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Botulinum toxin type A versus botulinum toxin type B for cervical dystonia

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Botulinum toxin type A versus botulinum toxin type B for cervical dystonia

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Abstract

Background

This is an update of a Cochrane review first published in 2003, and previously updated in 2009 (no change in conclusions). Cervical dystonia is the most common form of focal dystonia and is a disabling disorder characterized by painful involuntary head posturing. Botulinum toxin type A (BtA) is usually considered the first line therapy for this condition, although botulinum toxin type B (BtB) is an alternative option, with no compelling theoretical reason as to why it might not be as, or even more effective, than BtA.

Objectives

To compare the efficacy, safety, and tolerability of botulinum toxin type A versus botulinum toxin type B in cervical dystonia.

Search methods

We identified studies for inclusion in the review using the Cochrane Movement Disorders Group trials register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, reference lists of articles and conference proceedings, last run in October 2015. Search was unrestricted by language.

Selection criteria

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

Data collection and analysis

Two independent authors assessed records, selected included studies, extracted data using a paper pro forma and evaluated the risk of bias. Disagreements were solved by consensus or by a third author. We performed one meta-analysis for the comparison BtA versus BtB. We used random-effects models in the presence of considerable heterogeneity and fixed-effect models when there was no heterogeneity. We performed no subgroup analyses. The primary efficacy outcome was overall improvement on any validated symptomatic rating scale. The primary safety outcome was the proportion of participants with any adverse event.

Main results

Three RCTs of low-to-moderate overall methodological quality including 270 participants with cervical dystonia were included. Two studies exclusively enrolled patients known to have a positive response to BtA treatment, therefore including an enriched population with higher probability of benefit from BtA treatment. None of the trials were independently funded. All RCTs evaluated the effect of a single Bt treatment session using doses between 100 and 250U of BtA and 5000 to 10000U of BtB. We found no difference between the two types of botulinum toxin in terms of overall efficacy and safety, as assessed by the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and the number of adverse events, respectively. However, when compared to BtA, treatment with BtB was associated with an improvement of 0.99 points (95% CI: 0.12 to 1.85; $I^2=0\%$) on the TWSTRS pain sub-scale at weeks 2-4 after injection, as well as with an increased risk of treatment-related dysphagia with a risk ratio (RR) of 0.49, favouring the BtA group (95% CI: 0.32 to 0.75, $I^2=27\%$) and sore throat/dry mouth, with a RR of 0.42 favouring the BtA group (95% CI: 0.31 to 0.57, $I^2=77\%$). The two types of botulinum toxin were otherwise shown to be clinically non-distinguishable in all the remaining outcomes.

Authors' conclusions

A single treatment session of BtA and a single treatment session of BtB are equally effective and well tolerated in the treatment of adults with certain types of cervical dystonia. Treatment with BtB causes a greater decrease disease-associated pain whilst also increasing the rate of dysphagia and sore throat/dry mouth when compared to treatment with BtA. Overall, there is no clinical evidence to support or not support the preferential use of one form of botulinum toxin over another. There is no evidence from RCTs neither regarding comparative development of secondary non-responsiveness to botulinum toxin nor regarding quality of life domains with either treatment.

Resumo em Língua Portuguesa

A distonia cervical compreende uma patologia neurológica pouco frequente com impacto negativo na qualidade de vida dos doentes. O tratamento de primeira linha é com efetividade com recurso a injeções intramusculares de toxina botulínica, que está disponível comercialmente em dois tipos: a toxina botulínica tipo A e a toxina botulínica tipo B. Esta revisão sistemática Cochrane visa comparar estes dois compostos em relação à sua eficácia e segurança no tratamento da distonia cervical. Após um processo de pesquisa sistemática para ensaios aleatorizados sobre o tema, extração de dados e combinação dos mesmos com recurso a técnicas de combinação por meta-análise, demonstrou-se que não existem diferenças nos perfis de eficácia e segurança entre ambas as formulações de toxina botulínica, com as exceções de uma subescala de doença (avaliador dor) e a proporção de doentes com efeitos adversos específicos.

Plain language summary

A comparison of botulinum toxin type A versus botulinum toxin type B for involuntary positioning of the head, or cervical dystonia

Undesired, uncontrollable, and often painful, placement of the head, a disease called cervical dystonia or spasmodic torticollis, is a relatively uncommon condition (affecting 57 to 280 per million) that can be very disabling and can compromise quality of life. Most times the cause is unknown and no cure exists. As this is typically a chronic disease it requires long-term treatment.

Botulinum toxin is a natural powerful chemical produced by a bacterium called *Clostridium botulinum*, that can cause severe paralysis in animals and humans. It can also be used to treat many conditions, in particular

those with involuntary muscle contractions, such as cervical dystonia, by delivering intra-muscular botulinum toxin injections. There are different types of Bt, not all available for therapeutic purposes. Botulinum toxin type A (BtA) is normally the first-used treatment in cervical dystonia, but botulinum toxin type B (BtB) is considered an alternative option.

This update of a previous Cochrane review aimed to assess the effectiveness (reduction in severity, disability and pain) and safety of BtA compared with BtB in cervical dystonia.

We performed a literature search in October 2015 for studies that compared BtA with BtB in patients with cervical dystonia.

We found three studies comparing a single treatment sessions of both BtA and BtB in 270 patients.

There was low-to-moderate quality evidence that there is no difference between BtA and BtB. BtB-treated patients, however, have slightly less pain due to their condition and at the same time are at an increased risk of swallowing difficulties and feel dry mouth/sore throat.

Further studies are needed to establish the long-term comparative benefit of both types of treatment, including its impact on quality of life, and to find which, if any, treatment is associated with more patients becoming unresponsive to treatment.

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Summary of findings







Botulinum toxin type A versus Bptulinum toxin type B for Cervical Dystonia

Patient or population: Adults with Cervical Dystonia

Setting: Hospital-based, movement disorders clinics

Intervention: Botulinum toxin type A

Comparison: Botulinum toxin type B

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with BtB	Risk with BtA				
Overall Cervical Dystonia improvement as assessed with validated scales: change from baseline to week 4	The mean overall Cervical Dystonia improvement as assessed with validated scales: change from baseline to week 4 was 0	The mean overall Cervical Dystonia improvement as assessed with validated scales: change from baseline to week 4 in the intervention group was 1.44 fewer (3.58 fewer to 0.7 more)	-	231 (2 RCTs)	 LOW ¹	
Cervical Dystonia associated Pain: change from baseline to week 2-4 as assessed with validated scales	The mean cervical Dystonia associated Pain: change from baseline to week 2-4 as assessed with validated scales was 0	The mean cervical Dystonia associated Pain: change from baseline to week 2-4 as assessed with validated scales in the intervention group was 0.99 fewer (1.85 fewer to 0.12 fewer)	-	251 (3 RCTs)	 MODERATE ²	
Subjective change as assessed by the patient at week 4	The mean subjective change as assessed by the patient at week 4 was 0	The mean subjective change as assessed by the patient at week 4 in the intervention group was 0.2 more (0.17 fewer to 0.57 more)	-	138 (1 RCT)	 MODERATE ²	
Proportion of patients with adverse events	Study population		RR 0.72 (0.51 to 1.00)	111 (1 RCT)	 LOW ¹	
	661 per 1000	476 per 1000 (337 to 661)				
Dysphagia	Study population		RR 0.49 (0.32 to 0.75)	269 (3 RCTs)	 MODERATE ²	
	346 per 1000	170 per 1000 (111 to 260)				
Sore Throat/Dry Mouth	Study population		RR 0.42 (0.31 to 0.57)	249 (2 RCTs)	 LOW ^{2,3}	
	612 per 1000	257 per 1000 (190 to 349)				

*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; MD: Mean difference; RR: Risk ratio

GRADE Working Group grades of evidence

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

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

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

Background

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews 2003, Issue 3 (Costa 2003), evaluating the efficacy and safety of botulinum toxin type A (BtA) versus botulinum toxin type B (BtB) in the treatment of cervical dystonia.

Description of the condition

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 characterized by involuntary sustained or intermittent muscle contractions causing abnormal, often repetitive, movements or postures of the face, neck, trunk or limbs (Albanese 2013). 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, e.g. hemifacial spasm), multifocal dystonia (two or more nonadjacent regions), hemidystonia (ipsilateral regions) and generalized 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. At the average age of 40 years, almost half of the patients quit working or retire early due to dystonia, and 10 years later, only 25% of patients are working compared to 62% of the general population (Zoons 2012). Moreover, health-related quality of life is significantly diminished, mainly attributable to depression and anxiety, with scores comparable to patients 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 characterized by abnormal movements of 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 and/or shoulder pain occur in more than 70% of patients (Tarsy 2006; Chan 1991).

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). Complex torticollis, a combination of these abnormal patterns, is yet very frequent to find in clinical practice.

The etiology of most forms of dystonia is still not fully understood, with the exception of early-onset dystonia, for which an hereditary etiology 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 (Hallett 1998) resulting in abnormal sensorimotor integration. Cervical dystonia can also be secondary to brain injury, infections of the CNS, drugs (such as levodopa or antipsychotics), toxics, 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 observed 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 is seldom progressive to generalized dystonia, although it often extends to contiguous body regions. For most patients, cervical dystonia is a life-long disorder, with only about 10% undergoing spontaneous remissions (Jahanshani 1990).

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

Description of the intervention

Botulinum toxin (Bt) is a powerful biological toxin produced by *Clostridium botulinum*. The

active form of botulinum toxin is a di-chain polypeptide composed of two chains: a heavy chain (100 kDa) and a light chain (50 kDa), and by associating with certain auxiliary proteins (hemagglutinins and non-hemagglutinins), the toxin forms a complex of variable size (Simpson 2004). The nontoxic proteins aid in the formation of neutralizing antibodies, though beyond this their role is unclear (Frevort 2010). Bt binds to peripheral cholinergic nerve terminals of the neuromuscular junction as well as sympathetic ganglionic, parasympathetic ganglionic and postganglionic terminals (Simpson 2004). Bt, after binding to an acceptor protein, 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-ethylmaleimidesensitive 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). As the fusion of the vesicle membranes becomes inhibited, there is a temporary blockade of acetylcholine release at cholinergic synapses, causing a local chemodenervation. Temporary synapses are consequently formed via the process of axonal sprouting (Duchen 1971; Holland 1981; Juzans 1996).

