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[Intervention Review]

Botulinum toxin type A versus anticholinergics 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. Before BtA, anticholinergics were the most widely accepted treatment.

Objectives

To compare the efficacy, safety, and tolerability of BtA versus anticholinergic drugs in adults with cervical dystonia.

Search methods

We searched the Cochrane Movement Disorders' Trials Register to June 2003, screened reference lists of articles and conference proceedings to September 2018, and searched CENTRAL, MEDLINE, and Embase, with no language restrictions, to July 2020.

Selection criteria

Double-blind, parallel, randomised trials (RCTs) of BtA versus anticholinergic drugs 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 and quality of the evidence. We resolved disagreements by consensus or by consulting a third review author. If enough data had been available, we were to perform meta-analyses using a random-effects model for the comparison of BtA versus anticholinergic drugs to estimate pooled effects and corresponding 95% confidence intervals (95% CI). 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 one RCT of moderate overall risk of bias (as multiple domains were at unclear risk of bias), which included 66 BtA-naive participants with cervical dystonia. Two doses of BtA (Dysport; week 0 and 8; mean dose 262 to 292 U) were compared with daily trihexyphenidyl (up to 24 mg daily). The trial was sponsored by the BtA producer.

BtA reduced cervical dystonia severity by an average of 2.5 points (95% CI 0.68 to 4.32) on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity subscale 12 weeks after injection, compared to trihexyphenidyl. More participants reported adverse events in the

trihexyphenidyl treatment group (76 events), compared with the BtA group (31 events); however, the difference in dropouts due to adverse events was inconclusive between groups. There was a decreased risk of dry mouth, and memory problems with BtA, but the differences were inconclusive between groups for the other reported side effects (blurred vision, dizziness, depression, fatigue, pain at injection site, dysphagia, and neck weakness).

Authors' conclusions

We found very low-certainty evidence that BtA is more effective, better tolerated, and safer than trihexyphenidyl.

We found no information on a dose-response relationship with BtA, differences between BtA formulations or different anticholinergics, the utility of electromyography-guided injections, or the duration of treatment effect.

PLAIN LANGUAGE SUMMARY

Treatment with botulinum toxin type A or anticholinergic drugs for people with cervical dystonia (involuntary posturing of the head)

The review question

This is an update of a Cochrane Review. We assessed whether botulinum toxin type A (BtA) was more effective (reduction in severity, disability, and pain) and safer than anticholinergic drugs for people with cervical dystonia (involuntary positioning of the head).

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. It can be very disabling, and have a negative affect on a person's quality of life. In most cases, the cause is unknown; there is no cure. Since cervical dystonia is normally a long-term disorder, it requires long-term treatment.

Botulinum toxin type A and anticholinergic drugs are powerful chemical substances that cause a diverse range of responses in the human body. BtA causes severe localised paralysis (an inability to move in the part of the body where it is injected). Anticholinergics, usually taken by mouth, cause more widespread symptoms, and can result in a dry mouth, visual disturbances, bower and bladder difficulties, increased heart rate, sedation, and confusion or disorientation. Both can be used to treat many conditions, in particular, those with involuntary muscle contractions, such as cervical dystonia.

Study characteristics

We searched the medical literature to July 2020. We found one study that compared treatment with BtA (Dysport) versus an anticholinergic drug (trihexyphenidyl) for 12 weeks. The study included 66 participants, who had experienced cervical dystonia for an average of 9.4 years, but had never received BtA treatment. On average, they had moderate impairment. The average age of people in the study was 50.7 years. The trial was funded by the BtA drug manufacturer.

Key results

The results show that Dysport, when compared with trihexyphenidyl, may improve symptoms of cervical dystonia, pain, and quality of life. The risk of having an unpleasant or undesirable event, particularly dry mouth and memory issues, was increased in people taking trihexyphenidyl.

We found no information on the effects of different doses of BtA, different formulas of BtA or types of anticholinergics, the usefulness of guiding injections by electromyography, or how long the effects lasted.

Certainty in the evidence

Due to limitations in the study methods and size of the study, we have very little confidence in the results.

These conclusions may not apply to all people with cervical dystonia. They do not apply to long-term use of either treatment.

SUMMARY OF FINDINGS

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

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

Patient or population: cervical dystonia
Setting: any
Intervention: botulinum toxin type A (BtA)
Comparison: anticholinergics (trihexyphenidyl)

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		With anticholinergics	With BtA	Difference		
Cervical dystonia-specific improvement *assessed with TWSTRS disability subscale (0 to 33; higher = more disability)* follow-up: 12 weeks № of participants: 66 (1 RCT)	-	The median cervical dystonia-specific improvement with anticholinergics was 0	-	MD 2.5 points higher (0.68 higher to 4.32 higher)	⊕⊖⊖⊖ Very low[a,b]	The evidence is very uncertain about the effect of BtA on cervical dystonia-specific improvement compared with trihexyphenidyl.
Adverse events follow-up: 12 weeks № of participants: 66 (1 RCT)	• Participants in the BtA arm reported 31 adverse events • Participants in the trihexyphenidyl arm reported 76 adverse events. • No serious adverse events was reported.				⊕⊖⊖⊖ Very low[a,b]	
Subjective evaluation of clinical status	-	-	-	-	-	Outcome not reported.
Cervical dystonia-specific pain *assessed with TWSTRS pain subcale (0 to 20; higher = more pain)* follow-up: 12 weeks № of participants: 66 (1 RCT)	The study authors reported the mean improvement was 1 point in the trihexyphenidyl arm, and 3 points in the BtA arm. No measure of dispersion was given for this difference, and according to the authors it did not reach statistical significance.				⊕⊖⊖⊖ Very low[b,c]	
Health-related quality of life	The study authors reported the median change was -4 in the trihexyphenidyl arm, and +2 in the BtA arm).				⊕⊖⊖⊖ Very low[a,b]	

