

## Dystonia

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### ABSTRACT

**INTRODUCTION:** Dystonia is usually a lifelong condition with persistent pain and disability. Focal dystonia affects a single part of the body; generalised dystonia can affect most or all of the body. It is more common in women, and some types of dystonia are more common in people of Ashkenazi descent. **METHODS AND OUTCOMES:** We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of drug treatments, surgical treatments, and physical treatments for focal and generalised dystonia? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2013 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). **RESULTS:** We found 19 studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. **CONCLUSIONS:** In this systematic review, we present information relating to the effectiveness and safety of the following interventions: acupuncture, amantadine, baclofen, benztropine, biofeedback, botulinum toxins, bromocriptine, carbamazepine, carbidopa/levodopa, clonazepam, clozapine, deep brain stimulation of thalamus and globus pallidus, diazepam, gabapentin, haloperidol, lorazepam, myectomy (for focal dystonia), occupational therapy, ondansetron, physiotherapy, pregabalin, procyclidine, selective peripheral denervation (for focal dystonia), speech therapy, tizanidine, trazodone hydrochloride, and trihexyphenidyl.

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### Key points

- Dystonia is characterised by involuntary muscle contractions, resulting in abnormal postures and twisting of body parts.
  - It is often a lifelong condition, with persistent pain and disability.
  - Focal dystonia affects a single part of the body; generalised dystonia can affect most or all of the body.
  - It is more common in women, and some types of dystonia are more common in people of Ashkenazi descent.
- **Botulinum toxin** is effective at relieving cervical dystonia in adults.
  - Botulinum A toxin and botulinum B toxin are both effective treatments for focal dystonia.
  - We don't know whether botulinum toxins are effective for generalised dystonia.
- Although we assessed other treatments, we primarily found evidence for botulinum toxin, and it is currently the mainstay of treatment for focal dystonia.
- We don't know whether any other drug treatments (amantadine, baclofen, benztropine, bromocriptine, carbamazepine, carbidopa/levodopa, clonazepam, clozapine, diazepam, gabapentin, haloperidol, lorazepam, ondansetron, pregabalin, procyclidine, tizanidine, trazodone hydrochloride, and trihexyphenidyl) are effective for either focal or generalised dystonia.
- We don't know whether deep brain stimulation of thalamus and globus pallidus is effective for either focal or generalised dystonia. We don't know whether any other surgical interventions (selective peripheral denervation or myectomy) are effective for focal dystonia.
- Most people will see a physiotherapist after diagnosis, but there is no consistent approach to treatment. We don't know whether any other physical treatments (acupuncture, biofeedback, occupational therapy, or speech therapy) are effective for either focal or generalised dystonia.

**DEFINITION** Dystonia is a neurological disorder characterised by involuntary, abnormal muscle contractions that result in sustained abnormal postures, twisting, or both, and repetitive movements of body parts.<sup>[1]</sup> It arises from dysfunction of the motor control system within the central nervous system. Dystonia is most simply classified by location: **focal dystonia** involves a single body part; **multifocal dystonia** involves two or more unrelated body parts; **segmental dystonia** affects two or more adjacent parts of the body; **hemidystonia** involves the arm and leg on the same side of the body; and **generalised dystonia** affects most or all of the body. For the purpose of this review we have classified dystonia into focal dystonia and generalised/other dystonia. However, studies in which dystonia has been classified according to other classification systems are also covered. In addition to focal and generalised dystonia, classification may also be based on age at onset (**early onset** or **late onset**), or according to the cause of the dystonia: **primary dystonia** where dystonia is the only sign and no cause can be identified; **dystonia-plus syndrome** where dystonia is associated with other pathology (e.g., dopa-responsive dystonia and myoclonus dystonia); **heredodegenerative dystonia** where dystonia is a sign associated with neurological conditions, such as Parkinson's disease and Huntington's disease; and **secondary dystonia** where a cause (usually environmental) can be identified, such as head injury and use of drugs (e.g., neuroleptic drugs and metoclopramide).<sup>[2]</sup> Certain dystonias may also be classified as task specific; examples of task-specific focal hand dystonia include writer's cramp, typist's cramp, and musician's cramp (affects, for example, pianists

