Cochrane Clinical Answers

Question:

How does botulinum toxin A compare with placebo in people with cervical dystonia?

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Answer

Moderate-quality evidence shows that botulinum toxin A in adults with moderate to severe impairment due to cervical dystonia leads to a large improvement in cervical dystonia and a moderate improvement in pain. Duration of effect and quality of life were inconsistently reported across trials, but there seemed to be an improvement in quality of life.

Overall adverse events were more common with botulinum toxin A (on average, 545 vs 459 per 1000 people); when assessing specific events, more people experienced dysphagia (82 vs 27 per 1000 people) and diffuse weakness/tiredness with botulinum toxin A than with placebo (32 vs 18 per 1000 people).

Comparisons

1. Botulinum toxin A (BtA) versus placebo

Expand All »

OUTCOME 1.1 Improvement in cervical dystonia (4 to 6 weeks)

Narrative result

Seven RCTs with 833 participants found that improvement in cervical dystonia was greater with BtA than with placebo.

As the studies used different scales to assess this outcome, the reviewers calculated a standardized mean difference. These are hard to interpret clinically but rules of thumb in their interpretation suggest that 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect (Cohen J. Statistical Power Analysis in the Behavioral Sciences (2nd edition). Hillsdale (NJ): Lawrence Erlbaum Associates, Inc., 1988).

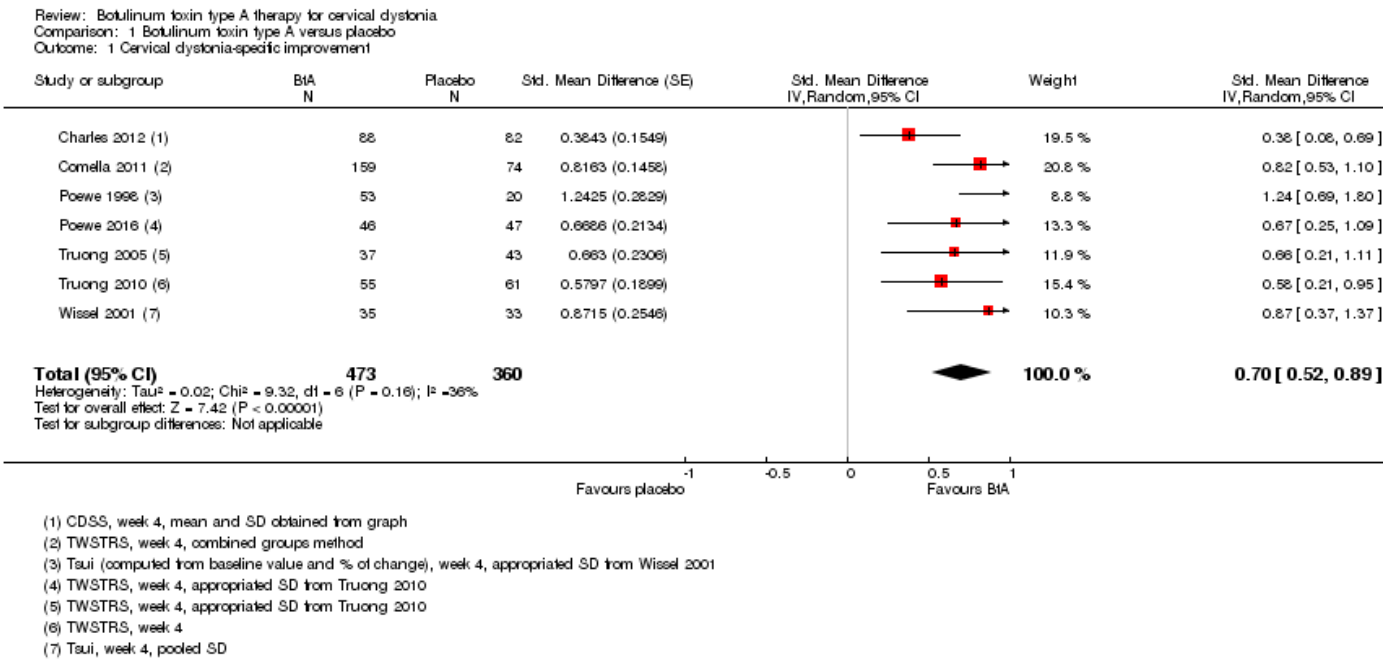
Most participants received a medium dose of BtA (545 participants; Botox/Xeomin 101 U to 200 U; Dysport 500 U), were administered Dysport (430 participants), and had an EMG-guided injection (522 participants); the results for these subgroups were similar to the main analysis. Most participants were assessed using the 0 85 point TWSTRS. (522 participants); the result for this subgroup showed that the improvement in cervical dystonia was greater with BtA than with placebo. Click below for details.[1]