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

Botulinum toxin is injected into the muscles involved in dystonia, with or without guidance by either electromyography (EMG) or ultrasound. As a general rule, the number of muscles injected and the number of injection sites per muscle are tailored to the severity of the case in question and the mass of the muscle, respectively. 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 Bt injection (Jankovic 2004). Eventually, the muscle paralysis subsides, and this is associated with the formation of new sprouts capable of

neurotransmission. Over time, synaptic activity resumes in the original nerve terminals, leading to sprout regression (de Paiva 1999).

Currently there are two commercially available botulinum toxin serotypes (BtA and BtB). The following products are commonly available (three BtA and one BtB): onabotulinumtoxinA (Botox®, Allergan Inc., Irvine, CA, USA), abobotulinumtoxinA (Dysport®/Reloxin®/Azzalure®, Ipsen Pharma, Boulogne Billancourt, France), incobotulinumtoxinA (Xeomin®/Bocouture® Merz GmbH, Frankfurt, Germany), and rimabotulinumtoxinB (Myobloc®/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®/Lantox® (Lanzhou Institute of Biological Products, China), PurTox® (Mentor Worldwide LLC, Santa Barbara, CA, USA), and Neuronox® (Medy-Tox Inc, South Korea)(Walker 2014).

How the intervention might work

The therapeutic potential of all Bt serotypes derives from its ability to inhibit the release of acetylcholine from the presynaptic nerve terminal into the synaptic cleft, causing local chemodenervation (Jankovic 2004). In addition to this, recent research has also suggested that Bt is active at the level multiple levels, namely sensory nerve terminals, and muscle spindles, which leads to a reduction in sensory input and fewer muscle contractions (Matak 2014; Filippi 1993; Rosales 1996; Rosales 2010).

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

Until recently, SNARE proteins were considered the only target-molecules of Bt. Thus, it was widely accepted that the therapeutic and toxic actions of Bt were exclusively mediated by SNARE cleavage preventing the release of synaptic neurotransmitters. However, recent studies have suggested that a number of Bt actions might not be mediated by SNARE cleavage, specifically regarding neuroexocytosis, cell cycle and apoptosis, neurogenesis and gene

expression (Matak 2015). The existence of unknown Bt molecular targets and modulation of unknown signalling pathways is a possibility that may prove to be pharmacologically relevant.

Why it is important to do this review

BtA is the toxin serotype that has been most intensively studied and approved for the treatment of the large number of focal dystonias. BtA is considered the first line therapy for cervical dystonia and has proven to be effective in the symptomatic management of this condition (Albanese 2013). However, not all patients have an adequate clinical response. Primary non-response to botulinum toxin is seen in cases where the first and subsequent treatment cycles do not elicit a response. Cases of secondary non-response, however, respond to initial treatment, but over the course of multiple treatment cycles, this effect wanes and is eventually lost. Secondary non-response is partially explained by the formation of neutralizing antibodies, though it is worth noting that there are cases of secondary non-responders without positive antibody titers (Hanna 1998; Lange 2009) as well as cases with positive titers but with an adequate sensitivity to Bt (Brin 2008; Müller 2009). An estimated 4-20% of patients develop neutralizing antibodies to the toxin (Brashear 2008; Fabbri 2015), and if secondary non-responsiveness occurs, it is partially related to the protein load, with higher protein load per dose generating higher antibody titers (Benecke 2012; Frevert 2010).

When clinical non-response occurs, other botulinum toxin serotypes are important treatment options for cervical dystonia (Cullis 2000; Eleopra 1997; Greene 1993). At the present time, BtB is the only approved non-BtA formulation available for the treatment of cervical dystonia in the European Union and North America.

Although different botulinum toxin subtypes have different molecular targets, to date we know of no evidence from systematic reviews or randomised controlled trials that presents conclusive evidence regarding the comparative effectiveness of BtA and BtB for treating cervical dystonia.

A Cochrane systematic review previously assessed the efficacy and safety of BtA versus BtB in patients with cervical dystonia. This is the second update of that review having been previously updated in 2009, with no changes to conclusions. The original review concluded that

it was not possible to make definitive comparisons between BtA and BtB for the treatment of cervical dystonia, having included zero trials.

Since the release of the original review, three trials were published (Comella 2005; Pappert 2008; Tintner 2005). Furthermore, Cochrane's criteria for evaluating studies' risk of bias and evidence quality have evolved and been updated. Therefore, the authors consider it important to update this review.

Objectives

To compare the clinical efficacy and safety of botulinum toxin type A (BtA) versus botulinum toxin type B (BtB) in the treatment of adults 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 efficacy and/or safety of treatment with BtA versus BtB in patients with cervical dystonia were eligible for inclusion in this review. We excluded trials in which allocation was not adequately concealed. Non-parallel study designs, namely cross-over trials among others, were excluded in this updated version of the review due to uncertainty whether this type of study design is appropriate to study patients with cervical dystonia, as well as methodological concerns with regards to detection and performance bias.

Types of participants

Participants of an adults age (≥ 18 years of age), in any setting with a clinical diagnosis, made by any physician, specialist or otherwise, of idiopathic cervical dystonia. Trials enrolling participants with any form of cervical dystonia, and additional or more widespread dystonias, were allowed for inclusion. Participants could have had prior exposure to BtA or BtB, and could be taking any concomitant medications if on stable regimens.

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

Types of interventions

Intramuscular injections of BtA compared to BtB. All administration schedules and injection techniques, performed with or without guidance by either EMG or echography, were included.

Types of outcome measures

Primary outcomes

The primary efficacy outcome was:

Overall improvement on any validated symptomatic rating scale, such as Cervical Dystonia Severity Scale (CDSS), Tsui scale, and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).

The primary safety outcome was:

Proportion of participants with any adverse event.

Secondary outcomes

The secondary outcomes were:

1. Change in subjective evaluation of clinical status evaluated both by patients and clinicians, as 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), and Physician Global Assessment of Change (PGAC), and Visual analogue scale (VAS) for symptom severity.
2. Changes in pain scores, as assessed with validated assessment tools such as Patient Assessment of Pain, TWSTRS-pain sub-scale score, and VAS Pain score.
3. Changes in quality of life assessments, as assessed with validated assessment tools such as Short Form 36 (SF-36) Quality-of-Life questionnaire.
4. Numbers of participants with specific adverse events, such as dysphagia, sore throat, and local injection-site pain.

5. Duration of effect, assessed by the number of days until need for reinjection or effect waning.

Search methods for identification of studies

For this update, the search strategy was expanded to capture all the search terms for BtA and BtB formulations that are currently available. The search strategy was designed to include other botulinum toxin formulations and other dystonic disorders that are also under current revision by our group.

Electronic searches

The final search for the original version of this review was run in June 2003, based on the search strategy developed for the Movement Disorders Group to identify all papers from 1977, the first year botulinum toxin was used therapeutically in any condition. The subsequent search for this update was run for the last time in October 2015.

For the identification of studies considered for inclusion in this review, detailed search strategies were developed for each database searched. Please see Appendix 1 for the MEDLINE search strategy, Appendix 2 for the EMBASE strategy, and Appendix 3 for the CENTRAL strategy.

Non-English papers were equally assessed, translated as necessary and evaluated for inclusion.

Databases searched:

- (1) Cochrane Movement Disorders Group trials register (June 2003);
- (2) Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2015, Issue 11);
- (3) MEDLINE (1977 to October 2015);
- (4) EMBASE (1977 to October 2015).

Searching other resources

The search strategy also included:

- (1) Search through reference lists of located trials and review articles concerning botulinum toxin;

(2) Handsearch of abstracts of international congresses relevant in the fields of movement disorders and botulinum toxins, i.e. American Academy of Neurology, Movement Disorders Society, International Association of Parkinsonism and Related Disorders, and International Neurotoxin Association (1985 to October 2015);

(3) Personal communication with other researchers in the field;

(4) Contact with drug manufacturers;

(5) Whenever necessary, authors of published trials were contacted for further information and unpublished data.

Data collection and analysis

Selection of studies

Two review authors independently screened the studies identified by the search strategy, reading each of the titles and abstracts, excluding studies that were not applicable. If there was no abstract, we opted to retrieve the full text of the study in question.

Two review authors then independently assessed the full-text articles to see if the studies fulfilled the inclusion criteria. Disagreements were resolved by discussion or, if necessary, consensus was reached with the participation of a third author.

Data extraction and management

Two authors independently extracted study data onto standardized forms, after which the forms were cross-checked for accuracy. Disagreements were resolved by discussion or, if necessary, arbitration by a third author. The following data was extracted from each study:

1. Participants: inclusion and exclusion criteria, demographics and clinical baseline characteristics, number and reasons for withdrawals, exclusions and lost to follow-up, if any.
2. Interventions: full description of intervention, duration of treatment period and follow-up, providers, and co-interventions, if any.
3. Comparisons: number of randomised participants to each arm, compliance and

dropouts, reasons for dropouts, and ability to perform an intention-to-treat analysis.

4. Outcomes: definition of outcomes, use of validated measurement tools, time-point measurements, change from baseline or post-interventional measures, and missing outcomes, if any.

5. Study design: interventional, randomised, controlled, double-blind.

Assessment of risk of bias in included studies

The recommended Cochrane tool for assessing risk of bias was used in this review. Two new criteria were added, in addition to the six specific domains of this tool (i.e. random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting). One extra domain, 'enriched population', was created to evaluate bias originating from either: 1. Exclusive enrolment of known positive responders to BtA or 2. The exclusion of known poor responders to BtA. A second criteria, to assess the study source of funding, was added in the 'other bias' domain and identified as 'independent funding'.

By excluding non-responders or preferentially including responders to BtA there is a possibility that these patients will respond more favourably to BtA than would a naive population. Whenever a study population consisted primarily of non-naive patients, this potential source of bias for subjective outcome assessment was taken into account. We also divided the domain 'blinding of outcome assessment' into two categories: subjective and objective assessment.

Two independent review authors performed critical assessments for each domain of the risk of bias tool. Disagreements were resolved by discussion and, if necessary, consensus was reached with the participation of a third author.