assessed with MOS-Quality of Life general health perception subscale (100-points; higher = better) follow-up: 12 weeks № of participants: 66 (1 RCT)	For the difference in medians, the authors only provide: 95% CI: 4 to 12, p-value = 0.0023.					
Tolerability *assessed by dropouts due to adverse events* follow-up: 12 weeks № of participants: 66 (1 RCT)	RR 0.33 (0.04 to 3.04)	Study population			⊕⊖⊖⊖ Very low[a,b]	The evidence is very uncertain whether botulinum toxin type A results in less tolerability (more dropouts)
		9.1%	3.0% (0.4 to 27.6)	6.1% fewer (8.7 fewer to 18.5 more)		
Duration of effect	-	-	-		-	Outcome not reported.

*__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).

MD: mean difference; **CI:** Confidence interval; **RR:** Risk 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 two levels due to serious imprecision, as the optimal information size was not reached
[b]Downgraded one level due to study limitations; concerns with allocation procedures, blinding of participants and personnel, and for-profit bias
[c]The total number of participants included was less than that required by sample size calculation, and the confidence interval included both appreciable benefit and harm

BACKGROUND

This review is an update of a Cochrane Review evaluating the efficacy and safety of botulinum toxin type A (BtA) versus anticholinergic drugs in the treatment of cervical dystonia (Costa 2005).

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 (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 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% 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 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 (Jancovic 2007). 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 presents frequently 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 people 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). Complex torticollis, a combination of these abnormal patterns, is frequently found 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; it 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, although it typically worsens over time. 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 (Jahnanshahi 1990).

To date, no curative or disorder-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); 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 Bt is local chemodenervation by the temporary blockade of acetylcholine release at cholinergic synapses. Temporary synapses are consequently formed via the process of axonal sprouting (Duchen 1971; Holland 1981; Juzans 1996).

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

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

injection sites per muscle is 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 Bt injection (Jankovic 2004). Eventually, the muscle paralysis subsides; this is associated with the formation of new sprouts capable of neurotransmission. Over time, synaptic activity resumes in the original nerve terminals, leading to sprout regression (de Paiva 1999).

Currently there are two commercially available 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)).

Anticholinergic drugs are chemicals that interfere with signal transmission mediated by acetylcholine molecules and acetylcholine receptors. These molecules reduce the effect of acetylcholine by competitively inhibiting its binding to acetylcholine receptors. Acetylcholine receptors exist in the central nervous system and in the periphery, including the peripheral nervous system, the autonomic effector cells, and others cell types, such as the vascular endothelium (Hilal-Dandan 2013).

These components are classified according to the receptors with which they have the most affinity. The anti-muscarinic agents operate on muscarinic acetylcholine receptors, and the anti-nicotinic agents on the nicotine acetylcholine receptors. Only the former are used to treat dystonia. Of the anti-muscarinic anticholinergic drugs, very few have good bio-availability within the central nervous system. A subclass of tertiary-amine muscarinic receptor antagonists is the exception, and compounds, such as trihexyphenidyl (non-proprietary), biperiden (Akineton®, Abbott, Chicago, USA), benztropine (non-proprietary), procyclidine (non-proprietary), and diphenhydramine (non-proprietary) have good penetration into the central nervous system (Hilal-Dandan 2013).

There are limitations to the use of anticholinergic agents. Although they are administered enterally, making them easy to take and sometimes preferred, they must be taken daily, and are often part of complex treatment regimen (Fahn 1987). They are systemically absorbed, meaning that their pharmacological effects can be felt diffusely across body systems where cholinergic receptors exist, including the central, peripheral, and autonomic nervous system. This characteristic is sometimes leveraged to treat forms of dystonia that affect several muscles and segments, but anticholinergics are avoided when possible, as the resulting side effects threaten the tolerability and limit the dosages that can be used (Fahn 1983). Some of these side effects include dryness of the mouth and other mucosae, vision alterations, bower and bladder difficulties, increased heart rate, sedation, and confusion or disorientation. These are especially relevant and bothersome in older adults and people with cognitive problems (Taylor 1991).

How the intervention might work

The therapeutic potential of all Bt serotypes derives from their ability to inhibit the release of acetylcholine from the presynaptic nerve terminal into the synaptic cleft, causing local chemodenervation (Jankovic 2004). Recent research has also suggested that Bt is active at multiple levels, namely sensory nerve terminals, and muscle spindles, which leads to a reduction in sensory input and fewer muscle contractions (Filippi 1993; Matak 2015; Rosales 1996; Rosales 2010).