Quality of the evidence

The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was moderate quality. Reported in the main text of the review

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of BtA (standardized mean difference 0.70, 95% CI 0.52 to 0.89).



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

Figure 1 Open in figure viewer

Forest plot from Cochrane Review

Reference

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. Search date October 2016

Subgroup analysis 1.1.1 Improvement in cervical dystonia – [subgroup: TWSTRS]

Narrative result

Four RCTs with 522 participants found that improvement in cervical dystonia was greater with BtA than with placebo. The TWSTRS scale ranges from 0 to 69, with lower scores denoting improvement.[2]

Quality of the evidence

The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was moderate quality. See Summary of findings from Cochrane review

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of BtA (mean difference 8.06 points, 95% CI 6.08 to 10.05).

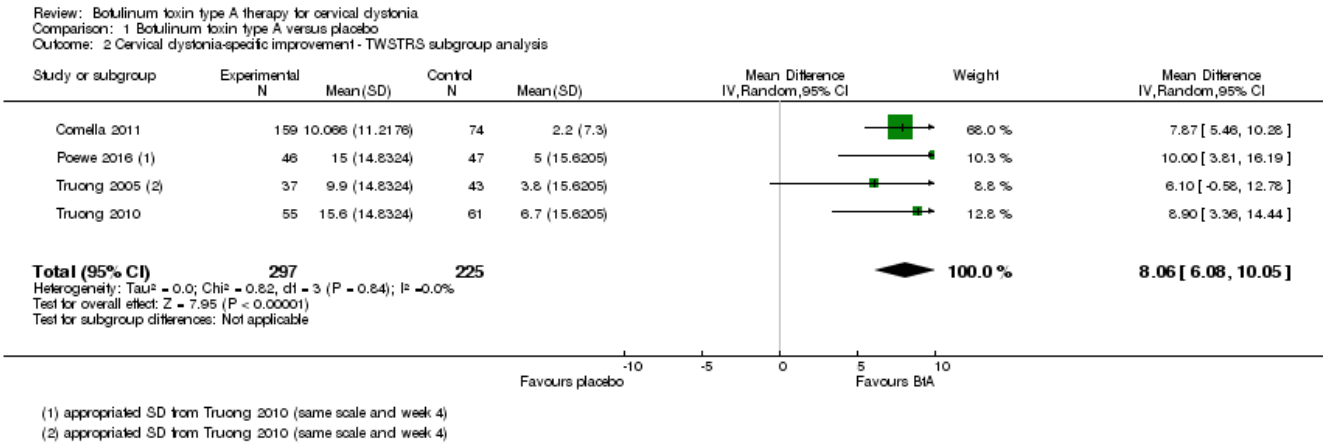


Figure 2 Open in figure viewer

Forest plot from Cochrane Review

This is equivalent to a standardized mean difference of 0.64, 95% CI 0.46 to 0.82), which is interpreted as a moderate effect magnitude.

Reference

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. Search date October 2016

OUTCOME 1.2 Duration of effect

Narrative result

One RCT with 75 participants reported that duration of effect was dose-dependent, with requests for re-injection occurring at week 8 in 39% of people receiving a high dose, 50% of people receiving a medium dose and 94% of participants receiving a low dose.

One RCT with 80 participants reported a mean to recurrence of symptoms of 22.8 weeks (range 9 to 46 weeks), and one RCT with 116 participants reported a mean time to retreatment of 14.4 weeks (range 4 to 30).