Measures of treatment effect

The improvement from baseline to weeks 3 to 6 in disease symptoms was compared between BtA and BtB arms. Whenever possible, continuous outcomes were extracted. These data were then pooled from the studies, where adequate, and used for comparison. We opted to preferentially use mean differences. When studies investigating the same outcome used different validated rating scales, a standardized

mean difference (SMD) was calculated. For interpretation of effect sizes with SMDs, a rule of thumb was used to define absence of effect (SMD < 0.2), a small effect (SMD = 0.2 to 0.49), a moderate effect (SMD = 0.5 to 0.79), or a large effect (SMD ≥ 0.80) (Cohen 1988). If necessary for comparison, rating scales were dichotomized using each author's own criteria for improvement or no improvement. If these criteria were not described, 'improvement' was defined as any beneficial change from baseline, and 'no improvement' as lack of improvement or any deterioration from baseline.

The proportion of participants with adverse events was compared between treatment arms, and further analysis was performed for the most frequent adverse events reported in trials.

A meta-analysis was planned for the duration of effect of both botulinum toxin formulations (using time-to-event data). Where there were no data that could be combined and subjected to such analysis, we undertook a narrative approach to result synthesis.

Unit of analysis issues

Studies with multiples treatment groups:

Whenever the included studies had multiple arms with different dosages of one (or two) of the botulinum toxins, all the groups were combined to create a single pair-wise comparison, using the RevMan5.3 Calculator. This avoided the duplication of the placebo group that would happen if multiple comparisons (e.g., dose1 versus BtX; dose2 versus BtX) were included in the meta-analysis, as well as the loss of information if one dosage group was chosen in detriment of the others. The importance of dosage was later analysed in a subgroup analysis.

Dealing with missing data

Where insufficient data were presented in the study report to combine information into the meta-analysis, the mean value and standard deviation (SD) of the outcome measurements were pooled through appropriate statistics, if available.

The generic inverse variance method was used when an effect estimate and a valid measure of uncertainty (e.g. standard error (SE), 95% confidence interval (CI) or exact P value) were reported in the study. When two reported groups needed to be combined into a single

group, a pooled standard deviation formula was used to obtain a valid approximation to the group standard deviation.

When change from baseline SD was not reported or possible to extract, alternative methods for imputing SD were used. If a study in the same review using the same scale, degree of error and time period measurements was available, SD was appropriated from that study. Where not possible, a pooled SD formula was used instead, assuming a lower degree of accuracy.

Assessment of heterogeneity

Heterogeneity between trial results was tested using a standard chi-squared test and an I² statistic was performed for quantifying inconsistency across studies. When considerable heterogeneity was present (i.e. I² > 50% or p < 0.1), the possible causes of heterogeneity were explored by conducting subgroup analysis. Where heterogeneity could not readily be explained by the exploratory analyses performed, it was incorporated into a Random-Effects (RE) meta-analysis model.

Assessment of reporting biases

Publication bias was assessed through visual inspection of funnel plots asymmetry and Peters' regression tests (Sterne 2001; Peters 2006), if more than 10 studies per outcome were available (Higgins 2011).

Data synthesis

Statistical analysis was performed with Review Manager version 5.3.

Dichotomous data were preferentially reported in this review as risk ratios (RR) using a Mantel-Haenszel fixed-effects (FE) model and 95% confidence intervals. If no risk estimate was available, the crude RR was derived from raw data. Continuous outcomes were reported as mean differences and 95% confidence intervals.

The number of participants needed to treat for an additional beneficial outcome (NNTB) and for an additional harmful outcome (NNTH) were calculated from meta-analysis estimates rather than treating data as if it came from a single trial as the last approach is more prone to bias, especially when significant imbalances between groups within one or more trials in the meta-analysis exists (Altman 2002). However, caution is needed in interpreting these findings

since they may be misleading because of variation in the event rates in each trial, differences in the outcomes considered, effects of secular trends on disease risk, and differences in clinical setting (Smeeth 1999).

Where data from the studies reports could not be combined into a meta-analysis, a narrative approach to result synthesis was included in the review text.

Subgroup analysis and investigation of heterogeneity

No a priori subgroups were defined for the current review.

Results

Description of studies

Three new studies were identified for inclusion in the current update of this review: Comella 2005; Pappert 2008; Tintner 2005. None of these were included in previous versions of this review.

Results of the search

See: Figure 1, flow diagram of study selection.

The search strategy returned 1667 records (436 through MEDLINE; 1042 through EMBASE; 189 through CENTRAL), resulting in 1450 records after removing all duplicates. After title and abstract screening, 3 articles were assessed for full-text screening, with all 3 being included for both the qualitative and quantitative syntheses. No unpublished trials were retrieved.

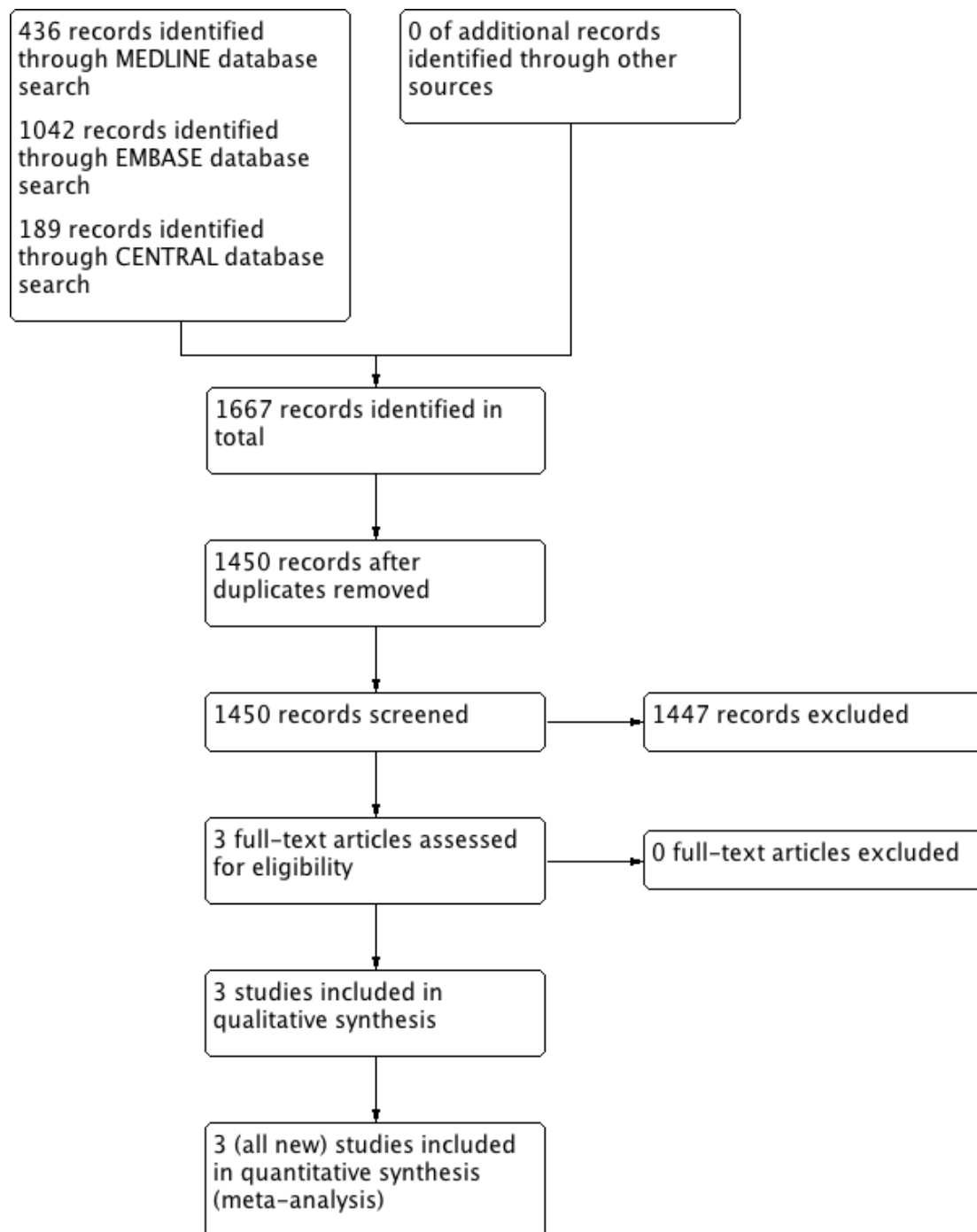


Figure 1 Flow diagram of study selection

Included studies

See Characteristics of included studies.

The three studies included in this review are parallel-group RCTs comparing BtA and BtB for adults (aged above 18 years old) with cervical dystonia. Trial size varied from 20 to 139 participants. Two of the included RCT were multi-centre studies conducted in the North America and Europe (Comella 2005; Pappert 2008), while the remaining trial was a single-

centred and conducted in the United States (Tintner 2005). All trials were conducted in the 2000's.

270 participants were enrolled overall, 171 of whom were female (63.3%). 141 of the participants included in this review were randomised to the BtA arm of their respective studies, with the remaining 129 participants randomised to the BtB arm. The average age of participants among the three trials was 53.3 years. The baseline mean cervical dystonia symptoms were moderate to severe in all participants, and well matched between study

arms, with baseline TWSTRS total scores of 41.8 and 45.6 for participants in Comella 2005 and Pappert 2008, respectively. Tintner 2005 did not provide data for baseline TWSTRS total score. The mean duration of cervical dystonia was 7.9 years and 6.6 years for participants in Comella 2005 and Pappert 2008, respectively. Tintner 2005 did not provide data for the number of years since dystonia diagnosis. Pappert 2008 enrolled exclusively patients without prior exposure to any form of botulinum toxin, while the remaining studies (Comella 2005; Tintner 2005) enrolled exclusively patients with a positive response to BtA, for a total of 58.9% known positive responders to BtA among all participants considered in this review. None of the included trials described the method of patient referral and recruitment prior to study enrolment. Overall, within studies and considered together, participants were well matched between the BtA and BtB arms.

All studies were designed to evaluate only a single treatment session. Two studies (Comella 2005; Pappert 2008) used doses from 100 to 250U of BtA and 5000 to 10000U of BtB, while the remaining study (Tintner 2005) refers only to botulinum doses being administered at a 1:50 ratio of BtA to BtB. Techniques and schema of botulinum toxin administration did not vary considerably among studies. In all trials, the toxin was injected into the involved cervical dystonia muscles selected by the investigator, with the use of electromyography left at discretion of the investigator performing the injection.