and flautists).<sup>[3]</sup> **Diagnosis:** the clinical diagnosis of dystonia is based on the hallmark features of the abnormal, involuntary, and prolonged muscle contractions with consistent directionality that lead to an abnormal posture of the area affected. There is no definitive diagnostic test for dystonia. Investigation typically involves history and clinical examination, laboratory tests, and imaging, to establish severity and potential cause. Laboratory tests and neuro-imaging may help to rule out metabolic or structural causes. Genetic testing, electrophysiological tests, and tissue biopsy may also be considered. The goal of accurate diagnosis is to facilitate treatment choice.

<b>INCIDENCE/ PREVALENCE</b>	Dystonia occurs worldwide, with prevalence estimates varying widely depending on study methodology. In the US, the prevalence of focal dystonia has been reported as 30 per 100,000 people. <sup>[4]</sup> Cervical dystonia (torticollis or 'wry neck') is the most common adult form of focal dystonia, with a prevalence in Europe of 5.7 per 100,000. <sup>[5]</sup> Other frequently occurring focal dystonias are blepharospasm (forceful eyelid closures), which affects 3.6 per 100,000 people, and limb dystonias (e.g., writer's cramp), which affect 1.4 per 100,000. <sup>[5]</sup> In the US, the prevalence of generalised dystonia has been reported as 0.2–6.7 per 100,000 population; <sup>[4]</sup> generalised dystonia affects more people of Ashkenazi descent. <sup>[6]</sup> In Europe, the prevalence of primary dystonia has been estimated at 15.2 per 100,000. <sup>[7]</sup> Studies identified to have rigorous methodology estimated the prevalence of early-onset (at <20 years of age) dystonia to be 11.1 per 100,000 for dystonia in people of Ashkenazi descent from the New York area, 60 per 100,000 for late-onset (at >20 years of age) dystonia in the overall population of Northern England, and 300 per 100,000 for late-onset dystonia in the Italian population (aged 50 years or older). <sup>[2]</sup> Dystonia occurs more frequently in women.
<b>AETIOLOGY/ RISK FACTORS</b>	The pathophysiology of dystonia remains unclear. Dystonia may occur because of abnormal neurochemical transmission in the basal ganglia, brainstem, or both, resulting in abnormal execution of motor control. <sup>[8]</sup> Focal dystonias have been associated with loss of inhibition, <sup>[9]</sup> abnormal plasticity in the motor cortex, <sup>[10]</sup> and impairments in spatial and temporal discrimination. <sup>[11]</sup> There is debate on the extent to which psychological factors cause dystonia, although they can undoubtedly exacerbate it. Dystonia can be classified as primary (where underlying cause is unknown) or secondary (related to known disorders). The primary disorders may be further classified as hereditary or sporadic. <sup>[12]</sup> Currently, 19 types of dystonia can be distinguished on a genetic basis, six of which are primary dystonias ( <i>DYT1</i> , 2, 4, 6, 7, and 13). <sup>[13]</sup> The remainder are secondary dystonia, dystonia-plus syndromes, and paroxysmal dystonias.
<b>PROGNOSIS</b>	Dystonia is often a lifelong disorder, once it has started, although a small minority experience complete remission. Most people with dystonia have a normal life expectancy, but with continued symptoms. The presence and severity of symptoms are unpredictable, as symptoms may fluctuate over time (e.g., stressful situations may make symptoms worse) or may disappear or stabilise for a time. Regardless of the cause, dystonic contractions may have a chronic course and may lead to severe persistent pain and disability. Also, embarrassment caused by the symptoms may lead to social withdrawal. Prognosis seems to depend on a number of factors, including age at onset, distribution, and cause. Focal dystonia may become generalised over time. Dystonia with a later age of onset has a lower likelihood of spreading compared with dystonia beginning in childhood. Similarly, dystonia starting in the neck is less likely to spread than dystonia starting in the limbs.
<b>AIMS OF INTERVENTION</b>	To improve quality of life by minimising: immediate symptoms (movement, posture, pain); limitation of activities; pain; and social consequences, with minimal adverse effects of treatment.
<b>OUTCOMES</b>	<b>Neurological disability:</b> In dystonia clinical trials, outcome is usually measured using disease-specific rating scales: Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), <sup>[14]</sup> Tsui Scale, <sup>[15]</sup> Cervical Dystonia Severity Scale (CDSS), <sup>[16]</sup> Jankovic Rating Scale (JRS), <sup>[17]</sup> and Blepharospasm Disability Index (BSDI); <sup>[18]</sup> see table 1, p 45 ). <b>Quality of life; adverse effects of treatment.</b>
<b>METHODS</b>	<i>Clinical Evidence</i> search and appraisal September 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to September 2013, Embase 1980 to September 2013, and The Cochrane Database of Systematic Reviews 2013, issue 2 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) Database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: RCTs and published systematic reviews of RCTs in English, including open studies