One RCT with 369 participants reported a greater response to BtA over five treatment cycles; duration of treatment effect for treatment responders was > 85 days from cycles 2 to 5, irrespective of dose used.[3]

Risk of bias of studies

The reviewers did not perform a GRADE assessment of the quality of the evidence. Of the four studies, one failed to report adequate allocation concealment, two did not report on random sequence generation, one did not report adequate blinding of participants/carers, none reported blinding of outcome assessors and one had high numbers of withdrawals.

Relative effect or mean difference

Results were reported narratively.

Reference

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. Search date October 2016

OUTCOME 1.3 Pain associated with cervical dystonia (4 to 6 weeks)

Narrative result

Six RCTs with 722 participants found that pain associated with cervical dystonia was lower with BtA than with placebo. When analyses were conducted for each BtA formulation (Botox, Dysport, Xeomin), or EMG-guided and unguided procedures, separately, results were similar to the main analysis.

As the studies used different scales to assess this outcome, the reviewers calculated a standardized mean difference. These are hard to interpret clinically but rules of thumb in their interpretation suggest that 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect (Cohen J. Statistical Power Analysis in the Behavioral Sciences (2nd edition). Hillsdale (NJ): Lawrence Erlbaum Associates, Inc., 1988).

Most participants were assessed using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS; 429 participants); the result for this subgroup showed that the improvement in cervical dystonia-was greater with BtA than with placebo. Click below for details.[4]

Quality of the evidence

The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was moderate quality. Reported in the main text of the review

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of BtA (standardized mean difference 0.50, 95% CI 0.35 to 0.65).

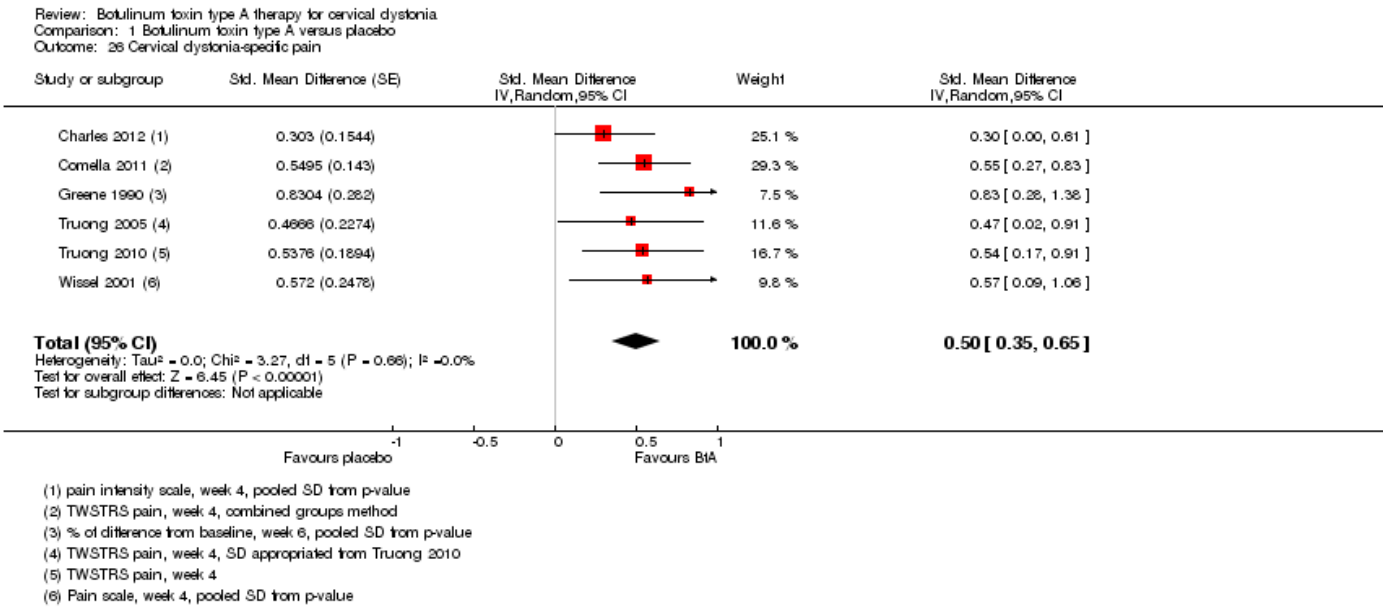


Figure 3 Open in figure viewer

Forest plot from Cochrane Review

Reference

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. Search date October 2016

- **Subgroup analysis 1.3.1 Pain associated with cervical dystonia – [subgroup: TWSTRS]**

Narrative result

Three RCTs with 429 participants found that more people had cervical dystonia-specific pain with BtA than with placebo. The TWSTRS pain subscale ranges from 0-20, with lower scores denoting improvement.[5]

Quality of the evidence

The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was moderate quality. See Summary of findings from Cochrane review

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of BtA (mean difference 2.11, 95% CI 1.38 to 2.83).

