = 7 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.53 (P = 0.13)
Test for subgroup differences: Not applicable




### Analysis 1.20. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 20: Headache

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Charles 2012 | 5 | 88 | 6 | 82 | 23.8% | 0.78 [0.25 , 2.45] |
| Greene 1990 | 3 | 28 | 0 | 27 | 3.7% | 6.76 [0.37 , 124.98] |
| Lew 2018 | 5 | 88 | 0 | 45 | 3.8% | 5.69 [0.32 , 100.58] |
| Poewe 1998 | 1 | 54 | 0 | 20 | 3.1% | 1.15 [0.05 , 27.02] |
| Poewe 2016 | 3 | 156 | 1 | 55 | 6.2% | 1.06 [0.11 , 9.96] |
| Truong 2005 | 9 | 37 | 10 | 43 | 50.8% | 1.05 [0.48 , 2.30] |
| Truong 2010 | 2 | 55 | 2 | 61 | 8.5% | 1.11 [0.16 , 7.61] |
| **Total (95% CI)** | | **506** | | **333** | **100.0%** | **1.12 [0.64 , 1.97]** |
| Total events: | 28 | | 19 | | | |

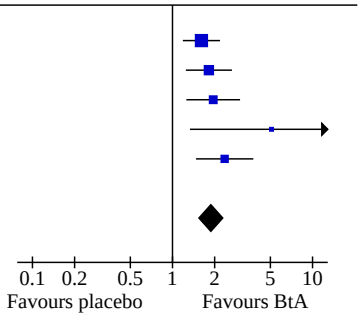
Heterogeneity: Tau² = 0.00; Chi² = 3.28, df = 6 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



## Analysis 1.21. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 21: Any improvement by subjective clinician assessment

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Charles 2012 (1) | 57 | 88 | 33 | 82 | 37.4% | 1.61 [1.19 , 2.18] |
| Comella 2011 (2) | 86 | 159 | 22 | 74 | 25.1% | 1.82 [1.25 , 2.66] |
| Lew 2018 (3) | 56 | 86 | 15 | 45 | 18.8% | 1.95 [1.26 , 3.04] |
| Poewe 1998 (4) | 27 | 53 | 2 | 20 | 2.1% | 5.09 [1.33 , 19.48] |
| Wissel 2001 (5) | 30 | 35 | 12 | 33 | 16.6% | 2.36 [1.47 , 3.78] |
| **Total (95% CI)** | | **421** | | **254** | **100.0%** | **1.88 [1.55 , 2.28]** |
| Total events: | 256 | | 84 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 4.18, df = 4 (P = 0.38); I² = 4%
Test for overall effect: Z = 6.32 (P < 0.00001)
Test for subgroup differences: Not applicable

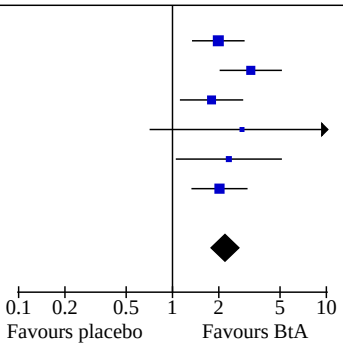



**Footnotes**
(1) Global Assessment Scale, week 4
(2) final visit (between 8 and 20 weeks)
(3) Clinical Global Impression of Change, 4 weeks
(4) Clinical Global Rating assessing efficacy and adverse events together, week 8
(5) week 4

## Analysis 1.22. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 22: Any improvement by subjective participant assessment

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Charles 2012 (1) | 49 | 88 | 23 | 82 | 27.7% | 1.99 [1.34 , 2.94] |
| Comella 2011 (2) | 104 | 159 | 15 | 74 | 19.8% | 3.23 [2.03 , 5.14] |
| Lew 2018 (3) | 48 | 86 | 14 | 45 | 19.1% | 1.79 [1.12 , 2.88] |
| Poewe 1998 (4) | 15 | 53 | 2 | 20 | 2.2% | 2.83 [0.71 , 11.28] |
| Truong 2005 (4) | 14 | 37 | 7 | 43 | 6.8% | 2.32 [1.05 , 5.14] |
| Wissel 2001 (5) | 30 | 35 | 14 | 33 | 24.3% | 2.02 [1.33 , 3.07] |
| **Total (95% CI)** | | **458** | | **297** | **100.0%** | **2.19 [1.78 , 2.70]** |
| Total events: | 260 | | 75 | | | |