and containing more than 20 individuals (with any split per arm), of whom at least 80% were followed up. There was no minimum length of follow-up. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 46 ). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website ([www.clinicalevidence.com](http://www.clinicalevidence.com)).

**QUESTION** What are the effects of drug treatments for focal dystonia?

**OPTION** BOTULINUM TOXINS FOR FOCAL DYSTONIA (E.G., BOTULINUM A TOXIN, BOTULINUM B TOXIN)

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- Botulinum toxin is effective at relieving cervical dystonia symptoms in adults.
- Botulinum A toxin and botulinum B toxin are both effective.
- We found most evidence for botulinum toxin, and it is the mainstay of modern treatment for focal dystonia.
- **Note:**  
We found no clinically important results from RCTs about botulinum A toxin in the treatment of people with focal dystonia of other body sites (eyelid, larynx, and hand). We found no clinically important results about other botulinum toxins, apart from botulinum A toxin and botulinum B toxin, in the treatment of focal dystonia.

**Benefits and harms**

**Botulinum A toxin versus placebo in cervical dystonia in adults:**

We found one systematic review (search date 2003) <sup>[19]</sup> and three subsequent RCTs. <sup>[20]</sup> <sup>[21]</sup> <sup>[22]</sup>

**Neurological disability**

*Botulinum A toxin compared with placebo* Botulinum A toxin is more effective at improving cervical dystonia at up to 20 weeks, as assessed by an improvement in Tsui Scale, Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), Cervical Dystonia Severity Scale (CDSS), physician- and patient-rated scores, and the proportion of people reporting pain relief (*moderate-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Neurological disability</b>					
<sup>[19]</sup> Systematic review	113 adults with cervical dystonia 3 RCTs in this analysis	<b>Improvement of at least 3 points on Tsui Scale , 3–6 weeks</b> 32/56 (57%) with botulinum A toxin 13/57 (23%) with placebo	OR 4.25 95% CI 2.00 to 9.05 P = 0.002 NNT 4 95% CI 3 to 6		botulinum A toxin
<sup>[19]</sup> Systematic review	353 adults with cervical dystonia 6 RCTs in this analysis	<b>Any improvement in Tsui Scale or Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) , 0–12 weeks</b> 97/174 (56%) with botulinum A toxin 31/179 (17%) with placebo	OR 5.47 95% CI 3.52 to 8.48 P = 0.002		botulinum A toxin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	510 adults with cervical dystonia 11 RCTs in this analysis	<b>Any improvement in subjective patient-related scales , 0–16 weeks</b> 161/273 (59%) with botulinum A toxin 46/237 (19%) with placebo	OR 6.58 95% CI 4.55 to 9.54 P = 0.00001 NNT 3 95% CI 3 to 3		botulinum A toxin
[19] Systematic review	350 adults with cervical dystonia 4 RCTs in this analysis	<b>Physicians reporting improvement , 0–16 weeks</b> 123/197 (62%) with botulinum A toxin 46/153 (30%) with placebo	OR 4.17 95% CI 2.70 to 6.44 P <0.00001 NNT 3 95% CI 3 to 5		botulinum A toxin
[19] Systematic review	162 adults with cervical dystonia 5 RCTs in this analysis	<b>Proportion of people reporting pain relief , time frame not reported</b> 60/84 (71%) with botulinum A toxin 9/78 (12%) with placebo	OR 11.92 95% CI 6.32 to 22.5 P <0.00001 NNT 2 95% CI 2 to 3		botulinum A toxin