In cervical dystonia, and in dystonia in general, the biological basis for the therapeutic effect of anticholinergic drugs is not completely understood. After crossing the blood-brain barrier, these compounds are thought to act on the acetylcholine receptors that mediate the response to the intrinsic cholinergic connections present in the neostriatum.

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 a number of focal dystonias (Duarte 2020; Duarte 2020a; Rodrigues 2020). BtA is considered first-line therapy for cervical dystonia (Albanese 2013; Castelão 2017; Rodrigues 2020). BtB has also been shown to be efficacious, but it has a different safety profile (Duarte 2016; Marques 2016). Even in moderately severe dystonia, there is evidence that people attach a considerable expectation of harm due to botulinum toxin (Duarte 2018). Since anticholinergics were the most widely accepted treatment before BtA became available, it is relevant to understand how these two treatments compare.

Since the release of the original review in 2005, no new trials have been published, but Cochrane's criteria for evaluating risk of bias and the certainty of the evidence have evolved and been updated. Therefore, the review authors considered it important to update this review (Costa 2005).

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), that were double-blind, parallel-designed, and which assessed the efficacy or safety, or both, of single or multiple doses of botulinum toxin type A (BtA) treatment versus anticholinergics, for any duration, in people with cervical dystonia. 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), in any setting, with a clinical diagnosis of idiopathic cervical dystonia, made by any physician, specialist, or other healthcare worker. We allowed trials that enrolled participants with any form of cervical dystonia, and additional, or widespread dystonias. Participants could have had prior exposure to BtA, and could be taking any concomitant medications, if they were on stable regimens.

Types of interventions

Intramuscular injections of BtA compared to anticholinergic drugs. 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 the Cervical Dystonia Severity Scale (CDSS), Tsui scale, Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS total score), or TWSTRS severity and disability subscales, measured 12 weeks after treatment (Consky 1994).

Adverse events

The proportion of participants with any adverse event, measured at any point during follow-up. In this item, we also evaluated adverse events of special interest, such as sore throat or dry mouth, neck weakness, dysphagia, injection site pain, voice change, or systemic complaints (e.g. diffuse muscle weakness, malaise, dizziness, or headache), measured at any point during follow-up.

Secondary outcomes

Subjective evaluation of clinical status

Evaluated by either participants, clinicians, or both, assessed with validated assessment tools, such as the 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), or a visual analogue scale (VAS) for symptom severity, measured between at 12 weeks.

Cervical dystonia-related pain

Assessed with validated assessment tools, such as the Patient Assessment of Pain, TWSTRS pain subscale, and VAS pain score, measured at 12 weeks.

Health-related quality of life

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

Tolerability

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

Duration of effect

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

Search methods for identification of studies

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

Electronic searches

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

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

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

We did not search trials registries.

Databases searched

- Cochrane Movement Disorders' Trials Register (June 2003);
- CENTRAL (2020, Issue 6) in the Cochrane Library (searched July 2020);
- MEDLINE (1977 to July 2020);
- Embase (1977 to July 2020).

Searching other resources

The search strategy also included:

- screening reference lists of identified trials and review articles concerning botulinum toxin;
- hand searching 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 September 2018));
- personal communication with other researchers in the field;
- contact with drug manufacturers.