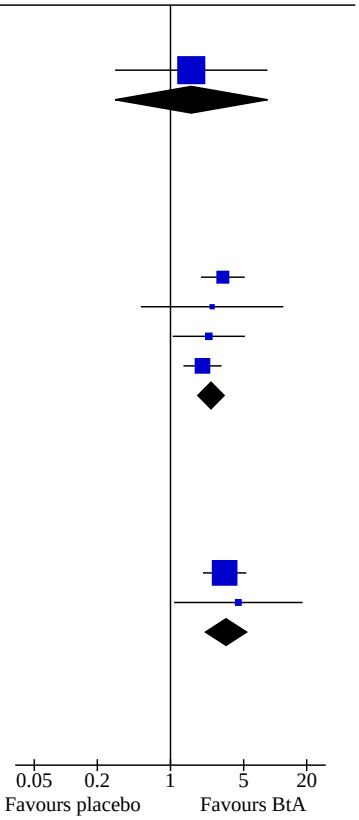
Heterogeneity: Tau² = 0.00; Chi² = 4.07, df = 5 (P = 0.54); I² = 0%
Test for overall effect: Z = 7.43 (P < 0.00001)
Test for subgroup differences: Not applicable




**Footnotes**
(1) Subjective Global Assessment Scale, week 4
(2) final visit (between 8 and 20 weeks)
(3) Patient Global Impression of Change, 4 weeks
(4) > 50% improvement (underestimate), week 4
(5) week 4

## Analysis 1.23. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 23: Any improvement by subjective participant assessment: doses subgroup analysis

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.23.1 Low dose** | | | | | | |
| Poewe 1998 (1) | 3 | 19 | 2 | 20 | 100.0% | 1.58 [0.30 , 8.43] |
| **Subtotal (95% CI)** | | **19** | | **20** | **100.0%** | **1.58 [0.30 , 8.43]** |
| Total events: | 3 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.53 (P = 0.59) | | | | | | |
| **1.23.2 Medium dose** | | | | | | |
| Comella 2011 (2) | 50 | 78 | 15 | 74 | 36.0% | 3.16 [1.95 , 5.12] |
| Poewe 1998 (1) | 4 | 16 | 2 | 20 | 3.4% | 2.50 [0.52 , 11.96] |
| Truong 2005 (1) | 14 | 37 | 7 | 43 | 13.2% | 2.32 [1.05 , 5.14] |
| Wissel 2001 (3) | 30 | 35 | 14 | 33 | 47.3% | 2.02 [1.33 , 3.07] |
| **Subtotal (95% CI)** | | **166** | | **170** | **100.0%** | **2.44 [1.82 , 3.25]** |
| Total events: | 98 | | 38 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.01$, df = 3 (P = 0.57); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 6.04 (P < 0.00001) | | | | | | |
| **1.23.3 High dose** | | | | | | |
| Comella 2011 (2) | 54 | 81 | 15 | 74 | 89.7% | 3.29 [2.04 , 5.30] |
| Poewe 1998 (1) | 8 | 18 | 2 | 20 | 10.3% | 4.44 [1.08 , 18.25] |
| **Subtotal (95% CI)** | | **99** | | **94** | **100.0%** | **3.39 [2.16 , 5.33]** |
| Total events: | 62 | | 17 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 5.29 (P < 0.00001) | | | | | | |
| Test for subgroup differences: $Chi^2 = 1.84$, df = 2 (P = 0.40), $I^2 = 0\%$ | | | | | | |




**Footnotes**

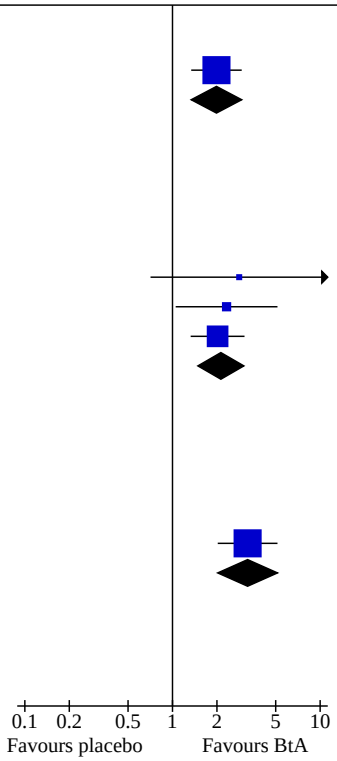
(1) > 50% improvement (underestimate), week 4