[20] RCT	116 adults with cervical dystonia	<b>Mean change in TWSTRS-Total score from baseline , at week 4</b> –15.6 with botulinum A toxin –6.7 with placebo	P <0.001 Intention-to-treat analysis		botulinum A toxin
[21] RCT <b>3-armed trial</b>	233 adults with cervical dystonia The remaining arm assessed incobotulinumtoxinA (240 U)	<b>Mean change in TWSTRS-Total score from baseline , at week 4</b> –9.9 with incobotulinumtoxinA (120 U) –2.2 with placebo	Adjusted mean difference –7.5 95% CI –10.4 to –4.6 P <0.001 Intention-to-treat analysis		botulinum A toxin
[21] RCT <b>3-armed trial</b>	233 adults with cervical dystonia The remaining arm assessed incobotulinumtoxinA (120 U)	<b>Mean change in TWSTRS-Total score from baseline , at week 4</b> –10.9 with incobotulinumtoxinA (240 U) –2.2 with placebo	Adjusted mean difference –9.0 95% CI –12.0 to –5.9 P <0.001 Intention-to-treat analysis		botulinum A toxin
[21] RCT <b>3-armed trial</b>	233 adults with cervical dystonia The remaining arm assessed incobotulinumtoxinA (240 U)	<b>Mean change in TWSTRS-Total score from baseline , at week 8</b> –6.9 with incobotulinumtoxinA (120 U) +0.4 with placebo	Adjusted mean difference –7.1 95% CI –10.1 to –4.2 P <0.001 Intention-to-treat analysis		botulinum A toxin
[21] RCT <b>3-armed trial</b>	233 adults with cervical dystonia The remaining arm assessed incobotulinumtoxinA (120 U)	<b>Mean change in TWSTRS-Total score from baseline , at week 8</b> –8.2 with incobotulinumtoxinA (240 U) +0.4 with placebo	Adjusted mean difference –8.6 95% CI –11.5 to –5.8 P <0.001 Intention-to-treat analysis		botulinum A toxin
[21] RCT <b>3-armed trial</b>	233 adults with cervical dystonia The remaining arm assessed incobotulinumtoxinA (240 U)	<b>Mean change in TWSTRS-Total score from baseline , up to 20 weeks</b> –3.6 with incobotulinumtoxinA (120 U) +1.7 with placebo	Adjusted mean difference –5.2 95% CI –7.4 to –3.0 P <0.001 Intention-to-treat analysis		botulinum A toxin




Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] RCT 3-armed trial	233 adults with cervical dystonia  The remaining arm assessed inco-botulinumtoxinA (120 U)	<b>Mean change in TWSTRS-Total score from baseline , up to 20 weeks</b> -4.6 with incobotulinumtoxinA (240 U) +1.7 with placebo	Adjusted mean difference -6.4 95% CI -8.6 to -4.2 P <0.001 Intention-to-treat analysis		botulinum A toxin
[22] RCT	170 adults with cervical dystonia and who previously responded to onabotulinumtoxinA injections; see further information on studies	<b>Cervical Dystonia Severity Scale (CDSS) , at week 6</b> Mean -1.81 points with known responders to onabotulinumtoxinA Mean -0.31 points with placebo	P = 0.012 Intention-to-treat analysis		botulinum A toxin
[22] RCT	170 adults with cervical dystonia and who previously responded to onabotulinumtoxinA injections; see further information on studies	<b>Improved Physician Global Assessment Scale scores , at week 6</b> 62% with known responders to onabotulinumtoxinA 42% with placebo	P = 0.022		botulinum A toxin

### Quality of life

No data from the following reference on this outcome. [\[19\]](#) [\[20\]](#) [\[21\]](#) [\[22\]](#)

### Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[19] Systematic review	421 adults with cervical dystonia 6 RCTs in this analysis	<b>Proportion of people with any adverse effect (neck weakness, dysphagia, voice changes/hoarseness, dry mouth/sore throat)</b> 131/226 (58%) with botulinum A toxin 89/195 (46%) with placebo	OR 2.10 95% CI 1.32 to 3.25 P = 0.002 NNH 6 95% CI 4 to 15		placebo
[19] Systematic review	605 adults with cervical dystonia 10 RCTs in this analysis	<b>Proportion of people with neck weakness</b> 62/339 (18%) with botulinum A toxin 9/266 (3%) with placebo	OR 4.86 95% CI 2.55 to 9.25 P <0.00001 NNH 8 95% CI 7 to 10		placebo
[19] Systematic review	210 adults with cervical dystonia 2 RCTs in this analysis	<b>Proportion of people with voice changes/hoarseness</b> 15/120 (13%) with botulinum A toxin 4/90 (4%) with placebo	OR 2.62 95% CI 0.98 to 7.01 P = 0.05		Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	401 adults with cervical dystonia 6 RCTs in this analysis	<b>Proportion of people with dry mouth/sore throat</b> 42/216 (19%) with botulinum A toxin 15/185 (8%) with placebo	OR 2.54 95% CI 1.42 to 4.55 P = 0.002 NNH 10 95% CI 7 to 21		placebo
[21] RCT 3-armed trial	233 adults with cervical dystonia	<b>Proportion of people with dysphagia</b> 8/78 (10%) with incobotulinumtoxinA (120 U) 13/81 (16%) with incobotulinumtoxinA (240 U) 2/74 (3%) with placebo	Significance not assessed		
[21] RCT 3-armed trial	233 adults with cervical dystonia	<b>Proportion of people with neck pain</b> 4/78 (5%) with incobotulinumtoxinA (120 U) 10/81 (12%) with incobotulinumtoxinA (240 U) 1/74 (1%) with placebo	Significance not assessed		
[21] RCT 3-armed trial	233 adults with cervical dystonia	<b>Proportion of people with muscle weakness</b> 5/78 (6%) with incobotulinumtoxinA (120 U) 8/81 (10%) with incobotulinumtoxinA (240 U) 1/74 (1%) with placebo	Significance not assessed		
[22] RCT	170 adults with cervical dystonia and who previously responded to onabotulinumtoxinA injections; see Further information on studies	<b>Proportion of people with treatment-related dysphagia</b> 7% with known responders to onabotulinumtoxinA 0% with placebo Absolute numbers not reported	P = 0.03		placebo
[22] RCT	170 adults with cervical dystonia and who previously responded to onabotulinumtoxinA injections; see Further information on studies	<b>Proportion of people with treatment-related neck pain</b> 1% with known responders to onabotulinumtoxinA 4% with placebo Absolute numbers not reported	Reported as not significant		Not significant

No data from the following reference on this outcome. [20]

### Botulinum B toxin versus placebo in cervical dystonia in adults:

We found one systematic review (search date 2003). [23]

#### Neurological disability

*Botulinum B toxin compared with placebo* Botulinum B toxin is more effective at 4 to 8 weeks at improving Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-total score and patient and physician assessments of global improvement in symptoms ([high-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Neurological disability</b>					
[23] Systematic review	122 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-total score >20 and TWSTRS-severity >10 Data from 1 RCT	<b>Improvement of at least 20% of TWSTRS-total score , 4 weeks</b> 60/92 (65%) with botulinum B toxin 8/30 (27%) with placebo	OR 4.69 95% CI 2.06 to 10.69 P = 0.0002 NNT 3 95% CI 2 to 6		botulinum B toxin
[23] Systematic review	122 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score >20 and TWSTRS-severity >10 Data from 1 RCT	<b>Improvement of at least 20% of TWSTRS-total score , 8 weeks</b> 40/92 (43%) with botulinum B toxin 5/30 (17%) with placebo	OR 3.13 95% CI 1.34 to 7.34 P = 0.0008		botulinum B toxin
[23] Systematic review	122 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score <20 and TWSTRS-severity <10 Data from 1 RCT	<b>Improvement of at least 20% of TWSTRS-total score , 12 weeks</b> 23/92 (25%) with botulinum B toxin 3/30 (10%) with placebo	OR 2.43 95% CI 0.89 to 6.61 P = 0.08		Not significant
[23] Systematic review	122 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score >20 and TWSTRS-severity >10 Data from 1 RCT	<b>Improvement of at least 20% of TWSTRS-total score , 16 weeks</b> 12/92 (13%) with botulinum B toxin 2/30 (7%) with placebo	OR 1.86 95% CI 0.51 to 6.75 P = 0.3		Not significant
[23] Systematic review	150 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score >20 and TWSTRS-severity >10 2 RCTs in this analysis	<b>Patient global assessment of change in symptoms , 0–4 weeks</b> with botulinum B toxin (10,000 U) with placebo Absolute results not reported	WMD 20.04 95% CI 14.22 to 27.45 P <0.00001		botulinum B toxin
[23] Systematic review	72 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score >20 and TWSTRS-severity >10	<b>Patient global assessment of change in symptoms , 0–4 weeks</b> with botulinum B toxin (5000 U) with placebo Absolute results not reported	WMD 17.00 95% CI 6.93 to 27.07 P <0.0009		botulinum B toxin




Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Data from 1 RCT				
[23] Systematic review	150 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score >20 and TWSTRS-severity >10 2 RCTs in this analysis	<b>Principal investigator global assessment of change in symptoms , 0–4 weeks</b> with botulinum B toxin (10,000 U) with placebo Absolute results not reported	WMD 12.52 95% CI 7.97 to 17.08 P <0.00001		botulinum B toxin
[23] Systematic review	72 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score >20 and TWSTRS-severity >10 Data from 1 RCT	<b>Principal investigator global assessment of change in symptoms , 0–4 weeks</b> with botulinum B toxin (5000 U) with placebo Absolute results not reported	WMD 13.30 95% CI 5.50 to 21.50 P = 0.001		botulinum B toxin
[23] Systematic review	150 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score >20 and TWSTRS-severity >10 2 RCTs in this analysis	<b>Patient analogue pain assessment , 0–4 weeks</b> with botulinum B toxin (10,000 U) with placebo Absolute results not reported	WMD 19.63 95% CI 11.69 to 27.56 P = 0.001		botulinum B toxin
[23] Systematic review	72 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score >20 and TWSTRS-severity >10 Data from 1 RCT	<b>Patient analogue pain assessment , 0–4 weeks</b> with botulinum B toxin (5000 U) with placebo Absolute results not reported	WMD 18.00 95% CI 5.69 to 30.31 P = 0.004		botulinum B toxin

### Quality of life

No data from the following reference on this outcome. [23]

### Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[23] Systematic review	307 adults with cervical dystonia 3 RCTs in this analysis	<b>Dry mouth</b> 45/203 (22%) with botulinum B toxin	OR 5.19 95% CI 2.69 to 10.03 P <0.00001		placebo







Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		3/104 (3%) with placebo	NNH 6 95% CI 6 to 8		
[23] Systematic review	307 adults with cervical dystonia 3 RCTs in this analysis	<b>Dysphagia</b> 39/204 (19%) with botulinum B toxin (10,000 U) 3/104 (3%) with placebo	OR 4.97 P <0.00003 NNH 8 95% CI 7 to 11		placebo

### Botulinum A toxin versus botulinum B toxin in cervical dystonia in adults:

We found one systematic review (search date 2003), which identified no RCTs. [24] We found three subsequent RCTs. [25] [26] [27]