Comella 2005 and Pappert 2008 both used TWSTRS total score at week 4 post-injection as the primary efficacy outcomes. Tintner 2005 was designed with the specific objective of comparing the autonomic effects of botulinum toxin, and thus used several measures of autonomic function (which will not be considered in this review) and reported only TWSTRS sub-scores at baseline and at week 3 post-injection. Comella 2005 and Pappert 2008 also studied subjective response as assessed by patients and clinicians. Regarding safety outcomes, all studies reported treatment-associated adverse events. Only one study (Pappert 2008) refers to the method of data analysis used, referring to using both per-protocol (PP) and intention-to-treat (ITT) analyses, though only reporting the PP analysis, saying that there was no difference between PP and ITT.

All trials were short-term, with an observational period lasting 16 to 20 weeks post-injection or until such time as reinjection was required.

Excluded studies

All reports that were entered for full-text screening were assessed as eligible for inclusion in this review.

Risk of bias in included studies

See Characteristics of included studies: 'Risk of Bias' table.

The included studies were evaluated using a modified version of the Cochrane risk of bias tool. See Figure 2 and Figure 3 for the risk of bias summary graphs. These assessments were based on the information available in the primary report data.

None of the included studies were considered to have a high risk of bias in all domains, though the "independent funding" domain was considered to have a high risk of bias in all studies, and the "selective reporting" domain was considered to have a high risk of bias in one study (Tintner 2005). All studies were additionally considered to have a low risk of bias with regards to the incomplete outcome data domain.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): Outcome group: Principal Investigator (PI)	Blinding of participants and personnel (performance bias): Outcome group: Rating Investigator (RI)	Blinding of participants and personnel (performance bias): Outcome group: Study Coordinator	Blinding of participants and personnel (performance bias): Outcome group:Independent Drug Preparer	Blinding of outcome assessment (detection bias): Outcome group: Objective Outcomes	Blinding of outcome assessment (detection bias): Outcome group: Subjective Outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Enriched population – exclusive enrolment of positive responders	Enriched population – exclusion of poor responders	Independent Funding
Comella 2005	+	+	+	+	+	+	+	+	+	+	?	?	-
Pappert 2008	+	+	+	+	+	+	+	+	+	+	+	?	-
Tintner 2005	?	?	?	?	?	?	?	?	+	-	?	+	-

Figure 2 Risk of bias graph 1

Allocation (selection bias)

Two studies (Comella 2005; Pappert 2008) adequately described the methods of allocation (permuted block allocation scheme and Interactive Voice Response system, respectively), and so were rated as having a low risk of bias. The remaining study (Tintner 2005) was rated as having an unclear risk of bias.

Blinding (performance bias and detection bias)

Two studies (Comella 2005; Pappert 2008) adequately reported the methods of guaranteeing blinding, being correctly executed double-blind controlled trials, and so were rated as having a low risk of bias. The remaining study (Tintner 2005) was rated as having an unclear risk of bias.

Incomplete outcome data (attrition bias)

All studies (Comella 2005; Pappert 2008; Tintner 2005) adequately reported the number and reasons for exclusions in both treatment arms, being furthermore evenly distributed across both treatment arms, and so were rated as having a low risk of bias.

Selective reporting (reporting bias)

Two studies (Comella 2005; Pappert 2008) adequately reported the number and reasons for exclusions in both treatment arms, being furthermore evenly distributed across both treatment arms, and so were rated as having a low risk of bias. The remaining study (Tintner 2005) was rated as having a high risk of bias. This is because it refers, in the method section, to having had selected several outcomes, though only two of these are reported in the results. Moreover, due to inherent BtA properties the outcome assessment usually last at least until the week 16 after the treatment session, which was not accomplished in this study.

Other potential sources of bias

Enriched Population

All included studies potentially had a form of enriched population. Two studies (Comella 2005; Tintner 2005) exclusively enrolled positive responders to treatment with BtA, though the minimal required effect in the case of Comella 2005, 30%, was not considered sufficient to be assessed as a high risk of bias, but rather unclear.

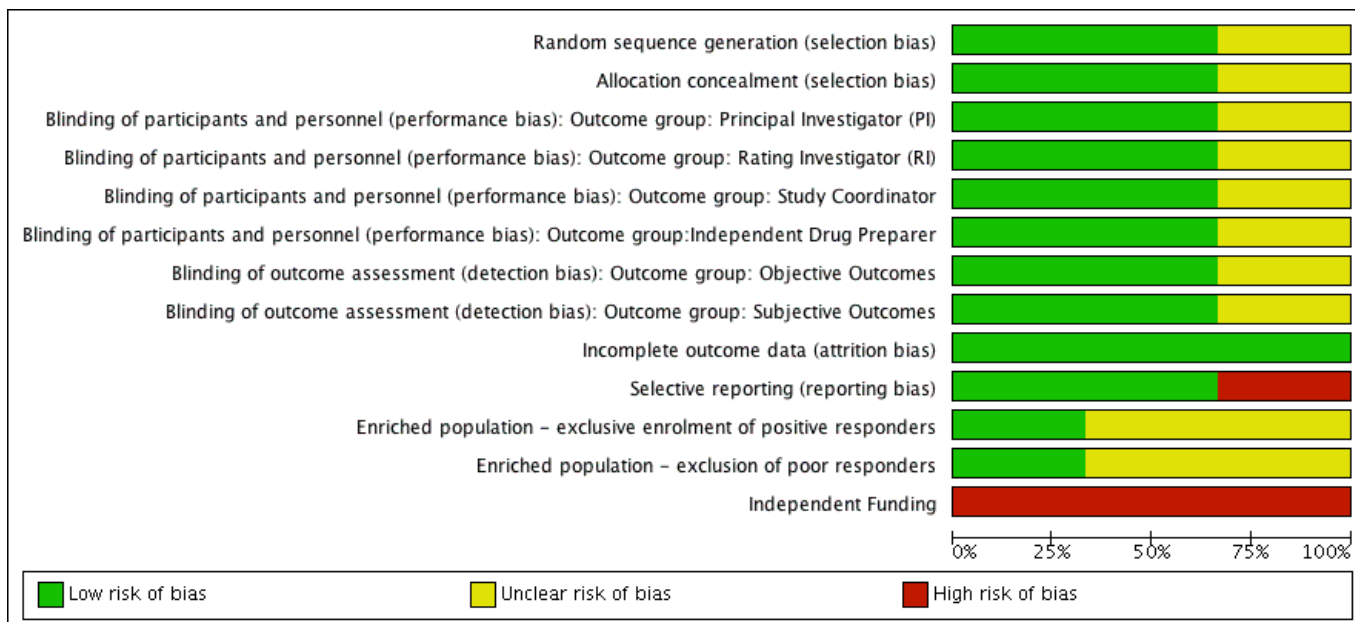
Tintner 2005 refers to the inclusion exclusively of participants known to have been responsive to BtA in the year prior to enrolling in the study, though, likewise, the significance of this is unclear as pertains to the effect on comparisons to BtB. Two studies (Comella 2005; Pappert 2008) excluded patients known to have poorer responses to treatment with botulinum toxin, namely patients with pure anterocollis and retrocollis were excluded from both trials.

Non-independent funding

All studies (Comella 2005; Pappert 2008; Tintner 2005) were supported, wholly or in part, by pharmaceutical companies (Allergan, Inc and Soltice Neurosciences, Inc).

Publication bias

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



Effects of interventions

The key results of the main comparison outcomes can be found in the ‘Summary of findings table 1’.

Preceding data analysis

Whenever necessary, appropriate imputation methods were used in order to combine the reported data into the meta-analysis with other studies for which full data were available (see Dealing with missing data). Cochrane’s software tool was used to calculate SD values from SE values presented in Pappert 2008. Sensitivity analyses were conducted for every study where imputation methods were applied. For Tintner

Figure 3 Risk of bias graph 2

2005, with regards to the three TWSTRS sub-scales (pain, severity and disability), we derived values for the standard deviation of the change from baseline values from a pooled SD formula.

Primary outcomes

1. Overall improvement on any validated symptomatic rating scale for cervical dystonia

The Toronto Western Spasmodic Torticollis Rating Scale (Consky 1994) is currently the most common clinical validated tool to assess and document the status of patients with cervical dystonia. The TWSTRS (total score range, 0 to 85) is composite of three sub-scales that evaluate different features of CD, namely severity (range, 0 to 35), disability (range, 0 to 30) and pain (range, 0 to 20). The higher the score, the greater the level of morbidity. In the absence of a validated value for a clinically meaningful change

in TWSTRS total score, we have considered a 10% change from patients' baseline status as a clinically meaningful change.

Two studies (n=231)(Comella 2005; Pappert 2008) reported data for the mean change from baseline in TWSTRS total score, with no difference between the BtA and BtB treatment groups, mean difference (MD) -1.44 (95% CI: -3.58 to 0.70; I²=0%)(Analysis 1.1).

We were able to use data from all three included studies to calculate the improvement on TWSTRS sub-scales, with there being no difference between the BtA and BtB groups with regards to both TWSTRS severity (MD: -0.31; 95% CI: -1.27 to 0.65) and TWSTRS disability (MD: -0.22; 95% CI: -1.21 to

0.76)(Analysis 1.2; Analysis 1.3).

2. Proportion of patients with adverse events

One study (n=111)(Pappert 2008) reported data concerning the proportion of participants with adverse events. In this study BtA and BtB treatment were not associated with different risks for adverse events, (risk ratio (RR) of 0.72; 95% CI: 0.51 to 1.00).

Secondary outcomes

1. Change in subjective evaluation of clinical status evaluated both by patients and clinicians

One study (138 participants)(Comella 2005) reported data with regards to subjective assessments by both clinicians and patients at

week 4 after treatment. The instruments used to measure this outcome were the Patient Global Assessment (PGA) and Subjective Global Assessment (SGA) scales. The PGA and SGA ratings ranged from 4 (marked worsening of CD signs) to 4 (complete abolishment of CD signs).

Both forms of subjective assessment, measured as mean change from baseline in PGA and SGA, did not find a difference between the BtA and BtB groups, (PGA MD: 0.20; 95% CI: -0.17 to 0.57; SGA MD: 0.17; 95% CI: -0.17 to 0.50).