(2) final visit (between 8 and 20 weeks)

(3) week 4

## Analysis 1.24. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 24: Any improvement by subjective participant assessment: Botox A formulation subgroup analysis

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.24.1 Botox** | | | | | | |
| Charles 2012 (1) | 49 | 88 | 23 | 82 | 100.0% | 1.99 [1.34 , 2.94] |
| **Subtotal (95% CI)** | | **88** | | **82** | **100.0%** | **1.99 [1.34 , 2.94]** |
| Total events: | 49 | | 23 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 3.41 (P = 0.0006) | | | | | | |
| **1.24.2 Dysport** | | | | | | |
| Poewe 1998 (2) | 15 | 53 | 2 | 20 | 6.7% | 2.83 [0.71 , 11.28] |
| Truong 2005 (2) | 14 | 37 | 7 | 43 | 20.4% | 2.32 [1.05 , 5.14] |
| Wissel 2001 (3) | 30 | 35 | 14 | 33 | 72.9% | 2.02 [1.33 , 3.07] |
| **Subtotal (95% CI)** | | **125** | | **96** | **100.0%** | **2.13 [1.49 , 3.04]** |
| Total events: | 59 | | 23 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 2 (P = 0.86); I² = 0% | | | | | | |
| Test for overall effect: Z = 4.13 (P < 0.0001) | | | | | | |
| **1.24.3 Xeomin** | | | | | | |
| Comella 2011 (4) | 104 | 159 | 15 | 74 | 100.0% | 3.23 [2.03 , 5.14] |
| **Subtotal (95% CI)** | | **159** | | **74** | **100.0%** | **3.23 [2.03 , 5.14]** |
| Total events: | 104 | | 15 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 4.93 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Chi² = 2.75, df = 2 (P = 0.25), I² = 27.3% | | | | | | |

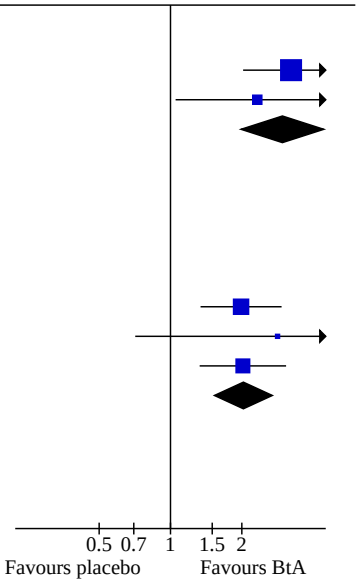



**Footnotes**

(1) Subjective Global Assessment Scale, week 4
(2) > 50% improvement (underestimate), week 4
(3) week 4
(4) final visit (between 8 and 20 weeks)

## Analysis 1.25. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 25: Any improvement by subjective participant assessment: EMG guided vs non-EMG-guided subgroup analysis

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.25.1 EMG-guided injection** | | | | | | |
| Comella 2011 (1) | 104 | 159 | 15 | 74 | 74.4% | 3.23 [2.03 , 5.14] |
| Truong 2005 (2) | 14 | 37 | 7 | 43 | 25.6% | 2.32 [1.05 , 5.14] |
| **Subtotal (95% CI)** | | **196** | | **117** | **100.0%** | **2.97 [1.99 , 4.43]** |
| Total events: | 118 | | 22 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 1 (P = 0.48); I² = 0% | | | | | | |
| Test for overall effect: Z = 5.31 (P < 0.00001) | | | | | | |
| **1.25.2 Non-EMG-guided injection** | | | | | | |
| Charles 2012 (3) | 49 | 88 | 23 | 82 | 51.0% | 1.99 [1.34 , 2.94] |
| Poewe 1998 (2) | 15 | 53 | 2 | 20 | 4.1% | 2.83 [0.71 , 11.28] |
| Wissel 2001 (4) | 30 | 35 | 14 | 33 | 44.8% | 2.02 [1.33 , 3.07] |
| **Subtotal (95% CI)** | | **176** | | **135** | **100.0%** | **2.03 [1.53 , 2.69]** |
| Total events: | 94 | | 39 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 2 (P = 0.89); I² = 0% | | | | | | |
| Test for overall effect: Z = 4.94 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Chi² = 2.30, df = 1 (P = 0.13), I² = 56.5% | | | | | | |