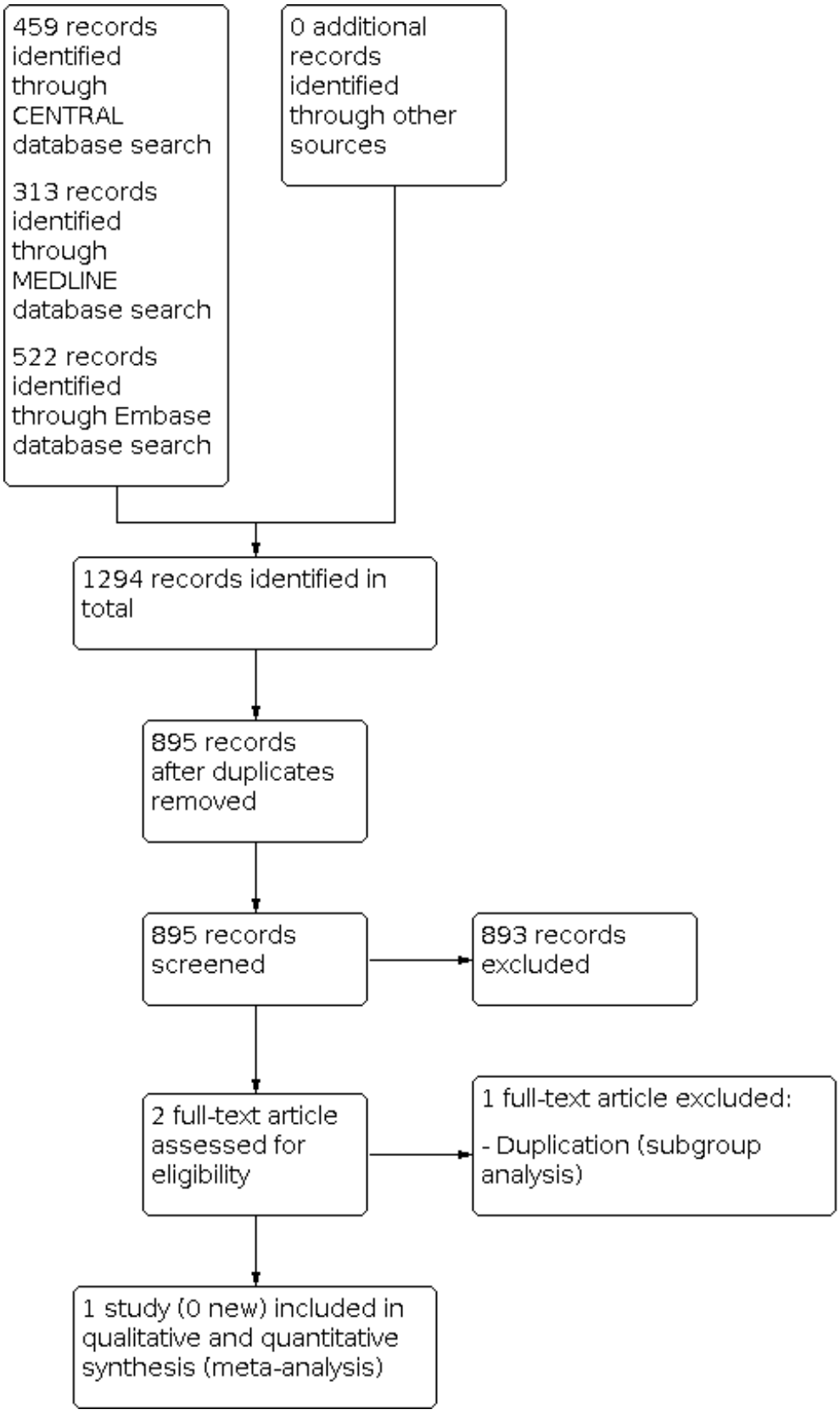
Data collection and analysis

Selection of studies

Two review authors independently screened all titles and abstracts identified from the 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 until they reached consensus; they consulted a third review author when

necessary. We linked multiple publications of the same trial under a single study ID in the review. We outlined the screening and selection process in a PRISMA flow chart (Liberati 2009). See Figure 1.

Figure 1. Study flow diagram (2020 search)



Data extraction and management

Two review authors extracted data independently from included studies, using a piloted data extraction form. We resolved any discrepancies by discussion until we reached consensus; we consulted a third review author when necessary. Data extracted included the following items from each study.

- Participants: inclusion and exclusion criteria, demographics and clinical baseline characteristics, number and reasons for dropouts, 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 participants randomised to each arm, compliance and dropouts, 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

Whenever necessary, we contacted authors of the trials for further information and unpublished data.

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.

Higgins 2011a

- Corbett 2014

Measures of treatment effect

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

Dichotomous data

We based analysis of these data on the number of events and the number of people assessed in the BtA and anticholinergic groups. We used these to calculate the risk ratio (RR) and 95% confidence interval (CI). Computational problems can occur when no events are observed in one or both groups in an individual study. For studies where no events were observed in one or both arms, we added a fixed value of 0.5 to all cells of study results tables.

Continuous data

We based analysis of these data on the mean, standard deviation (SD), and number of participants assessed for both the BtA and anticholinergic 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 planned to 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 planned to dichotomise rating scales, using each study author's own criteria for improvement or no improvement.

Time-to-event data

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

Unit of analysis issues

If future included studies have multiple arms with different dosages of botulinum toxin, we will combine all groups to create a single pair-wise comparison, using the Review Manager 5 (RevMan 5) calculator (Review Manager 2014), according to the methods suggested by Cochrane (Higgins 2011b). We will create a single, pair-wise comparison when multiple treatment groups use different interventions (e.g. onabotulinumtoxinA and abobotulinumtoxinA) but the same comparator.

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

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

Dealing with missing data

For future updates, if we include studies with missing outcome or summary data, we will use imputation methods to derive the missing data (where possible) and report any assumptions in the review. We will carry out sensitivity analyses to investigate the effects of any imputed data on pooled effect estimates.

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

If we are unable to use studies from the review to calculate a correlation coefficient, and if there is at least one sufficiently large and similar study, we will use a single imputation, based on this study (Furukawa 2006; Higgins 2011b).

Lastly, if there are sufficient included studies with complete information, we will use multiple imputation methods to derive missing data (Carpenter 2013; Rubin 1991).

If none of these methods prove successful, we will conduct a narrative synthesis for the data in question.

Assessment of heterogeneity

In future updates, if we include more studies, we will assess whether they are similar enough to enable us to pool the data in a meta-analysis. We will assess the degree of heterogeneity by visual inspection of forest plots, and by examining the Chi^2 test for heterogeneity (Deeks 2011). We will quantify heterogeneity using the I^2 statistic (Higgins 2003). We will consider an I^2 value of 50% or more to represent substantial levels of heterogeneity, but will interpret this value in light of the size and direction of effects, and the strength of the evidence for heterogeneity, based on the P value from the Chi^2 test.

Assessment of reporting biases

We only included one study in this review, so we did not construct a funnel plot (Sterne 2001), or conduct formal testing of asymmetry, which may indicate publication bias (Peters 2006). Should we include 10 or more studies in future updates, we will undertake these analyses.

Data synthesis

We planned to analyse the data using Review Manager 5 (Review Manager 2014), Stata version 14 (Stata), and Trial Sequential Analysis (Thorlund 2011; TSA 2011).