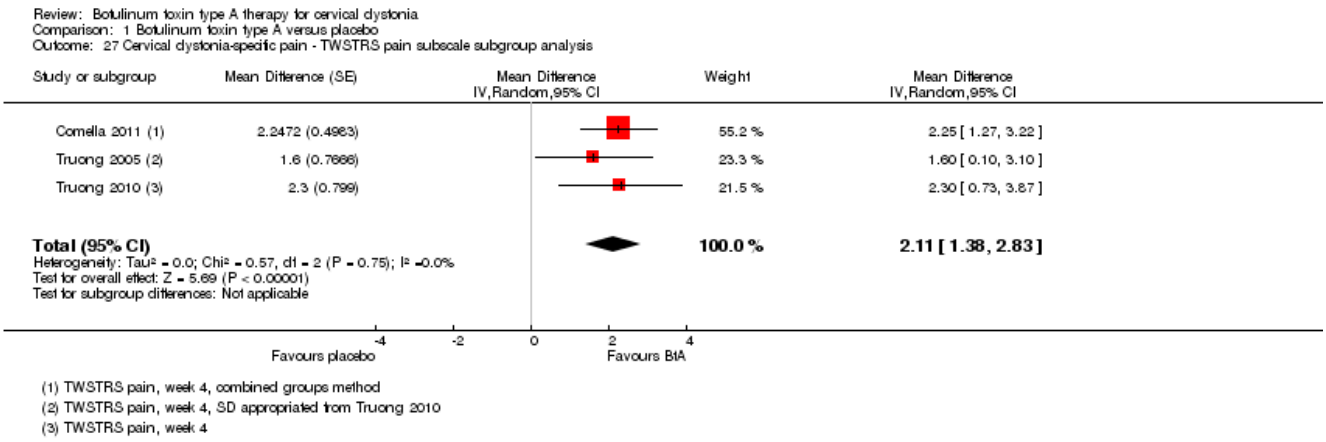


Figure 4 Open in figure viewer

Forest plot from Cochrane Review

Reference

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. Search date October 2016

OUTCOME 1.4 Quality of life

Narrative result

One RCT with 213 participants reported statistically significant improvements in total Cervical Dystonia Impact Profile (CDIP)-58 score, with lower scores denoting improvement. (49.3 with BtA vs 59.4 with placebo; P < 0.0001) and all eight subscales (head and neck symptoms, pain and discomfort, sleep, upper limb activities, walking, annoyance, mood and psychosocial functioning; P < 0.0003).

Two RCTs with 1960 participants reported either the number of participants with improvement (odds ratio) or changes in quality of life from baseline (mean difference) to week 8 in the physical function domain of the SF-36 (OR 1.60, P 0.011 [1 trial] or mean difference 10.10 points, 95% CI 2.95 to 17.25 [1 trial]), but no benefit in social functioning (OR 0.30, 95% CI 0.23 to 0.82 [1 trial] or mean difference 6.90 points, 95% CI 2.16 to 15.96 [1 trial]) when compared with placebo.[6]

Risk of bias of studies

The reviewers did not perform a GRADE assessment of the quality of the evidence. Of the three studies, one failed to report adequate allocation concealment, one did not report on random sequence generation, one did not report adequate blinding of participants/carers, two did not report blinding outcome assessors and one had high numbers of withdrawals.

Relative effect or mean difference

Results were reported narratively.

Reference

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. Search date October 2016

OUTCOME 1.5 Adverse events

Narrative result

Seven RCTs with 952 participants found that more people experienced an adverse event with BtA than with placebo. Overall, 55.3% of participants receiving BtA and 46.5% of participants receiving placebo experienced an adverse event.