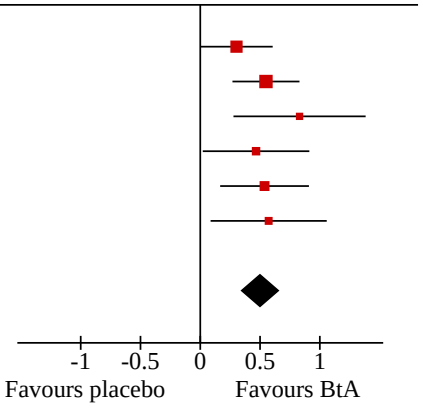

**Footnotes**

(1) final visit (between 8 and 20 weeks)
(2) > 50% improvement (underestimate), week 4
(3) Subjective Global Assessment Scale, week 4
(4) week 4

### Analysis 1.26. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 26: Cervical dystonia-specific pain

| Study or Subgroup | SMD | SE | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|
| Charles 2012 (1) | 0.303 | 0.1544 | 25.1% | 0.30 [0.00 , 0.61] |
| Comella 2011 (2) | 0.5495 | 0.143 | 29.3% | 0.55 [0.27 , 0.83] |
| Greene 1990 (3) | 0.8304 | 0.282 | 7.5% | 0.83 [0.28 , 1.38] |
| Truong 2005 (4) | 0.4666 | 0.2274 | 11.6% | 0.47 [0.02 , 0.91] |
| Truong 2010 (5) | 0.5376 | 0.1894 | 16.7% | 0.54 [0.17 , 0.91] |
| Wissel 2001 (6) | 0.572 | 0.2478 | 9.8% | 0.57 [0.09 , 1.06] |
| **Total (95% CI)** | | | **100.0%** | **0.50 [0.35 , 0.65]** |

Heterogeneity: Tau² = 0.00; Chi² = 3.27, df = 5 (P = 0.66); I² = 0%
Test for overall effect: Z = 6.45 (P < 0.00001)
Test for subgroup differences: Not applicable



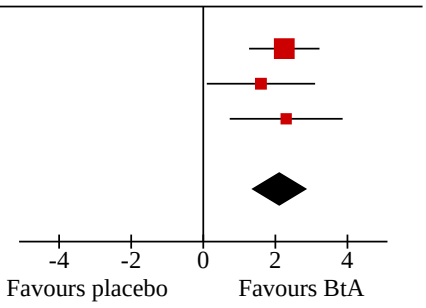

**Footnotes**

(1) pain intensity scale, week 4, pooled SD from P value
(2) TWSTRS pain, week 4, combined groups method
(3) % of difference from baseline, week 6, pooled SD from P value
(4) TWSTRS pain, week 4, SD appropriated from Truong 2010
(5) TWSTRS pain, week 4
(6) Pain scale, week 4, pooled SD from P value

### Analysis 1.27. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 27: Cervical dystonia-specific pain: TWSTRS pain subscale subgroup analysis

| Study or Subgroup | MD | SE | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|
| Comella 2011 (1) | 2.2472 | 0.4983 | 55.2% | 2.25 [1.27 , 3.22] |
| Truong 2005 (2) | 1.6 | 0.7666 | 23.3% | 1.60 [0.10 , 3.10] |
| Truong 2010 (3) | 2.3 | 0.799 | 21.5% | 2.30 [0.73 , 3.87] |
| **Total (95% CI)** | | | **100.0%** | **2.11 [1.38 , 2.83]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 5.69 (P < 0.00001)
Test for subgroup differences: Not applicable