Meta-analysis

In future updates, if we include more studies, we will base the decision to meta-analyse data on an assessment of whether the interventions in the included trials have similar enough participants, settings, interventions, comparisons, and outcome measures to ensure meaningful conclusions from a statistically pooled result. We will use a random-effects model for the data synthesis.

We will pool effect measures by applying the Mantel-Haenszel method for dichotomous outcomes, and the inverse-variance or generic inverse-variance method for continuous outcomes. If we have the data, we will pool time-to-event data using the generic inverse-variance method. We will present all results with 95% CI.

We will calculate the number of participants needed to treat for an additional beneficial outcome (NNTB) and for an additional harmful outcome (NNTH) from meta-analysis estimates, rather than treating data as if they came from a single trial, as the latter approach is more prone to bias, especially when there are significant imbalances between groups within one or more trials in the meta-analysis (Altman 2002). We will be cautious when interpreting 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).

Since there were no data to combine, we undertook a narrative approach to synthesise the result.

Trial Sequential Analysis

If we include more studies in an update, we will conduct a Trial Sequential Analysis (TSA) to explore whether the cumulative data are of adequate power to evaluate the primary outcomes of the review (Wetterslev 2008), and calculate 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-analyses 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 will calculate the required information size and compute the trial sequential monitoring boundaries, using the O'Brien-Fleming approach (O'Brien 1979). We will based the required information size on the event proportion or standard deviation in the control group; an 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). We will not give any consideration to the risk of bias within trials.

Schünemann 2011 GRADEpro GDT

- Guyatt 2011

Balshem 2011

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 anticholinergic agents
- 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 had planned to conduct sensitivity analyses for every study for which we applied imputation methods.

Summary of findings and assessment of the certainty of the evidence

Assessing the certainty in the evidence

Two review authors independently assessed the evidence for each outcomes using the following domains: study limitations, inconsistency, indirectness, imprecision, and publication bias (Schünemann 2011). In case of disagreement, the authors attempted to reach consensus, consulting an independent third review author if necessary. We used the GRADEpro GDT software tool to assess the certainty, and then exported a 'Summary of findings' table into the review manuscript (GRADEpro GDT).

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

- Study limitations: we downgraded once if more than 30% of the 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 and the GRADE analysis. Version 3 was used for ease of interpretation (Carrasco-Labra 2016).

RESULTS

Description of studies

We did not identify any new studies in this update.

Overall, we included a single parallel-designed study, comparing BtA (Dysport) with trihexyphenidyl, with a total of 66 participants with cervical dystonia.

See also Characteristics of included studies.

Results of the search

See Figure 1, flow diagram of study selection.

We last ran the updated electronic search in July 2020. The search returned 1294 records (459 through CENTRAL; 313 though MEDLINE; 522 through Embase), resulting in 895 records after removing all duplicates. After title and abstract screening, we retrieved two articles for full-text screening, and only one was eligible for both the qualitative and quantitative syntheses (Brans 1996). This study was already included in the original review.

We did not retrieve any unpublished trials.

Included studies

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

The included study enrolled a total of 66 adult participants, with a mean age of 50.65 years, 40 of whom were female (60%).It was performed in four centres in the Netherlands. The mean duration of cervical dystonia was 9.4 years. The overall disorder impairment at baseline was moderate, with a mean score of 15.9 on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS, *range 0 - 85, higher is worse*) disability subscale (*range 0 - 30, higher is worse*), and 14.7 on the Tsui scale (*range 1 - 25, higher is worse*). The trial excluded people who had been previously exposed to Bt. All forms of idiopathic cervical dystonia were eligible, as long as they were not multifocal, generalised, or secondary. The number of dropouts was small (one in each arm (3%)).

Study design and interventions

The included trial had two arms. In the BtA arm, participants received intramuscular BtA at week zero and week eight, plus placebo tablets. In the trihexyphenidyl arm, participants received intramuscular placebo at week zero and week eight, and 2 mg trihexyphenidyl tablets.

In both groups, tablets were taken daily, starting with half a tablet per day, and increasing by one-half every three days, up to the maximum tolerated or maximum allowed dose (three tablets, four times a day).

All injections were given with EMG guidance. The volume injected was left to the discretion of the investigator (mean BtA dose in the BtA arm: 292 U at week zero; 262 U at week eight). In one centre, five participants received half the planned BtA dose due to an error in dilution.

The trial lasted for 12 weeks. Efficacy was evaluate using a modified intent-to-treat (ITT) analysis, which included all participants who received treatment.