Pappert 2008 also refers to have studied subjective evaluation of clinical status by both patients and clinicians, though the final report does not include any data regarding this analysis, referring only to the fact that all evaluations were similar between treatment arms.

2. Changes in pain scores, as assessed with validated assessment tools

All of the included trials provided data in the form of mean change from baseline on TWSTRS pain sub-scores (range: 0 to 20), and reported an improvement in participants treated with BtB compared to BtA with a MD of -0.99 (95% CI: -1.85 to -0.12; $I^2=0\%$)(Analysis 1.7).

3. Changes in quality of life assessments

None of the included trials studied the effect of BtA or BtB on the quality of life of patients with cervical dystonia.

4. Proportion of participants with specific adverse events

The most frequently reported adverse events were dysphagia (n=269)(Comella 2005; Pappert 2008; Tintner 2005) with a RR of 0.49, favouring the BtA group (95% CI: 0.32 to 0.75, $I^2=27\%$) and sore throat/ dry mouth (n=249)(Comella 2005; Pappert 2008), with a RR of 0.42 favouring the BtA group (95% CI: 0.31 to 0.57, $I^2=77\%$) (Analysis 1.8; Analysis 1.9, respectively)

For all the other adverse events no statistically significant difference was found. The most frequent adverse event that was equally present in both treatment groups was local pain.

5. Duration of effect, or number of days until need for reinjection or effect waning

This item was reported in two studies (n=231)(Comella 2005; Pappert 2008), though the data were not eligible for quantitative synthesis (meta-analysis) due to this outcome being reported as survival time for the median of each arm (Michiels 2005).

Pappert 2008 reported that among its 93 participants both formulations of botulinum toxin did not differ from one another - median treatment duration of effect was 13.1 weeks in the BtA arm and 13.7 weeks in the BtB arm (hazard ratio (HR): 0.95; 95% CI: 0.56 to 1.59; log rank p=0.833). A subgroup analysis for participants who showed a change at week 4 (n=83) was also conducted, without a difference between the groups (HR: 0.79; 95% CI: 0.45 to 1.41; log rank p=0.414).

Comella 2005 reported that among its 138 participants both formulations of botulinum toxin did not differ from one another - median treatment duration of effect was 13.0 weeks in the BtA arm and 11.7 weeks in the BtB arm (95% CI: 0.55 to 1.07). A subgroup analysis for participants who showed a change at week 4 was conducted, and the difference in median time to loss of benefit was 14 weeks for BtA and 12.1 weeks for BtB. Having run a log rank statistic, these two distributions were shown to differ (95% CI: 0.43 to 0.98).

Discussion

Summary of main results

This updated review included three randomised, parallel-designed, placebo-controlled trials, enrolling 270 patients with cervical dystonia, of whom 62.3% had been previously treated with BtA. BtA and BtB were equally effective in reducing overall disease impairment, including disease severity and disability, though patients treated with BtB benefited from greater reductions in disease-associated pain. Subjective assessments by both patients and clinicians were likewise equivalent between BtA and BtB. The comparative impacts of both forms of botulinum toxin on other domains of participants' quality of life, such as social functioning or mental health, have not been addressed in included trials.

Overall adverse event rates were not different between groups. However, the short duration of the trials, as well as the reduced sample size precludes strong conclusions with regards to the lack of differences between BtB and placebo. The most common adverse events that were different between the BtA and BtB groups were dysphagia and sore throat/dry mouth, both considered related to treatment and being between 2 and 3 times more frequent among BtB-treated patients, with an NNTH of 12 and 6, respectively. No fatalities or serious adverse events were considered related to either treatment in any of the trials. Data for special subpopulations, as children and pregnant women, was not available.

Low to moderate statistical heterogeneity was found for most efficacy and safety (except for sore throat/dry mouth) outcome estimates.

Overall completeness and applicability of evidence

All included trials addressed the primary research question directly, using the same assessment tool (TWSTRS). However, data was not fully reported for all outcomes, and in some cases results could not be pooled and compared across studies. This limits the amount of data available and, consequently, the confidence in overall conclusions.

Four noteworthy factors challenge the implementation of the evidence in this review. First, there was a limited and considerably heterogeneous regional distribution, with all trials being conducted in Europe or North America. Differences in clinical practice, training of experts, and local guidelines in other regions of the world may conceivably present an obstacle to application of the evidence here demonstrated. Second, the total number of participants across all outcomes was less than the number of participants that is calculated by a standard sample size calculation for a single adequately powered study. More studies are needed to provide robust backing for the evidence presented. Third, it is frequent for patients to have concomitant medications for their condition, such as muscle relaxants and benzodiazepines. In trials, such medications are reasonably required to be on a stable dose for many weeks to avoid confounding factors. As a result, little is currently known about the impact of these drug regimens with regards to implementation of the evidence in this review. Fourth, several outcomes of interest were either poorly reported or omitted completely. Namely, no quality of life assessments were reported in

any of the included studies; subjective assessments by both patients and clinicians was not reported in two of the included studies; and the proportion of participants with adverse events was also not reported in two of the included studies.

Quality of the evidence

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

We considered all studies to be at high risk of bias due to their being non-independently funded. We additionally considered Tintner 2005 to be at a high risk of reporting bias, since it did not report outcomes that were collected, and without providing any explanation for this option. Tintner 2005 is additionally at an unclear risk of bias for all domains with the exception of attrition bias. We consider the risk of bias due to an enriched population to be unclear in all studies. Finally, statistical heterogeneity was low-to-moderate for all studied outcomes with the exception of the proportion of participants with sore throat/ dry mouth.

Some outcomes could not be compared across studies, as some studies lack reporting of relevant data. Imbalances between baseline characteristics of the participants and incomplete description of the variables precluded us to confidently impute values for missing data, further reducing the amount of combinable data, and therefore the precision of the results.

The included trials enrolled between 20 and 139 participants, and taken as a whole, the the total number of participants across all outcomes was less than the number of participants that is calculated by a standard sample size calculation for a single adequately-powered study. Taken together, we consider that there is low-to-moderate quality evidence that a single treatment session of BtA and a single treatment session of BtB, in certain types of cervical dystonia, are equally efficacious in reducing disease impairment, including severity and disability, with treatment with BtB providing a greater reduction in pain. However, the quality of the evidence is low and no robust conclusions can be made regarding safety and tolerability, as well as regarding continued responsiveness and long-term efficacy, which are important aspects in a chronic condition such as cervical dystonia. Quality of evidence is, however, moderate in relation to the increased risk of dysphagia in patients treated with BtB.

Potential biases in the review process

Although we followed the methods recommended by Cochrane in order to minimize bias in the review process, certain areas are deserving of attention. Despite having contacted experts in the area, not having searched all available clinical trial registries opens the current review to two potential problems: firstly, possibly having missed trials and also the possibility of introducing publication bias.

An additional bias was that we could not obtain data for all outcomes in the included trials. A further limitation of this review is the small number of participants, with each outcome not having an adequate sample size for a single adequately powered study. Thus, the results of the pooled analysis should be thought with caution specially in the presence of statistically heterogeneity, as further studies may have an important impact in effect size estimations.

Agreements and disagreements with other studies or reviews

The current review is, to our knowledge, the first systematic review with data that addresses the question of whether one type of botulinum toxin is superior to another or not. All the RCTs addressing the same question have been included in the current review.

Authors' conclusions

Implications for practice

In this updated Cochrane review we found that a single treatment session of BtA and a single treatment session of BtB are equally effective and well tolerated in the treatment of adults with certain types of cervical dystonia. Treatment with BtB causes a greater decrease disease-associated pain whilst also increasing the rate of dysphagia and sore throat/dry mouth when compared to treatment with BtA. Overall, there is no clinical evidence to support or not support the preferential use of one form of botulinum toxin over another. No conclusions can be made regarding patients with pure retrocollis or anterocollis as these were predominantly excluded in the clinical trials.

Implications for research

We did not have access to the full research data produced so far for BtA versus BtB in cervical dystonia. Thus, it is difficult to determine which and how many resources should be invested in future research.

The net benefit of both a single BtA and BtB injection in the treatment of cervical dystonia has been established in the published trials. Nonetheless, further studies are needed to establish the relative effectiveness of different doses of BtB, assessing efficacy, safety, duration of effect and quality of life across regimes. Because therapy typically requires optimising a dose for each patient rather than administering fixed units of botulinum toxin, such a line of research would be important to support the physician's management of doses and allow for a more solid and safe individualization of a patient's treatment.

Future research concerning all formulations of botulinum neurotoxin should endeavour to establish clinical effectiveness not only based on changes from baseline, but preferably based on validated measures of Minimal Clinically Important Difference/ Change (Brožek 2006). Research is required in order to establish such a parameter for the TWSTRS, currently the most widely used and disseminated clinical scale in the field. We are, however, aware of an effort to create a new clinical scale in dystonia - the Comprehensive Cervical Dystonia Rating Scale (Comella 2015), which will include a revision of the TWSTRS, to be named TWSTRS-2, with a Minimal Clinically Important Change validation being planned.

It is currently uncertain whether or not the clinical effectiveness of botulinum toxin decays over time, with repeated treatment sessions, and/or whether a possible lost of effectiveness occur in all clinical domains. Another related aspect is the possible development of BtB-non-responsiveness, as there is no plausible theoretical reason as to why this would not occur. Future studies comparing BtA and BtB should address the comparative proportion of patients who develop 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 is in other areas (Tugwell 2007). The definition of a set of core outcome measures to be included in future research, via well-established methodology to determine the

inclusion of patient-reported outcomes (Macefield 2014) would be relevant to promote research in this field, as well as to support the clinical effectiveness of BtB.

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Contributions of authors

Conceiving the review - JC, JJF, CS, APM

Designing the review - JC, JJF, CS, APM

Coordinating the review - JC

Designing search strategies – FBR, JC

Undertaking searches – FBR, GSD

Screening search results – FRB, GSD, MF, REM

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

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

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

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

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

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

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

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

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

Writing the review - FRB, GSD, REM, MF, JC

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

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

Declarations of interest

Costa J, Ferreira JJ, and Sampaio C were investigators in clinical trials sponsored by Elan, Allergan, and Ipsen. Ferreira JJ and Sampaio C were speakers in symposiums promoted by Elan, Allergan, and Ipsen.