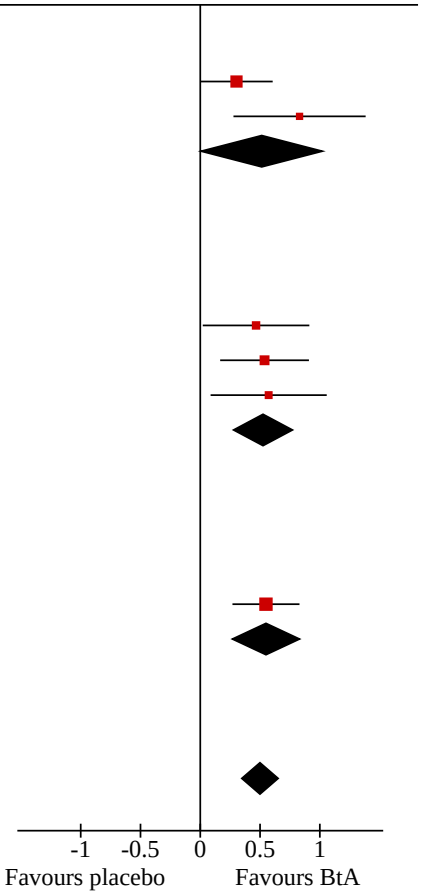



**Footnotes**

(1) TWSTRS pain, week 4, combined groups method
(2) TWSTRS pain, week 4, SD appropriated from Truong 2010
(3) TWSTRS pain, week 4

**Analysis 1.28. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 28: Cervical dystonia-specific pain: Botox A formulation subgroup analysis**

| Study or Subgroup | SMD | SE | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|
| **1.28.1 Botox** | | | | |
| Charles 2012 (1) | 0.303 | 0.1544 | 25.1% | 0.30 [0.00 , 0.61] |
| Greene 1990 (2) | 0.8304 | 0.282 | 7.5% | 0.83 [0.28 , 1.38] |
| **Subtotal (95% CI)** | | | **32.7%** | **0.51 [0.01 , 1.02]** |
| Heterogeneity: Tau² = 0.09; Chi² = 2.69, df = 1 (P = 0.10); I² = 63% | | | | |
| Test for overall effect: Z = 1.99 (P = 0.05) | | | | |
| **1.28.2 Dysport** | | | | |
| Truong 2005 (3) | 0.4666 | 0.2274 | 11.6% | 0.47 [0.02 , 0.91] |
| Truong 2010 (4) | 0.5376 | 0.1894 | 16.7% | 0.54 [0.17 , 0.91] |
| Wissel 2001 (5) | 0.572 | 0.2478 | 9.8% | 0.57 [0.09 , 1.06] |
| **Subtotal (95% CI)** | | | **38.0%** | **0.52 [0.28 , 0.77]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 2 (P = 0.95); I² = 0% | | | | |
| Test for overall effect: Z = 4.18 (P < 0.0001) | | | | |
| **1.28.3 Xeomin** | | | | |
| Comella 2011 (6) | 0.5495 | 0.143 | 29.3% | 0.55 [0.27 , 0.83] |
| **Subtotal (95% CI)** | | | **29.3%** | **0.55 [0.27 , 0.83]** |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 3.84 (P = 0.0001) | | | | |
| **Total (95% CI)** | | | **100.0%** | **0.50 [0.35 , 0.65]** |
| Heterogeneity: Tau² = 0.00; Chi² = 3.27, df = 5 (P = 0.66); I² = 0% | | | | |
| Test for overall effect: Z = 6.45 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 0.02, df = 2 (P = 0.99), I² = 0% | | | | |

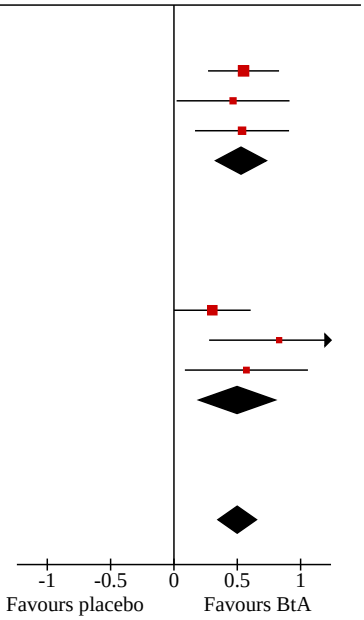



**Footnotes**

(1) pain intensity scale, week 4, pooled SD from P value
(2) % of difference from baseline, week 6, pooled SD from P value
(3) TWSTRS pain, week 4, SD appropriated from Truong 2010
(4) TWSTRS pain, week 4
(5) Pain scale, week 4, pooled SD from P value
(6) TWSTRS pain, week 4, combined groups method