Excluded studies

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

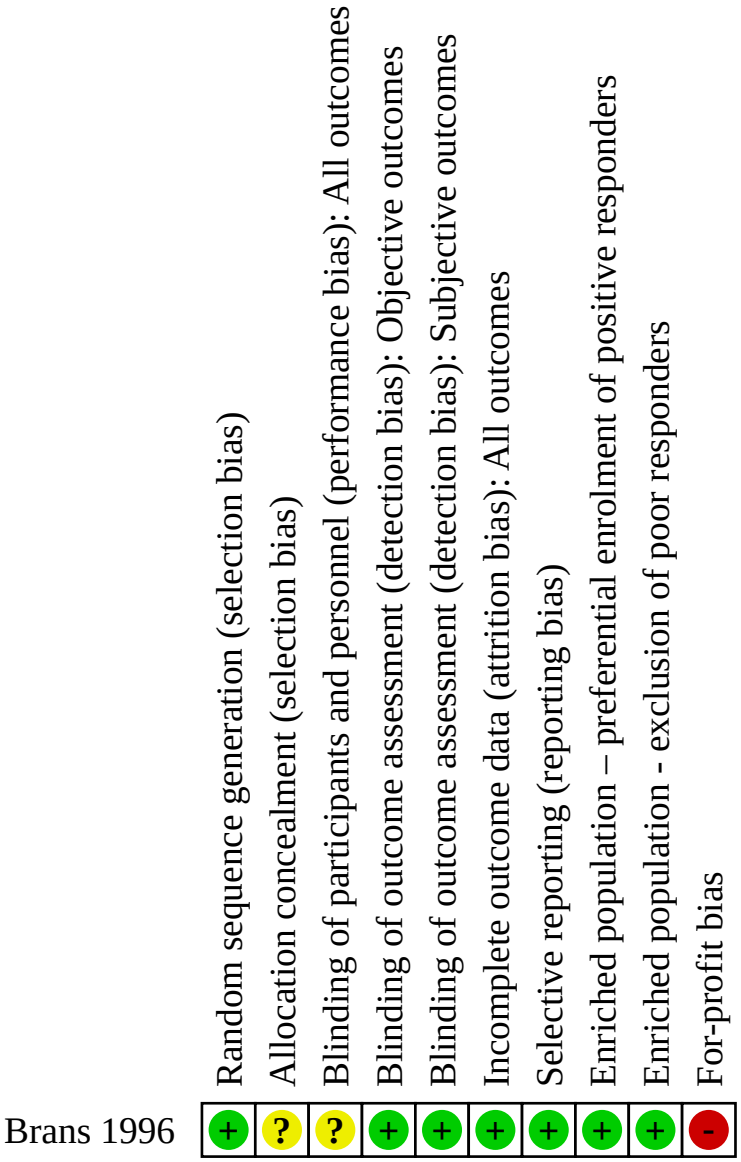
We excluded one publication for being a duplicate (post-hoc subgroup analysis of Brans 1998).

Risk of bias in included studies

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

See Figure 2 for the 'Risk of bias' summary graphs. We based these assessments on the information available in the primary report data.

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study



Allocation

The process of random sequence generation was clearly described in the study (low risk), but the allocation concealment was not described (unclear risk).

Blinding

We judged the blinding of participants and personnel involved in the trail to be at low risk, as the trial was double-blind and double-dummy, and the assessments were performed by a single independent and blinded investigator not involved in the treatment of the participants. However the higher frequency of adverse events in the trihexyphenidyl arm could have confounded the blinding and possibly contributed to performance bias. As so, we rated this item as unclear risk.

Incomplete outcome data

The reasons for missing data were summarised in the study report; we rated the study to be at low risk of bias for incomplete outcome data.

Selective reporting

We considered the study to be at low risk for reporting bias.

Other potential sources of bias

Enriched population

Only Bt-naive participants were eligible for the included trial, and the inclusion criteria do not seem to exclude less responsive forms of cervical dystonia. We rated this domain at low risk of bias.

For-profit bias

The study declared funding and supply of study interventions from industry sources, so we rated it at high risk of bias for funding and potential conflicts of interest.

Publication bias

We intended to use funnel plots to explore publication bias. However, due to only one study being available, we did not conduct this analysis (Sterne 2011).

Effects of interventions

See: **Summary of findings 1** Botulinum toxin type A compared to anticholinergics 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.

All results were extracted from the study report (Brans 1996).

Primary outcomes

Cervical dystonia-specific improvement

The included study assessed the primary outcome at week 12 following an injection session at week 0 and another at week 8.Tarsy 1997

DISCUSSION

Summary of main results

This updated review included one randomised, parallel-designed trial, that enrolled 66 people with cervical dystonia, none of whom had been previously treated with botulinum toxin (Bt) for their condition.

As can be seen in the Summary of findings 1, in comparison to trihexyphenidyl, the effect of botulinum toxin type A (BtA) for cervical dystonia remains very uncertain for cervical dystonia-associated overall impairment, and associated pain, health-related quality of life, tolerability, and adverse events.

Treatment with trihexyphenidyl increased the risk of experiencing two specific adverse events: dry mouth and memory problems. No fatalities or serious adverse events were considered to be related to the BtA or trihexyphenidyl treatments in the trial. Data for special subpopulations, such as children or pregnant women, were not available.

We found no information on subjective improvement, a dose-response relationship with BtA, differences between BtA formulations or different anticholinergics, the utility of EMG-guided injections, or the duration of treatment effect.

Overall completeness and applicability of evidence

The included trial addressed the primary research question directly, using validated assessment tools. However, it did not report data for all outcomes. This limited the amount of data available, and consequently, the confidence in overall conclusions. The number of adverse events was high in both the BtA and anticholinergic 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).

The participants included in the trial were not fully representative of the overall population of people with cervical dystonia. By selecting Bt-naive participants, we were unable to draw conclusions concerning all people with this condition. In clinical practice, clinicians may choose from more than one anticholinergic medication. Since the trial tested a single anticholinergic only, generalisation is limited.