Most participants received a medium dose of BtA (664 participants; Botox/Xeomin 101 U to 200 U; Dysport 500 U), were administered Dysport (549 participants), and had an EMG-guided injection (640 participants); the results for these subgroups were similar to the main analysis.

When individual adverse events were analyzed (dysphagia, diffuse weakness/tiredness, neck weakness, malaise/upper respiratory tract infection, local/injection site pain, headache), only dysphagia and weakness/tiredness showed statistically significant differences between groups, with these being more commonly associated with BtA. Click below for details.[7]

Quality of the evidence

The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was moderate quality. See Summary of findings from Cochrane review

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of placebo (RR 1.19, 95% CI 1.03 to 1.36).

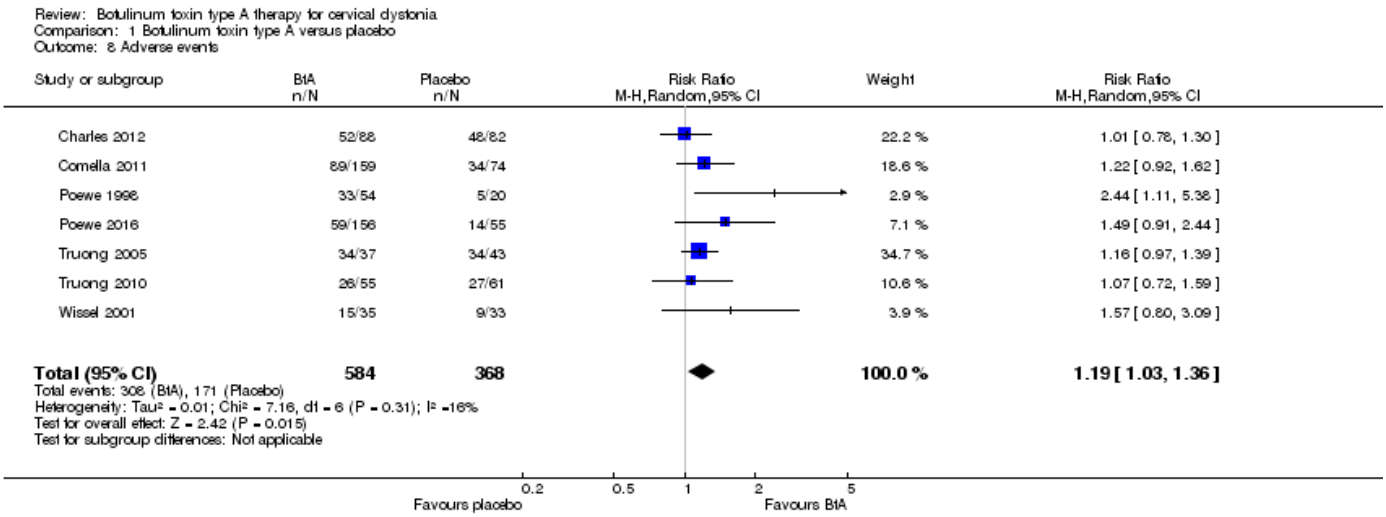


Figure 5 Open in figure viewer

Forest plot from Cochrane Review

Absolute effect

545 per 1000 people (95% CI 475 to 625) with BtA compared with 459 per 1000 people with placebo.

Reference

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. Search date October 2016

› **Subgroup analysis 1.5.1 Adverse events – [subgroup: Dysphagia]**

Narrative result

Eight RCTs with 1007 participants found that more people experienced dysphagia with BtA than with placebo.[8]

Quality of the evidence

The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was moderate quality. See Summary of findings from Cochrane review

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of placebo (RR 3.04, 95% CI 1.68 to 5.50).