## Analysis 1.29. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 29: Cervical dystonia-specific pain: EMG-guided vs non-EMG-guided subgroup analysis

| Study or Subgroup | SMD | SE | BtA Total | Placebo Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.29.1 EMG-guided injection** | | | | | | |
| Comella 2011 (1) | 0.5495 | 0.143 | 159 | 74 | 29.3% | 0.55 [0.27 , 0.83] |
| Truong 2005 (2) | 0.4666 | 0.2274 | 37 | 43 | 11.6% | 0.47 [0.02 , 0.91] |
| Truong 2010 (3) | 0.5376 | 0.1894 | 55 | 61 | 16.7% | 0.54 [0.17 , 0.91] |
| **Subtotal (95% CI)** | | | **251** | **178** | **57.6%** | **0.53 [0.33 , 0.73]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 2 (P = 0.95); I² = 0% | | | | | | |
| Test for overall effect: Z = 5.19 (P < 0.00001) | | | | | | |
| **1.29.2 Non-EMG-guided injection** | | | | | | |
| Charles 2012 (4) | 0.303 | 0.1544 | 88 | 82 | 25.1% | 0.30 [0.00 , 0.61] |
| Greene 1990 (5) | 0.8304 | 0.282 | 28 | 27 | 7.5% | 0.83 [0.28 , 1.38] |
| Wissel 2001 (6) | 0.572 | 0.2478 | 0 | 0 | 9.8% | 0.57 [0.09 , 1.06] |
| **Subtotal (95% CI)** | | | **116** | **109** | **42.4%** | **0.50 [0.20 , 0.80]** |
| Heterogeneity: Tau² = 0.02; Chi² = 2.96, df = 2 (P = 0.23); I² = 33% | | | | | | |
| Test for overall effect: Z = 3.24 (P = 0.001) | | | | | | |
| **Total (95% CI)** | | | **367** | **287** | **100.0%** | **0.50 [0.35 , 0.65]** |
| Heterogeneity: Tau² = 0.00; Chi² = 3.27, df = 5 (P = 0.66); I² = 0% | | | | | | |
| Test for overall effect: Z = 6.45 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0% | | | | | | |



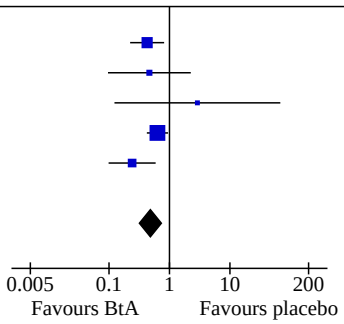

**Footnotes**

(1) TWSTRS pain, week 4, combined groups method
(2) TWSTRS pain, week 4, SD appropriated from Truong 2010
(3) TWSTRS pain, week 4
(4) pain intensity scale, week 4, pooled SD from P value
(5) % of difference from baseline, week 6, pooled SD from P value
(6) Pain scale, week 4, pooled SD from P value

## Analysis 1.30. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 30: Tolerability: dropouts

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Charles 2012 (1) | 11 | 88 | 24 | 82 | 27.7% | 0.43 [0.22 , 0.82] |
| Comella 2011 (2) | 3 | 159 | 3 | 74 | 6.5% | 0.47 [0.10 , 2.25] |
| Greene 1990 (3) | 1 | 28 | 0 | 27 | 1.7% | 2.90 [0.12 , 68.15] |
| Lew 2018 (4) | 29 | 86 | 24 | 45 | 46.8% | 0.63 [0.42 , 0.95] |
| Truong 2010 (5) | 5 | 55 | 23 | 61 | 17.2% | 0.24 [0.10 , 0.59] |
| **Total (95% CI)** | | **416** | | **289** | **100.0%** | **0.48 [0.32 , 0.73]** |
| Total events: | 49 | | 74 | | | |

Heterogeneity: Tau² = 0.05; Chi² = 5.24, df = 4 (P = 0.26); I² = 24%
Test for overall effect: Z = 3.41 (P = 0.0006)
Test for subgroup differences: Not applicable



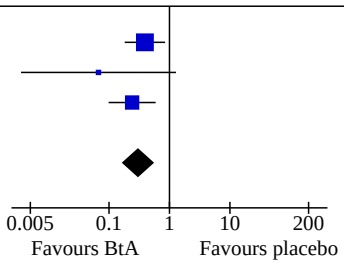

**Footnotes**

(1) BtA: 8 due to therapeutic failure, 3 due to other reasons; placebo: 19 due to therapeutic failure, 5 due to other reasons
(2) BtA: 3 adverse events (1 pain, muscle and neck weakness, 1 nausea and dizziness, 1 muscle weakness); Placebo: 3 due to therapeutic failure
(3) BtA: 1 dysphagia
(4) BtA: 1 due to adverse events, 1 was a participant decision, 1 was a sponsor decision, 1 participant withdrew consent, 25 due to transition to open la
(5) BtA: 5 due to therapeutic failure; placebo: 23 due to therapeutic failure