Finally, the sample size of the included trial was small, and many outcomes addressing clinically relevant questions were underpowered. More studies are needed to provide definitive evidence for these questions.

Quality of the evidence

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

We considered the included trial to be at high risk for for-profit bias, unclear risk of bias for allocation concealment and blinding of personnel and participants, and low risk of bias for the other domains. Results from all outcomes were below the optimal information size, and many crossed the line of no effect. This represented a major methodological limitation that may have resulted in a biased assessment of the intervention effect.

Taken together, there is very low certainty in the evidence that BtA improves cervical dystonia-associated impairment, health-related quality of life, and pain in cervical dystonia, more than trihexyphenidyl. There is very low certainty that tolerability is not different between BtA and trihexyphenidyl, based on the likelihood of participants dropping out of the trial.

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, with the exception of the Cochrane clinical trial registry. Although this opens the current review to the potential bias of having missed trials, we consider this possibility highly unlikely, because we contacted other experts in this field, and USA and European trials in this area are well-known.

We were also unable to obtain data for all outcomes in the included trial, reducing the amount of data available for analysis.

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). They are also aligned with the current clinical practice guidelines of the American Academy of Neurology affirming that "BtA is probably more efficacious and better tolerated than trihexyphenidyl"(Simpson 2016) while the European Academy of Neurology reiterates that "No new class A or B [evidence/recommendations] are available for oral medications"(Albanese 2011).

AUTHORS' CONCLUSIONS

Implications for practice

Based on very low-quality evidence, we are uncertain how the effects of botulinum toxin type A (BtA) compare with trihexyphenidyl.

We found very low-certainty evidence that BtA is more effective, better tolerated, and safer than trihexyphenidyl. People treated with BtA experienced improved disability, pain, and quality of life compared with people treated with trihexyphenidyl. Adverse events were less frequent with BtA.

We cannot draw conclusions about other anticholinergic drugs, drug-dose response, or benefits associated with the use of EMG-guided injections. We cannot draw conclusions about people who are not BtA-naive, or people who have other forms of dystonia, as the trial excluded them.

Implications for research

The efficacy and tolerability of BtA in cervical dystonia is well established (Castelão 2017; Duarte 2016; Marques 2016), making it difficult to determine which and how many resources should be invested in future research. The magnitude of benefit, as with other movement disorders, varies in a real-world setting (Duarte 2018; Rodrigues 2019).

Castelão 2017 Duarte 2016 Marques 2016

We only had access to published research data from one trial of BtA versus anticholinergic drugs in adults with cervical dystonia. The role of anticholinergic drugs in people who do not get benefit with BtA should be further explored, and further studies are needed to establish the relative effectiveness of different anticholinergic drugs, assessing efficacy, safety, duration of effect, and quality of life across regimes.

Future research on cervical dystonia should endeavour to establish clinical effectiveness, based on both changes from baseline, and validated measures of minimal clinically important difference or change (Brożek 2006).

It is still uncertain whether the clinical effectiveness of botulinum toxin or anticholinergic drugs decays over time, or with repeated treatment sessions of Bt, and whether a possible loss of effectiveness occurs in all clinical domains.

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 uncertainty in the results, mainly due to the low statistical power of the analysis, future efforts to update this review would be justified, as long as new trials are published.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Brans 1996

Study characteristics	
Methods	Randomised, double-blind, parallel design **Randomisation:** minimization with a computer software **Setting:** multicentre (4 centres in the Netherlands) **Duration:** 12 weeks
Participants	66 participants enrolled (BtA group = 33; trihexyphenidyl group = 33) **% Female:** BtA: 48%; trihexyphenidyl: 73% **Mean age, range:** BtA: 50.1 years; trihexyphenidyl: 51.2 years **Mean CD duration:** BtA: 9.1 years; trihexyphenidyl: 8.6 years **Mean CD severity (SD) for TWSTRS total:** BtA: 15.9 (5.4); trihexyphenidyl: 15.8 (5.2) **Inclusion criteria:** • 21 to 75 years of age • idiopathic CD **Exclusion criteria:** • pregnancy • multifocal or generalized dystonia • neurological diseases, coagulation disorder, or secondary dystonia • duration of illness less than 1 year • previous treatment with BtA If participants were already receiving trihexyphenidyl prior to the study, this drug was tapered off during 4 weeks before study entry. Other medications for focal dystonia, such as benzodiazepines, were not changed during the study.
Interventions	**BtA arm:** Dysport (abobotulinumtoxinA); 20 U diluted in 0.1 mL of saline + 2 mg placebo tablets **Trihexyphenidyl arm:** 2 mg trihexyphenidyl tablets + saline injection **Study drug preparation:** vials and providers not mentioned **Muscles injected:** the number of injection sites per muscle was determined at the discretion of the investigator **EMG guidance:** all participants **BtA or injection dose per participant:** the volume injected was determined at the discretion of the investigator