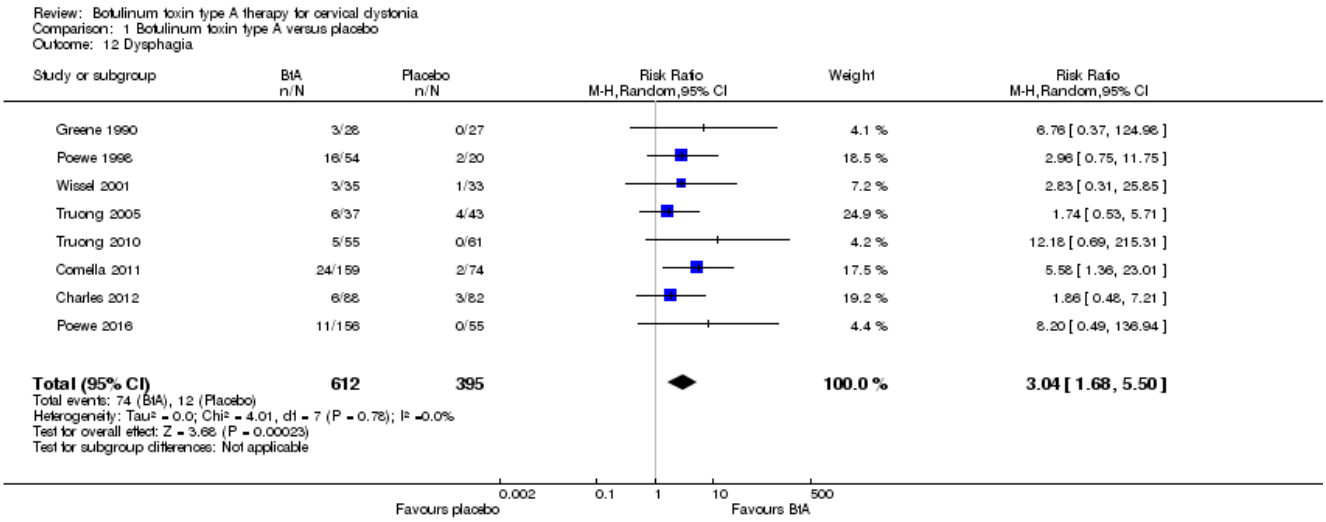


Figure 6 Open in figure viewer

Forest plot from Cochrane Review

Absolute effect

82 per 1000 people (95% CI 45 to 149) with BtA compared with 27 per 1000 people with placebo.

Reference

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. Search date October 2016

› Subgroup analysis 1.5.2 Adverse events – [subgroup: Diffuse weakness/tiredness]

Narrative result

Six RCTs with 823 participants found that more people experienced diffuse weakness/tiredness with BtA than with placebo.[9]

Quality of the evidence

The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was moderate quality. See Summary of findings from Cochrane review

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of placebo (RR 1.78, 95% CI 1.08 to 2.94).

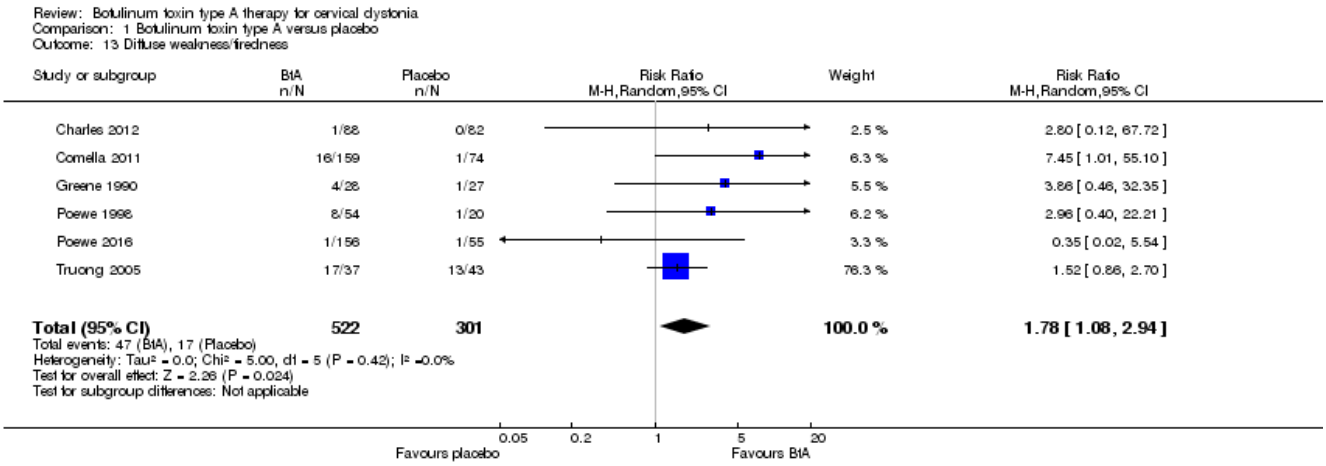


Figure 7 Open in figure viewer

Forest plot from Cochrane Review

Absolute effect

32 per 1000 people (95% CI 20 to 53) with BtA compared with 18 per 1000 people with placebo.