## Analysis 1.31. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 31: Tolerability: dropouts due to lack of efficacy subgroup analysis

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Charles 2012 (1) | 8 | 88 | 19 | 82 | 55.4% | 0.39 [0.18 , 0.85] |
| Comella 2011 (2) | 0 | 159 | 3 | 74 | 3.8% | 0.07 [0.00 , 1.28] |
| Truong 2010 (3) | 5 | 55 | 23 | 61 | 40.8% | 0.24 [0.10 , 0.59] |
| **Total (95% CI)** | | **302** | | **217** | **100.0%** | **0.30 [0.17 , 0.53]** |
| Total events: | 13 | | 45 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 4.11 (P < 0.0001)
Test for subgroup differences: Not applicable



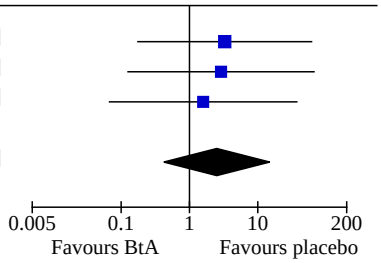

**Footnotes**

(1) BtA: 8 due to therapeutic failure; placebo: 19 due to therapeutic failure
(2) Placebo: 3 due to therapeutic failure
(3) BtA: 5 due to therapeutic failure; placebo: 23 due to therapeutic failure

**Analysis 1.32. Comparison 1: Botulinum toxin type A (BtA) versus placebo, Outcome 32: Tolerability: dropouts due to adverse events subgroup analysis**

| Study or Subgroup | BtA Events | BtA Total | Placebo Events | Placebo Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Comella 2011 (1) | 3 | 159 | 0 | 74 | 36.6% | 3.28 [0.17 , 62.72] |
| Greene 1990 (2) | 1 | 28 | 0 | 27 | 31.9% | 2.90 [0.12 , 68.15] |
| Lew 2018 (3) | 1 | 86 | 0 | 45 | 31.5% | 1.59 [0.07 , 38.17] |
| **Total (95% CI)** | | **273** | | **146** | **100.0%** | **2.51 [0.42 , 14.94]** |
| Total events: | 5 | | 0 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable




**Footnotes**

(1) BtA: 3 adverse events (1 pain, muscle and neck weakness, 1 nausea and dizziness, 1 muscle weakness)
(2) BtA: 1 dysphagia
(3) BtA: colon neoplasm (considered by the investigator to be unrelated)

## 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 |
| **Cervical dystonia or spasmodic torticollis** | A common movement disorder in which people have abnormal movements or postures of the head and neck 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. |
| **Electromyography** | An examination that displays the electrical activity of muscles using pieces of metal attached to the skin or inserted into the muscle. |
| **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. |

**BtA:** botulinum toxin type A

**Table 2. Summary of included studies - participants and drug administration**

| Study ID | Number of participants | Number of dropouts | Age mean, range (years) | Baseline CD impairment BtA/placebo | % participants naive to Bt | BtA formulation | Total dose per participant | EMG guidance | Study duration (weeks) |
|---|---|---|---|---|---|---|---|---|---|
| Charles 2012 | 170 | 35 (11 in BtA) | 55, 31 to 76 | 9.2/9.3 (CDSS) | 0 | Botox (OnaBtA) | 236 U | No | 10 |
| Comella 2011 | 233 | 14 (8 in BtA) | 53 | 42.4/41.8 (TWSTRS) | 39 | Xeomin (IncoBtA) | 120 U or 240 U | At discretion | 20 |
| Greene 1990 | 55 | 3 (3 in BtA) | 50 | 21% severe/ 41% severe | 100 | Botox (OnaBtA) | 150 U to 165 U | No | 12 |
| Poewe 1998 | 75 | 2 (2 in BtA) | 47, 26 to 82 | 13.9/14.4 (Tsui scale) | 100 | Dysport (AboBtA) | 250 U, 500 U, or 1000 U | No | 8 |
| Poewe 2016 | 213 | N/A | 49 | 46/47 (TWSTRS) | 10 | Dysport (AboBtA) | 500 U | N/A | 12 |
| Truong 2005 | 80 | 56 (22 in BtA) | 54, 27 to 78 | 45.1/46.2 (TWSTRS) | 26 | Dysport (AboBtA) | 500 U | At discretion | 20 |
| Truong 2010 | 116 | 33 (10 in BtA) | 53, 20 to 79 | 43.8/45.8 (TWSTRS) | 17 | Dysport (AboBtA) | 500 U | At discretion | 12 |
| Wissel 2001 | 68 | 0 | 48, 18 to 75 | 11.1/11.5 (Tsui scale) | 31 | Dysport (AboBtA) | 500 U | No | 16 |