Brans 1996 *(Continued)*

	Trihexyphenidyl or placebo tablet dose per participant: started at half a tablet per day, which was increased by one half every 3 days up to the maximum tolerated dose or the maximum allowed dose (3 tablets, 4 times a day).
Outcomes	**Primary outcomes:** • TWSTRS disability subscale (range 0 to 33) at week 12 **Secondary outcomes:** • Improvement (3-point change) on the TWSTRS disability subscale at week 12 • Tsui Scale (range 0 to 25) at week 12 • Improvement (3-point change) on the Tsui Scale at week 12 • TWSTRS pain subscale (range 0 to 20) at week 12 • General Health Perception Subscale of the MOS Quality of Life Scale (Dutch version;100-point scale) at week 12 • Adverse events
Notes	**Study dropouts:** BtA arm: n = 1 (3%) Trihexyphenidyl arm: n = 3 (9%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was accomplished with a computer program that allowed for minimisation according to type of dystonia, degree of disability, duration of illness and treatment center"
Allocation concealment (selection bias)	Unclear risk	Comment: method of concealment not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "If tablets contained placebo, injection fluid consisted of BtA, and if tablets contained trihexyphenidyl, the injection fluid was saline. The tablets containing trihexyphenidyl or placebo were similar in appearance" and " ... BtA was diluted (…) by an independent pharmacist and aspirated in 1 mL syringes. Placebo injections consisted of an equivalent volume of 0.9% saline" Comment: There was a significantly higher number of adverse events, and specific adverse events in the trihexyphenidyl arm. This could have confounded the blinding in the trial.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Quote: "If tablets contained placebo, injection fluid consisted of BtA, and if tablets contained trihexyphenidyl, the injection fluid was saline. The tablets containing trihexyphenidyl or placebo were similar in appearance" and " ... BtA was diluted (…) by an independent pharmacist and aspirated in 1-mL syringes. Placebo injections consisted of an equivalent volume of 0.9% saline" and "All patients were assessed on clinical rating scales before treatment (baseline) and after 12 weeks (week 12) by the same assessor (R.L.), who was not involved in the treatment of the patients" and "When the trial was completed, the recordings were edited into random order and scored by an assessor (J.B.), who had no knowledge of which treatment had been given and who was not involved in the treatment of the patients."
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote: "If tablets contained placebo, injection fluid consisted of BtA, and if tablets contained trihexyphenidyl, the injection fluid was saline. The tablets containing trihexyphenidyl or placebo were similar in appearance" and " ...

Brans 1996 *(Continued)*

		BtA was diluted (…) by an independent pharmacist and aspirated in 1-mL syringes. Placebo injections consisted of an equivalent volume of 0.9% saline"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Two patients dropped out before they received trial treatment, one in each treatment group, because of the occurrence of a colon carcinoma in one patient and withdrawal of cooperation in the other. The remaining 64 patients completed the trial and have been included in the analysis of efficacy and safety." 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.
Enriched population – preferential enrolment of positive responders	Low risk	Quote: "Patients were excluded if (...) previous treatment with BtA"
Enriched population - exclusion of poor responders	Low risk	Comment: Not stated
For-profit bias	High risk	Quote: "Supported by Speywood Pharmaceuticals and Allergan BV"

BtA - botulinum toxin type A
TWSTRS - Toronto Western Spasmodic Torticollis Rating Scale

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

Study	Reason for exclusion
Brans 1998	This is a post-hoc subgroup analysis of Brans 1996. They looked at EMG changes after BtA or trihexyphenidyl.

ADDITIONAL TABLES

Table 1. Glossary of terms

Term	Definition
Botulinum toxin type A (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	Discomfort or difficulty when swallowing.

Table 1. Glossary of terms *(Continued)*

Dystonia	A painful and disabling disorder, characterised by painful, involuntary posturing of the affected body region(s).
Electromyography (EMG)	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.

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
7 January 2021	New citation required but conclusions have not changed	New search. No new trials included
25 July 2020	New search has been performed	Methods updated. No new trial included.

HISTORY

Protocol first published: Issue 3, 2003
Review first published: Issue 1, 2005

Date	Event	Description
11 August 2014	New search has been performed	No new data
30 October 2013	New search has been performed	New database search
8 October 2004	New citation required and conclusions have changed	Substantive amendment

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Designing search strategies – FBR, GSD, JC

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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

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DECLARATIONS OF INTEREST

J Costa, JJ Ferreira, and C Sampaio have been investigators in clinical trials sponsored by Elan, Allergan, and Ipsen. JJ Ferreira and C Sampaio were speakers in symposia promoted by Elan, Allergan, and Ipsen. AP Moore has received fees from various companies marketing botulinum toxin for speaking at meetings and for advice. His unit has received funds for research.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this updated review, we restricted the accepted study designs to parallel-group studies, and opted not to exclude based on allocation concealment. We made no changes to the type of participants included or 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 also considered the proportion of participants with the most frequent adverse events, which was not stated in the original protocol. We included an assessment of the duration of effect as a new secondary outcome measure.

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

We used the latest recommended Cochrane tool for assessing risk of bias in this review, which was expanded to include two additional criteria, added by the review authors. We opted to include the enriched population domains, since a known positive response to botulinum toxin type A and certain disorder subtypes are known to influence the magnitude of response to the intervention. As has been verified in a recent Cochrane methodology systematic 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.

Trial Sequential Analysis was not in the original review protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Botulinum Toxins, Type A [*therapeutic use]; Cholinergic Antagonists [*therapeutic use]; Neuromuscular Agents [*therapeutic use]; Torticollis [*drug therapy]

MeSH check words

Humans