Moore AP has received fees from various companies marketing botulinum toxin for speaking at meetings and for advice. His unit has received funds for research.

Differences between protocol and review

For this updated review the study designs accepted were restricted to parallel-group. No changes were made in 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. In this safety analysis we considered also the proportion of participants with the most frequent adverse events, not stated in the original protocol. An assessment of the duration of effect was included as a new secondary outcome measure.

The search strategy was prolonged from the inception to October 2015.

New approaches were assumed to deal with missing data and unit of analysis issue.

The latest recommended Cochrane tool for assessing risk of bias was used in this review, which was expanded to include two additional criteria, added by the review authors. Blinding of outcome assessment was analysed in two new

subcategories: subjective and objective
assessment.

A 'Summary of findings table' was also added.

Characteristics of studies

Characteristics of included studies

Comella 2005

Methods	<p>Randomised, double-blind, controlled study. Randomisation in permuted block allocation schemes.</p> <p>Data was collected at baseline, week 4, and subsequently every 2 weeks up to 20 weeks post-injection.</p> <p>Data analysed on a ITT basis.</p>
Participants	<p>The study was conducted in the outpatient offices of unspecified dystonia study centres.</p> <p>Mean age of participants was 56.7 years; 68% were female; the combined duration of cervical dystonia of 7.9 years. The mean TWSTRS total score was 41.8.</p> <p>All participants had previously been exposed to a form of botulinum neurotoxin, and were required to have moderate severity CD, as well as a minimum of 15 on the TWSTRS motor severity subsection, for inclusion. Predominant anterocollis and retrocollis were exclusionary criteria.</p> <p>There was a total of 139 randomised participants.</p>
Interventions	<p>Participants were randomised into two groups, the Botox group, containing 74 participants, and the MyoBloc group, containing 65 participants.</p> <p>Botox was commercially obtained in vials containing 100 U Clostridium botulinum toxin type A, 0.5 mg albumin (human), and 0.9 mg sodium chloride in a sterile in a vacuum-dried form without a preservative. BoNTA was stored at a temperature at or below -5°C and reconstituted within 4 hours of administration with 1 mL of 0.9% sterile unpreserved saline to provide a final concentration of 100 U/mL. Subjects randomised to Botox received a maximal dose of 250 U (2.5 mL). Subjects were injected with a volume of the appropriate study drug based on previous injection amounts. Muscle selection, dosing into each muscle, number of injection sites, and use of electromyography were at the discretion of the injecting physician.</p> <p>MyoBloc was obtained in vials containing at least 5000 U Clostridium botulinum toxin type B, 0.05% albumin (human), 0.01 M sodium succinate, and 0.1 M sodium chloride buffer at a pH of 5.6. Commercially available vials of MyoBloc contain overfill of approximately 0.1 to 0.2 mL or 500 to 1,000 U MyoBloc. MyoBloc was stored at a temperature between 2° and 8°C. Each vial of MyoBloc was diluted with 0.25 mL of 0.9% sterile unpreserved saline to provide a concentration of at least 4000 U/mL. Subjects randomized to MyoBloc received a maximal dose of 10000 U (2.5 mL).</p>
Outcomes	<p>The primary outcome measures were the change in total TWSTRS score at week 4, the duration of clinical effect (the time in days until the target TWSTRS score was reached), and adverse effects evaluated by spontaneous report and adverse events interviews.</p> <p>The secondary outcomes measured were the Physician Global Assessment of Change (-4 is very marked worsening, 0 is no change and +4 is complete remission), Patient Global Assessment and pain and discomfort at baseline injection.</p> <p>There was no Neutralising Antibody Testing performed.</p>
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Random assignments were generated by the study biostatistician, were stratified by center, and used permuted block allocation schemes with blocks of randomly allocated lengths of two or four. The study biostatistician ensured that the initial assignments were balanced across centers. The permuted block approach prevented imbalances in the numbers randomized to each treatment arm..”
Allocation concealment (selection bias)	Low risk	“Random assignments were generated by the study biostatistician, were stratified by center, and used permuted block allocation schemes with blocks of randomly allocated lengths of two or four. The study biostatistician ensured that the initial assignments were balanced across centers. The permuted block approach prevented imbalances in the numbers randomized to each treatment arm..”
Blinding of participants and personnel (performance bias) Outcome group: Principal Investigator (PI)	Low risk	“The principal/treating investigator (PI) enrolled the subjects, assessed the inclusion and exclusion criteria, obtained informed consent, applied and evaluated the UBI (<i>Unilateral Brow Injection</i>), performed the injection of study drug (BoNTA or BoNTB), reported complications associated with injection, assessed adverse events, and determined when subjects reached the defined end point of the study. (...) The PI, RI, and coordinator were blinded to serotype administered to each subject.”
Blinding of participants and personnel (performance bias) Outcome group: Rating Investigator (RI)	Low risk	“The rating investigator (RI) reviewed the TWSTRS teaching tape to ensure uniform ratings and assessed subjects using the TWSTRS (motor severity, disability, and pain) and the physician's global assessment (PGA). The RI did not perform other study procedures. (...) The PI, RI, and coordinator were blinded to serotype administered to each subject.”
Blinding of participants and personnel (performance bias) Outcome group: Study Coordinator	Low risk	“The study coordinator scheduled study visits, recorded concomitant medications, obtained the subjective global assessment (SGA), and completed study-related questionnaires. (...) The PI, RI, and coordinator were blinded to serotype administered to each subject.”
Blinding of participants and personnel (performance bias) Outcome group: Independent Drug Preparer	Low risk	“The drug preparer obtained the randomization code for each subject from the study biostatistician and prepared the BoNTA or BoNTB.” The drug preparer was not involved in other study procedures.
Blinding of outcome assessment (detection bias) Outcome group: Objective Outcomes	Low risk	“The PI, RI, and coordinator were blinded to serotype administered to each subject.”
Blinding of outcome	Low risk	All participants had previous successful treatment with

assessment (detection bias) Outcome group: Subjective Outcomes		BtA, which could have led to the recognition of the expected effect, or to the lack of it. However, this would presumably not have an effect as the comparison arm was also a botulinum toxin formulation.
Incomplete outcome data (attrition bias)	Low risk	Only one post-randomisation withdrawal occurred, in the BTA group (inability to travel to the study site). The ITT analysis of the primary outcome variables for the TWSTRS and adverse events was done for all participants examined at week 4.
Selective reporting (reporting bias)	Low risk	The expected outcomes that are usually evaluated in intervention trials for this condition were reported in this study.
Enriched population - exclusive enrolment of positive responders	Unclear risk	“All subjects were followed up in outpatient clinics and had previous successful treatment with BoNTA, with a subjective report of at least 30% benefit.” “At the baseline visit, the PI evaluated the UBI (<i>Unilateral Brow Injection</i>) and excluded subjects with UBI indicating clinical resistance (no effacement of brow wrinkling). Subjects were then randomized to either BoNTA or BoNTB”
Enriched population - exclusion of poor responders	Unclear risk	“Subjects were also excluded if they had predominant anterocollis or retrocollis”
Independent Funding	High risk	“Supported primarily by an unrestricted research grant from Allergan Inc., Irvine, CA.”

Pappert 2008

Methods	Randomised, double-blind, controlled trial. Randomisation was done via a Interactive Voice Response system, which created a subject randomisation number which was then forwarded to the site pharmacist who prepared the study drug. Data was collected at baseline, week 4 post-injection and every 4 weeks until there was a further need for botulinum therapy. Both Per Protocol and Intention To Treat analyses were performed but the study reports only the PP analysis.
Participants	This multi-centre trial was conducted in 24 sites in Europe (Poland, Hungary, UK, Italy, Spain, Germany, Slovakia, France and Portugal). Mean age of participants was 48.9 years; 55.9% were female; and the average duration of Cervical Dystonia was 6.6 years. Pure anterocollis and retrocollis, as well as previous treatment with botulinum toxin were exclusionary criteria. There was a total of 111 randomised participants.
Interventions	Patients were randomised into two groups, the BoNT-A group, with 56 participants, and the BoNT-B, containing 55 participants. BoNT-A (BOTOX) was commercially obtained by the pharmacy (100 U of vacuum-dried BoNT-A neurotoxin complex) and stored at or below -5°C . An unblinded pharmacist prepared the study drug by reconstituting two vials of BoNT-A with sterile unpreserved saline (1.3 mL/vial). The pharmacist drew up 1 mL of solution (BoNT-A) from each vial into two syringes (1 mL/syringe). The final concentration of BoNT-A was 150 U/2 mL. Electromyography was used at the discretion of the investigator providing the injection. BoNT-B (MYOBLOCR/NEUROBLOCR) was supplied by the manufacturer in insulated shipping boxes, and maintained at 2 to 8°C . BoNT-B is a clear, colorless to light yellow, sterile injectable solution containing 5,000 units (U) of

	BoNT-B per mL (10,000 U/2 mL) in an isotonic solution of 0.05% human serum albumin/0.01M succinate/0.1M sodium chloride buffer at an approximate pH of 5.6. An unblinded pharmacist prepared two syringes with 1 mL of BoNT-B (5,000 U/mL) in each syringe. The final concentration of BoNT-B was 10,000 U/2 mL. Electromyography was used at the discretion of the investigator providing the injection.
Outcomes	The primary outcome measure of the study was change in total TWSTRS score at 4 weeks post-injection. The secondary outcome measures were change in TWSTRS subscores (ie, Pain, Severity and Disability), Subject Pain Assessment on Visual Analogue Scale, Primary Investigator and Patient Global Assessment (5-points scale for both frequency and intensity) on Visual Analogue Scale at week 4, and adverse events by spontaneous reporting and on investigation. There was no Neutralising Antibody Testing performed.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Subjects were randomized in a 1:1 ratio of BoNT-A to BoNT-B. The site Principal Investigator (PI) contacted an Interactive Voice Response system for a Subject Randomization Number."
Allocation concealment (selection bias)	Low risk	"Treatment allocation for the randomization number was forwarded to the site pharmacist who prepared the study drug and had no contact with the subject or injector. All other study personnel were blinded."
Blinding of participants and personnel (performance bias) Outcome group: Principal Investigator (PI)	Low risk	"At screening (≤ 21 days prior to baseline visit), the PI performed a history, examination, and confirmed inclusion/exclusion criteria. At baseline, prior to injection, the PI performed the TWSTRS (...). At week 4 and all subsequent visits, the PI performed the TWSTRS and Investigator Global VAS [0 mm (much worse) to 100 mm (much better) at the time of evaluation compared to baseline]." "All other study personnel were blinded"
Blinding of participants and personnel (performance bias) Outcome group: Rating Investigator (RI)	Low risk	"At baseline, prior to injection, (...) the AI administered the subject Pain Visual Analogue Scale (VAS) [0 mm (worst pain ever) to 100 mm (no pain)]. The Administrative Investigator conducted the remaining visits including collection of AEs and the administration of the Subject Pain VAS and Subject Global VAS [ranging from 0 mm (much worse) to 100 mm (much better) at the time of evaluation compared to baseline]." "All other study personnel were blinded"
Blinding of participants and personnel (performance bias) Outcome group: Study Coordinator	Low risk	"At baseline, prior to injection, (...) the AI administered the subject Pain Visual Analogue Scale (VAS) [0 mm (worst pain ever) to 100 mm (no pain)]. The Administrative Investigator conducted the remaining visits including collection of AEs and the administration of the Subject Pain VAS and Subject Global VAS [ranging from 0 mm (much worse) to 100 mm (much better) at the time of evaluation compared to baseline]." "All other study personnel were blinded"