Reference

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. Search date October 2016

OUTCOME 1.6 Withdrawal due to adverse events

Narrative result

Two RCTs with 288 participants found no statistically significant difference between groups; event rates were extremely low.[10]

Quality of the evidence

The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was moderate quality. Reported in the main text of the review

Relative effect or mean difference

There was no statistically significant difference between groups (RR 3.10, 95% CI 0.36 to 26.74).

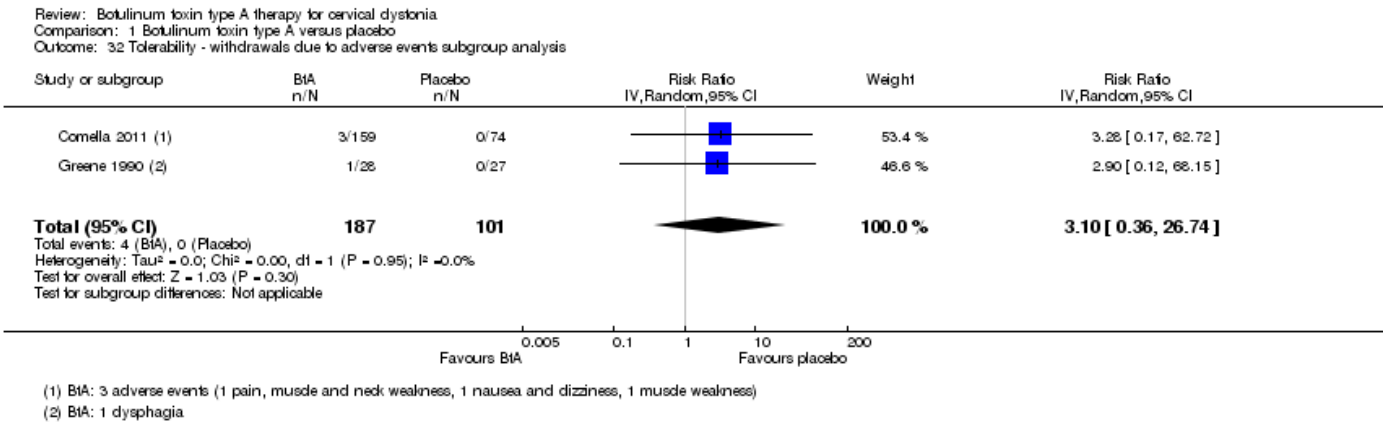


Figure 8 Open in figure viewer

Forest plot from Cochrane Review

Absolute effect

We could not calculate absolute results for this outcome because of low event rates.

Reference

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. Search date October 2016

Population, Intervention, Comparator

Population

Adults (mean age 52 years [age range 18 to 82 years]; 64% women) with moderate to severe impairment due to cervical dystonia (mean duration 4.8 to 12.1 years). Score on Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS); range from 0 (best) to 85 (worst), at baseline ranged from 42 to 46. Prior exposure to BtA was zero in two trials and 61% to 100% in the other six trials (time since last injection 10 to 16 weeks)

Intervention

BtA: most commonly 500 U Dysport as a fixed dose (5 trials); other formulations included 250 U or 1000 U Dysport, 95 U to 360 U Botox, and 120 U to 240 U Xeomin. Doses were classified by review authors as low (Botox/Xeomin < 100 U; Dysport = 250 U), medium (Botox/Xeomin 101 U to 200 U; Dysport = 500 U), or high (Botox/Xeomin > 201 U; Dysport = 1000 U)

Comparator

Placebo

Additional Information

DOI:

https://doi.org/10.1002/cca.2053 scolaris.information.information.copy.clipboard

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