### Neurological disability

*Botulinum A toxin compared with botulinum B toxin* We don't know how effective botulinum A toxin and botulinum B toxins are, compared with each other, at up to 4 weeks at improving Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) disease-activity rating scores (*low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Neurological disability</b>					
[25] RCT	139 adults who previously responded to botulinum A toxin	<b>Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-total score , 0–4 weeks</b> 10.2 with botulinum A toxin 9.3 with botulinum B toxin	P = 0.75		Not significant
[25] RCT	139 adults who previously responded to botulinum A toxin	<b>TWSTRS-severity score , 4 weeks</b> 3.7 with botulinum A toxin 3.7 with botulinum B toxin	Reported as not significant RR not reported P = 0.90		Not significant
[25] RCT	139 adults who previously responded to botulinum A toxin	<b>TWSTRS-disability score , 0–4 weeks</b> 2.4 with botulinum A toxin 2.5 with botulinum B toxin	Reported as not significant RR not reported P = 0.71		Not significant
[25] RCT	139 adults who previously responded to botulinum A toxin	<b>TWSTRS-pain score , 0–4 weeks</b> 3.2 with botulinum A toxin 4.0 with botulinum B toxin	Reported as not significant RR not reported P = 0.24		Not significant
[25] RCT	139 adults who previously responded to botulinum A toxin	<b>Median duration of effect of treatment</b> 13 weeks with botulinum A toxin 11.7 weeks with botulinum B toxin	Reported as not significant RR not reported P = 0.095		Not significant
[26] RCT	20 adults who responded to botulinum A toxin within the previous year	<b>TWSTRS-severity score , 2 weeks</b> 14 with botulinum A toxin 15 with botulinum B toxin	Reported as not significant RR not reported		Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[26] RCT	20 adults who responded to botulinum A toxin within the previous year	<b>TWSTRS-pain score , 2 weeks</b> 6 with botulinum A toxin 4 with botulinum B toxin	Reported as not significant RR not reported	↔	Not significant
[26] RCT	20 adults who responded to botulinum A toxin within the previous year	<b>TWSTRS-disability score , 2 weeks</b> 10 with botulinum A toxin 12 with botulinum B toxin	Reported as not significant RR not reported	↔	Not significant
[27] RCT	111 adults with cervical dystonia, not previously treated with botulinum toxin (toxin naive), 93/111 (84%) included in analysis	<b>Improvement in TWSTRS-total score , 4 weeks</b> 8.8 with botulinum A toxin 11.0 with botulinum B toxin	Difference -2.2 95% CI -5.4 to +1.1 Not intention-to-treat analysis	↔	Not significant
[27] RCT	111 adults with cervical dystonia, not previously treated with botulinum toxin (toxin naive), 93/111 (84%) included in analysis	<b>Improvement in TWSTRS-severity score , 4 weeks</b> 4.7 with botulinum A toxin 5.4 with botulinum B toxin	Difference -0.7 95% CI -2.2 to +0.8 Not intention-to-treat analysis	↔	Not significant
[27] RCT	111 adults with cervical dystonia, not previously treated with botulinum toxin (toxin naive), 93/111 (84%) included in analysis	<b>Improvement in TWSTRS-disability score , 4 weeks</b> 2.5 with botulinum A toxin 2.9 with botulinum B toxin	Difference -0.5 95% CI -2.0 to +1.0 Not intention-to-treat analysis	↔	Not significant
[27] RCT	111 adults with cervical dystonia, not previously treated with botulinum toxin (toxin naive), 93/111 (84%) included in analysis	<b>Improvement in TWSTRS-pain score , 4 weeks</b> 1.7 with botulinum A toxin 2.7 with botulinum B toxin	Difference -1.0 95% CI -2.2 to +0.2 Not intention-to-treat analysis	↔	Not significant

### Quality of life

No data from the following reference on this outcome. [\[25\]](#) [\[26\]](#) [\[27\]](#)

### Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[25] RCT	139 adults who previously responded to botulinum A toxin	<b>Dysphagia , 4 weeks</b> 19% with botulinum A toxin 48% with botulinum B toxin Absolute numbers not reported	P = 0.0005	○○○	botulinum A toxin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[25] RCT	139 adults who previously responded to botulinum A toxin	<b>Dry mouth , 4 weeks</b> 41% with botulinum A toxin 80% with botulinum B toxin Absolute numbers not reported	P <0.0001	○○○	botulinum A toxin
[26] RCT	20 adults who responded to botulinum A toxin within the previous year	<b>Dysphagia</b> 18% with botulinum A toxin 55% with botulinum B toxin Absolute numbers not reported	P = 0.081	↔	Not significant
[26] RCT	20 adults who responded to botulinum A toxin within the previous year	<b>Constipation</b> 0/11 (0%) with botulinum A toxin 3/9 (33%) with botulinum B toxin	P = 0.037	○○○	placebo
[27] RCT	111 adults, not previously treated with botulinum toxin (toxin naive)	<b>Dysphagia</b> 8/55 (15%) with botulinum A toxin 9/56 (16%) with botulinum B toxin	P = 1	↔	Not significant
[27] RCT	111 adults with cervical dystonia, not previously treated with botulinum toxin (toxin naive)	<b>Dry mouth</b> 4/55 (7%) with botulinum A toxin 22/56 (39%) with botulinum B toxin	P = 0.0001	○○○	botulinum A toxin
[27] RCT	111 adults with cervical dystonia, not previously treated with botulinum toxin (toxin naive)	<b>Injection site pain</b> 3/55 (5%) with botulinum A toxin 0/56 (0%) with botulinum B toxin	P = 0.12	↔	Not significant

