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*Cochrane Database of Systematic Reviews* 2017, Issue 12. Art. No.: CD003633.
DOI: 10.1002/14651858.CD003633.pub3.

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[Intervention Review]

# Botulinum toxin type A therapy for cervical dystonia

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**Editorial group:** Cochrane Movement Disorders Group.
**Publication status and date:** New search for studies and content updated (no change to conclusions), published in Issue 12, 2017.

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

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## ABSTRACT

### Background

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

### Objectives

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

### Search methods

To identify studies for this review we searched Cochrane Movement Disorders' Trials Register, CENTRAL, MEDLINE, Embase, reference lists of articles and conference proceedings. All elements of the search, with no language restrictions, were run in October 2016.

### Selection criteria

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

### Data collection and analysis

Two review authors independently assessed records, selected included studies, extracted data using a paper pro forma, and evaluated the risk of bias. We resolved disagreements by consensus or by consulting a third review author. We performed meta-analyses using a random-effects model for the comparison of BtA versus placebo to estimate pooled effects and corresponding 95% confidence intervals (95% CI). In addition, we performed preplanned subgroup analyses according to BtA dose used, the BtA formulation used, and the use or not of guidance for BtA injection. 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 eight RCTs of moderate overall risk of bias, including 1010 participants with cervical dystonia. Six studies excluded participants with poorer responses to BtA treatment, therefore including an enriched population with a higher probability of benefiting from this therapy. Only one trial was independently funded. All RCTs evaluated the effect of a single BtA treatment session, using doses from 150


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U to 236 U of onabotulinumtoxinA (Botox), 120 U to 240 U of incobotulinumtoxinA (Xeomin), and 250 U to 1000 U of abobotulinumtoxinA (Dysport).

BtA was associated with a moderate-to-large improvement in the participant's baseline clinical status as assessed by investigators, with reduction of 8.06 points in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS total score) at week 4 after injection (95% CI 6.08 to 10.05; $I^2 = 0\%$) compared to placebo, corresponding on average to a 18.7% improvement from baseline. The mean difference (MD) in TWSTRS pain subscore at week 4 was 2.11 (95% CI 1.38 to 2.83; $I^2 = 0\%$). Overall, both participants and clinicians reported an improvement of subjective clinical status. There were no differences between groups regarding withdrawals due to adverse events. However, BtA treatment was associated with an increased risk of experiencing an adverse event (risk ratio (RR) 1.19; 95% CI 1.03 to 1.36; $I^2 = 16\%$). Dysphagia (9%) and diffuse weakness/tiredness (10%) were the most common treatment-related adverse events (dysphagia: RR 3.04; 95% CI 1.68 to 5.50; $I^2 = 0\%$; diffuse weakness/tiredness: RR 1.78; 95% CI 1.08 to 2.94; $I^2 = 0\%$). Treatment with BtA was associated with a decreased risk of participants withdrawing from trials. We have moderate certainty in the evidence across all of the aforementioned outcomes.

We found no evidence supporting the existence of a clear dose-response relationship with BtA, nor a difference between BtA formulations, nor a difference with use of EMG-guided injection.

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

### Authors' conclusions

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

## PLAIN LANGUAGE SUMMARY

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

### The review question

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

### Background

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

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

### Study characteristics

We performed a rigorous search of the medical literature in October 2016 and found eight studies that compared treatment with BtA versus placebo. These studies included a total of 1010 participants, with on average a moderate disease impairment. The participants remained in the majority of studies for a short period of time - between 16 and 20 weeks after the treatment. The average age of people in the studies was 52.3 years, and they had had cervical dystonia for an average of 4.8 to 12.1 years before taking part in the trials. Most, 64%, of the people in the studies were women. Seven of the eight trials were funded by drug manufacturers with possible interests in the results of the studies.

### Key results

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


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**Certainty in the evidence**

The certainty in the evidence for overall and pain improvement, the risk of undesired events, self-evaluation, the risk of swallowing difficulties, and the risk of participants not tolerating treatment, is moderate.

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

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


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