Blinding of participants and personnel (performance bias) Outcome group: Independent Drug Preparer	Low risk	“An unblinded pharmacist prepared the study drug”. “pharmacist who prepared the study drug and had no contact with the subject or injector”.
Blinding of outcome assessment (detection bias) Outcome group: Objective Outcomes	Low risk	“All other study personnel were blinded.”
Blinding of outcome assessment (detection bias) Outcome group: Subjective Outcomes	Low risk	All participants were toxin-naïve. However, this would presumably not have an effect as the comparison arm was also a botulinum toxin formulation.
Incomplete outcome data (attrition bias)	Low risk	Post-randomisation exclusions were low and roughly distributed evenly between groups (‘BoNT-A’ group=8; ‘BoNT-B’ group=10). The reasons for exclusion were presented. Five of the exclusions in the ‘BoNT-B’ group, and all of them (8) in the ‘BoNT-A’ group, were due to “Protocol Violations”, which were not specified. However, the authors describe that “all 13 subjects that were excluded for protocol violations in the PPP were from one site where the study personnel had not been appropriately trained.”
Selective reporting (reporting bias)	Low risk	The expected outcomes that are usually evaluated in intervention trials for this condition were reported in this study.
Enriched population - exclusive enrolment of positive responders	Low risk	“Exclusion criteria included: (...) previous treatment with BoNT”
Enriched population - exclusion of poor responders	Unclear risk	“Exclusion criteria included: pure antero- or retrocollis”
Independent Funding	High risk	“Eric J. Pappert, MD and Terry Germanson, PhD for The Myobloc/Neurobloc European Cervical Dystonia Study Group” “The first named author (EJP) is an employee of Solstice Neurosciences, Inc. maker of MYOBLOC® (BoNT-B) and took charge of the publication and analysis after the study was completed. (...) The statistical consultant (TG) is an independent contractor paid for her analytic time by Solstice Neurosciences, Inc. and has nothing further to disclose.”

Tintner 2005

Methods	Randomised, double-blind, controlled trial. Randomisation method not explained. Data was collected at baseline and at week 2 post-injection. It is unclear whether the data was analysed per protocol or by an intention-to-treat method.
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Participants	The location in which the study was conducted is not mentioned. Mean ages were 55 for the BTX-A group and 64 for the BTX-B group. 14 of the 20 participants were female. The duration of diseases of the participants is unknown. Participants were required to have a previous response to BTX-A within the last year of sufficient magnitude for functional improvement. There was a total of 20 randomised participants.
Interventions	There were 11 participants allocated to the BTX-A group and 9 to the BTX-B group. No information was provided in relation to the name of the drugs, the dose or frequency of administration of BTX therapy. No information about follow-up time was provided.
Outcomes	The primary outcomes in this study were the TWSTRS sub-score at week 2 post-injection. Secondary outcomes were heart rate, blood pressure, orthostatic heart rate regulation, heart rate variation with respiration, saliva production, ocular autonomic testing, the Composite Autonomic Scoring Scale, and the Visual Functional Questionnaire.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The text refers to this trial being randomized, though method of randomization was not specified
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not specified.
Blinding of participants and personnel (performance bias) Outcome group: Principal Investigator (PI)	Unclear risk	The text refers to this trial being double-blind, though no evidence of adequate participant blinding is made.
Blinding of participants and personnel (performance bias) Outcome group: Rating Investigator (RI)	Unclear risk	The text refers to this trial being double-blind, though no evidence of adequate participant blinding is made.
Blinding of participants and personnel (performance bias) Outcome group: Study Coordinator	Unclear risk	The text refers to this trial being double-blind, though no evidence of adequate participant blinding is made.
Blinding of participants and personnel (performance bias) Outcome group: Independent Drug Preparer	Unclear risk	The text refers to this trial being double-blind, though no evidence of adequate participant blinding is made.

Blinding of outcome assessment (detection bias) Outcome group: Objective Outcomes	Unclear risk	The text refers to this trial being double-blind, though no evidence of adequate investigator blinding is made.
Blinding of outcome assessment (detection bias) Outcome group: Subjective Outcomes	Unclear risk	The text refers to this trial being double-blind, though no evidence of adequate investigator blinding is made.
Incomplete outcome data (attrition bias)	Low risk	“20 subjects with cervical dystonia responsive to BTX-A were randomized and completed the study”
Selective reporting (reporting bias)	High risk	Although the report refers, in the method section, to having had selected several outcomes, only two of these are reported in the results. Moreover, due to inherent BtA proprieties the outcome assessment usually last at least until the week 16 after the treatment section, which was not accomplished in this study.
Enriched population - exclusive enrolment of positive responders	Unclear risk	Subjects were required to be known responders to the effects of BTA within the past year.
Enriched population - exclusion of poor responders	Low risk	No reference made to exclusion of poor responders
Independent Funding	High risk	Refers to this study having been supported by a grant from Allergan Inc.

Characteristics of excluded studies

References to studies

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[DOI: 10.1212/01.wnl.0000183055.81056.5c]

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Other published versions of this review**Costa 2003**

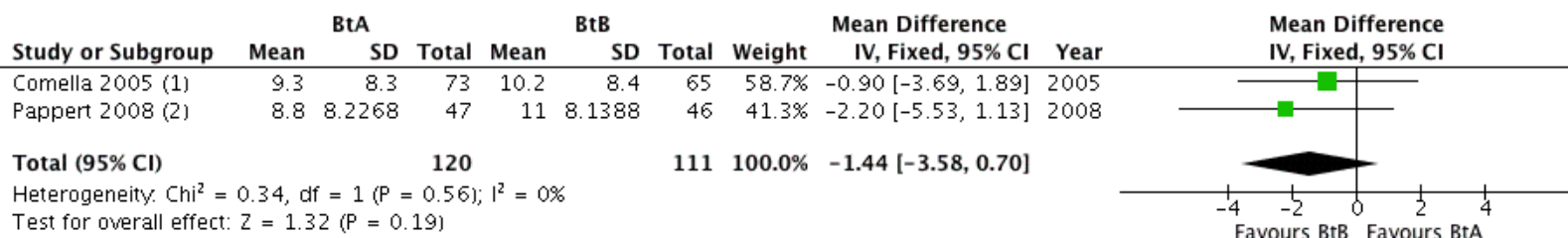
Costa J, Borges AA, Espírito-Santo CC, Ferreira J, Coelho MM, Moore P, Sampaio C. Botulinum toxin type A versus botulinum toxin type B for cervical dystonia. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD004314. DOI: 10.1002/14651858.CD004314.pub2.

Data and analyses

Botulinum toxin type A versus Botulinum toxin type B

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Overall Cervical Dystonia improvement as assessed with validated scales: change from baseline to week 4	2	231	Mean Difference (IV, Fixed, 95% CI)	-1.44 [-3.58, 0.70]
1.2 Cervical Dystonia associated Severity: change from baseline to week 2-4 as assessed with validated scales	3		Mean Difference (IV, Fixed, 95% CI)	-0.31 [-1.27, 0.65]
1.3 Cervical Dystonia associated Disability: change from baseline to week 2-4 as assessed with validated scales	3		Mean Difference (IV, Fixed, 95% CI)	-0.22 [-1.21, 0.76]
1.4 Proportion of patients with adverse events	1	111	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.51, 1.00]
1.5 Subjective change as assessed by the patient at week 4	1	138	Mean Difference (IV, Random, 95% CI)	0.20 [-0.17, 0.57]
1.6 Subjective change as assessed by clinician at week 4	1	138	Std. Mean Difference (IV, Random, 95% CI)	0.17 [-0.17, 0.50]
1.7 Cervical Dystonia associated Pain: change from baseline to week 2-4 as assessed with validated scales	3		Mean Difference (IV, Fixed, 95% CI)	-0.99 [-1.85, -0.12]
1.8 Dysphagia	3	269	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.32, 0.75]
1.9 Sore Throat/Dry Mouth	2	249	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.31, 0.57]
1.10 Local Pain (Injection Site)	1	111	Risk Ratio (M-H, Fixed, 95% CI)	7.13 [0.38, 134.80]

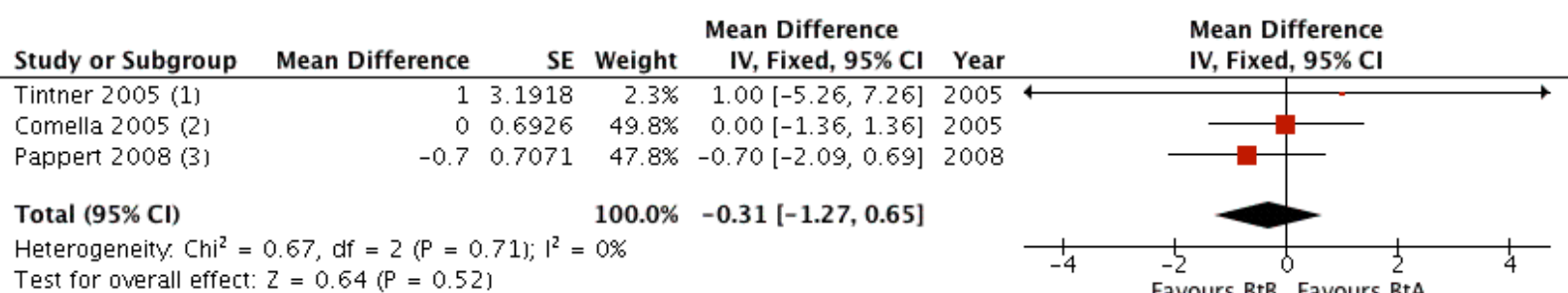
Analyses



Footnotes

(1) Change in total TWSTRS score at week 4. Botox 250 U; Myobloc 10000 U.