**Bt:** botulinum toxin; **CD**: cervical dystonia; **CDSS**: Cervical Dystonia Severity Scale; **EMG**: electromyography; **TWSTRS**: Toronto Western Spasmodic Torticollis Rating Scale

# 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 |
|---|---|---|
| 9 October 2020 | New citation required but conclusions have not changed | We included one new trial, enrolling 134 participants, in the review and meta-analysis (Lew 2018). |
| 25 July 2020 | New search has been performed | We included one new trial, enrolling 134 participants, in the review and meta-analysis (Lew 2018). |

## HISTORY

Protocol first published: Issue 2, 2002
Review first published: Issue 1, 2005

| Date | Event | Description |
|---|---|---|
| 14 November 2016 | New citation required but conclusions have not changed | New authorship, accumulation of changes, re-assessment, and rewriting according to new quality standards, added a 'Summary of findings' table |

| Date | Event | Description |
|---|---|---|
| 6 October 2016 | New search has been performed | We included three new trials, enrolling a total of 562 participants, in the meta-analysis and review (Comella 2011; Poewe 2016; Truong 2010) |
| 6 October 2008 | Amended | Converted to new review format. |
| 25 October 2004 | New citation required and conclusions have changed | Substantive amendment |

## CONTRIBUTIONS OF AUTHORS

Austen P 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

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Designing the review - APM, CS, JC, JJF

Co-ordinating the review - JC

Designing search strategies – FBR, GSD, JC

Undertaking searches – FBR, GSD

Screening search results – FRB, GSD, MC, REM

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

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

Appraising quality of papers - FRB, GSD, MC, REM

Extracting data from papers - FRB, GSD, MC, REM

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

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

Entering data into Review Manager 5 - FRB, GSD, MC, REM

Analysis of data - FRB, GSD, MC, REM

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

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GRADE assessment - GSD, FBR

Providing general advice on the review – APM, 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). Searching for studies, selection of studies, data extraction and analysis (including risk of bias), and GRADE assessment were performed by authors (FBR, GSD, MC, REM), who were not trialists. JJF and CS were speakers at symposia promoted by Elan, Allergan, and Ipsen.

APM has received royalties from Ipsen for the use of the 'LIVEchart' scoring system for botulinum toxin treatment efficacy. He has 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 for other purposes.

## SOURCES OF SUPPORT

### Internal sources

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### External sources

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this updated review, we restricted the study designs accepted to parallel-group studies, and we opted not to exclude studies based on allocation concealment. No changes were made to the type of participants included, or in the interventions allowed.

Adverse events, which were originally a secondary outcome, were included in this updated review as a primary safety outcome. Also, in this safety analysis we considered the proportion of participants with the most frequent adverse events, which was not stated in the original protocol. An assessment of the duration of effect was included as a new secondary outcome measure.

We no longer consider immunogenicity to be an outcome of interest, as we believe it does not enhance patient's, physician's, or policymaker's ability to make decisions regarding the question of this review. At most, it is an inadequate surrogate measure of the risk of developing clinical non-responsiveness.

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

We used the latest recommended Cochrane tool to assess risk of bias, which the review authors expanded to include two additional criteria. We opted to include the enriched population domains, since a known positive response to botulinum toxin type A and certain disease subtypes are known to influence the magnitude of response to the intervention. As has been verified in a recent 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 analysed blinding of outcome assessment in two new subcategories: subjective and objective assessment, and also added a ‘Summary of findings' table. The search strategy was prolonged to July 2020.

We added Trial Sequential Analysis, which was not in the original review protocol.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Botulinum Toxins, Type A [adverse effects] [*therapeutic use]; Deglutition Disorders [etiology]; Muscle Weakness [etiology]; Neuromuscular Agents [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Torticollis [*drug therapy]

### MeSH check words

Humans