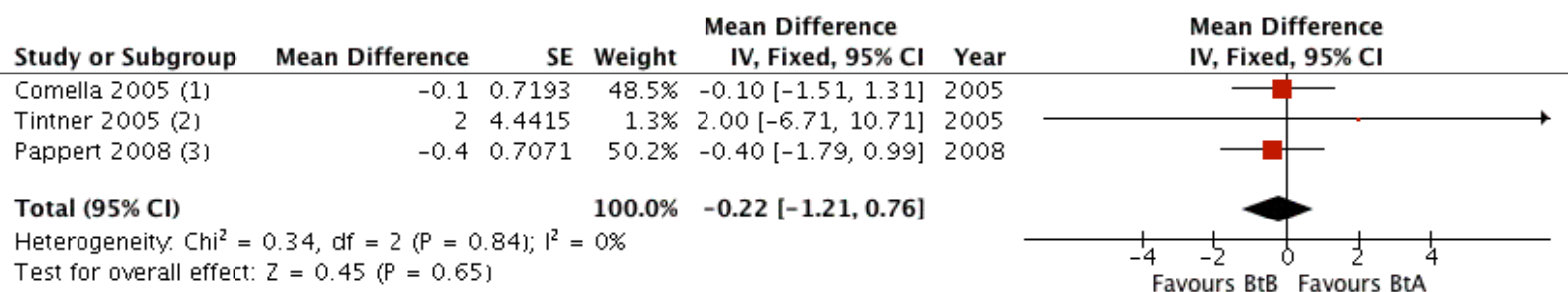
Figure 4 Analysis 1.1



Footnotes

- (1) week 2, TWSTRS severity, diff baselines -> pooled SD
- (2) week 4, TWSTRS severity
- (3) week 4, TWSTRS severity

Figure 6 Analysis 1.2



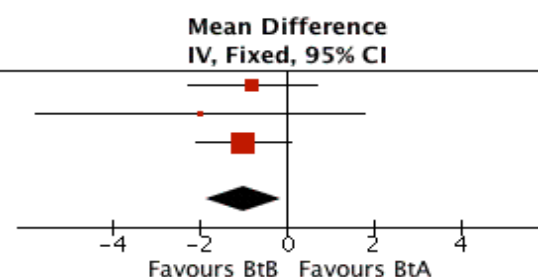
Footnotes

- (1) week 4, TWSTRS severity
- (2) week 2, TWSTRS severity, diff baselines -> pooled SD
- (3) week 4, TWSTRS severity

Figure 5 Analysis 1.3

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI	Year
Comella 2005 (1)	-0.8	0.7674	33.3%	-0.80 [-2.30, 0.70]	2005
Tintner 2005 (2)	-2	1.9261	5.3%	-2.00 [-5.78, 1.78]	2005
Pappert 2008 (3)	-1	0.5657	61.4%	-1.00 [-2.11, 0.11]	2008
Total (95% CI)			100.0%	-0.99 [-1.85, -0.12]	

Heterogeneity: $\text{Chi}^2 = 0.34$, $\text{df} = 2$ ($P = 0.85$); $I^2 = 0\%$
 Test for overall effect: $Z = 2.23$ ($P = 0.03$)



Footnotes

- (1) week 4, TWSTRS pain
- (2) week 2, TWSTRS severity, diff baselines -> pooled SD
- (3) week 4, TWSTRS pain

Figure 7 Analysis 1.7

Study or Subgroup	BtA		BtB		Weight	Risk Ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
Comella 2005	14	73	31	65	69.5%	0.40 [0.24, 0.69]	2005
Tintner 2005	2	11	5	9	11.6%	0.33 [0.08, 1.30]	2005
Pappert 2008	8	55	9	56	18.9%	0.91 [0.38, 2.17]	2008
Total (95% CI)		139		130	100.0%	0.49 [0.32, 0.75]	
Total events	24		45				

Heterogeneity: $\text{Chi}^2 = 2.73$, $\text{df} = 2$ ($P = 0.26$); $I^2 = 27\%$
 Test for overall effect: $Z = 3.29$ ($P = 0.0010$)

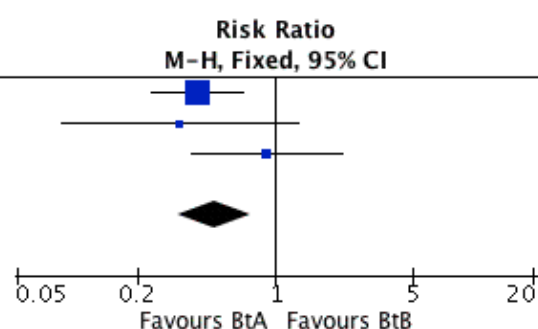


Figure 9 Analysis 1.8

Study or Subgroup	BtA		BtB		Weight	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Comella 2005	30	73	52	65	71.6%	0.51 [0.38, 0.69]
Pappert 2008	4	55	22	56	28.4%	0.19 [0.07, 0.50]
Tintner 2005 (1)	0	0	0	0		Not estimable
Total (95% CI)		128		121	100.0%	0.42 [0.31, 0.57]
Total events	34		74			

Heterogeneity: $\text{Chi}^2 = 4.30$, $\text{df} = 1$ ($P = 0.04$); $I^2 = 77\%$
 Test for overall effect: $Z = 5.60$ ($P < 0.00001$)

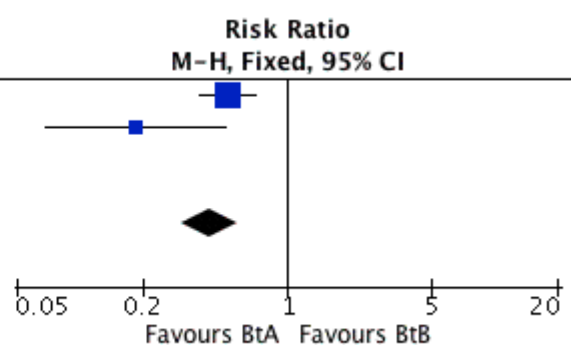


Figure 8 Analysis 1.9

Sources of support

Internal sources

- Cochrane Movement Disorders Group, Portugal
- The Walton Centre for Neurology and Neurosurgery, UK

External sources

- No sources of support provided

Appendices

1 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 animals/ not humans.sh.

#10 ((randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial) not (animals not humans)).af,pt.

#11 exp botulinum toxins/

#12 exp botulinum toxins, type A/

#13 (botul\$ adj2 tox\$).ti,ab.

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

#15 11 or 12 or 13 or 14

#16 exp animals/ not humans/

#17 ((botulinum toxins or botulinum toxins, type A or (botul\$ adj2 tox\$) or (botox or dysport or xeomin or myobloc or rimabotulinum\$ or abobotuli\$ or onabotulinum\$ or oculinum or purtox or CNBTX or Neuronox)) not

(animals not humans)).af.

#18 (cervic\$ adj2 dysto\$).ti,ab.

#19 blepharosp\$.ti,ab.

#20 (hem\$ adj2 spasm\$).ti,ab.

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

#22 (crani\$ adj2 dysto\$).ti,ab.

#23 (foca\$ adj2 dysto\$).ti,ab.

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

#25 torticol\$.ti,ab.

#26 exp dystonic disorders/

#27 exp dystonia/

#28 exp torticollis/

#29 exp blepharospasm/

#30 exp meige syndrome/

#31 exp hemifacial spasm/

#32 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31

#33 exp animals/ not humans/

#34 (((cervic\$ adj2 dysto\$) or blepharosp\$ or (hem\$ adj2 spasm\$) or (meige and (dysto\$ or syndrom\$)) or

(crani\$ adj2 dysto\$) or (foca\$ adj2 dysto\$) or (write\$ and (cramp\$ or dysto\$)) or torticol\$ or dystonic disorders or

dystonia or torticollis or blepharospasm or meige syndrome or hemifacial spasm) not (animals not humans)).af.

#35 10 and 17 and 34

2 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 5

#7 limit 6 to human

#8 (cervic\$ adj2 dysto\$).ti,ab.

#9 blepharosp\$.ti,ab.

#10 (hem\$ adj2 spasm\$).ti,ab.

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

#12 (crani\$ adj2 dysto\$).ti,ab.

#13 (foca\$ adj2 dysto\$).ti,ab.

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

#15 torticol\$.ti,ab.

#16 exp Dystonic Disorders/

#17 exp Dystonia/

#18 exp torticollis/

#19 exp blepharospasm/

#20 exp Meige Syndrome/

#21 exp Hemifacial Spasm/

#22 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

#23 22

#24 limit 23 to human

#25 (botul\$ adj2 tox\$).ti,ab.

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

#27 exp Botulinum Toxins/

#28 exp Botulinum Toxins, Type A/

#29 25 or 26 or 27 or 28

#30 29

#31 limit 30 to human

#32 7 and 24 and 31

3 CENTRAL search strategy

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

#2 MeSH descriptor: [Botulinum Toxins, Type A] explode all trees

#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: [Animals] explode all trees

#7 MeSH descriptor: [Humans] explode all trees

#8#6 not #7

#9#5 not #8

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

#11 blepharosp*:ti,ab

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

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

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

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

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

#17 torticol*:ti,ab

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

#19 MeSH descriptor: [Dystonia] explode all trees

#20 MeSH descriptor: [Torticollis] explode all trees

#21 MeSH descriptor: [Blepharospasm] explode all trees

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

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

#24 {or #10-#23}

#25 MeSH descriptor: [Animals] explode all trees

#26 MeSH descriptor: [Humans] explode all trees

#27 #25 not #26

#28 #24 not #27