#### Low-dose (100 U Botox/250 U Dysport) versus high-dose (>200 U Botox/960 U Dysport) botulinum A toxin in cervical dystonia in adults:

We found one systematic review (search date 2003). It found no RCTs directly comparing high- and low-dose botulinum A toxin. [28] We found one additional RCT. [29]

#### Neurological disability

*Low-dose compared with high-dose botulinum A toxin* We don't know whether high-dose botulinum A toxin is more effective than low-dose botulinum A toxin at improving Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) disease-activity rating score and increasing patient- and physician-rated improvements in symptoms ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Neurological disability</b>					
[29] RCT	31 adults	<b>Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-severity score , 4 weeks</b> 0.27 with botulinum A toxin (125 U/mL) 1.07 with botulinum A toxin (500 U/mL)	P = 0.19	↔	Not significant
[29] RCT	31 adults	<b>TWSTRS-disability score , 4 weeks</b>	P = 0.26	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		2.6 with botulinum A toxin (125 U/mL) 1.2 with botulinum A toxin (500 U/mL)			
[29] RCT	31 adults	<b>TWSTRS-total score , 4 weeks</b> 5.6 with botulinum A toxin (125 U/mL) 4.4 with botulinum A toxin (500 U/mL)	P = 0.63	↔	Not significant

### Quality of life

No data from the following reference on this outcome. [29]

### Adverse effects

No data from the following reference on this outcome. [29]

### Low-dose (2500–5000 U) versus high-dose (10,000 U) botulinum B toxin in cervical dystonia in adults:

We found one systematic review (search date 2003). [23]

### Neurological disability

*Low-dose compared with high-dose botulinum B toxin* Low-dose botulinum B toxin may be less effective than high-dose botulinum B toxin at improving pain, as assessed by Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-pain subscale, at 4 weeks; however, we don't know how effective low-dose or high-dose botulinum B toxin are, compared with each other, at improving TWSTRS-total scores at 4 to 16 weeks (*low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Neurological disability</b>					
[23] Systematic review	92 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-total score >20 and TWSTRS-severity >10 Data from 1 RCT	<b>Improvement in TWSTRS-pain subscale , 4 weeks</b> 39/62 (63%) with botulinum B toxin (2500–5000 U) 25/30 (83%) with botulinum B toxin (10,000 U)	OR 0.39 95% CI 0.15 to 0.99 P = 0.05	○○○	high-dose botulinum B toxin
[23] Systematic review	92 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score >20 and	<b>Improvement of at least 20% in TWSTRS-total score , 4 weeks</b> 37/62 (60%) with botulinum B toxin (2500–5000 U) 23/30 (77%) with botulinum B toxin (10,000 U)	OR 0.50 95% CI 0.20 to 1.25	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	TWSTRS-severity >10 Data from 1 RCT				
[23] Systematic review	92 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score >20 and TWSTRS-severity >10 Data from 1 RCT	<b>Improvement of at least 20% in TWSTRS-total score , 8 weeks</b> 24/62 (39%) with botulinum B toxin (2500–5000 U) 16/30 (53%) with botulinum B toxin (10,000 U)	OR 0.56 95% CI 0.23 to 1.33	↔	Not significant
[23] Systematic review	92 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score >20 and TWSTRS-severity >10 Data from 1 RCT	<b>Improvement of at least 20% in TWSTRS-total score , 12 weeks</b> 14/62 (23%) with botulinum B toxin (2500–5000 U) 9/30 (30%) with botulinum B toxin (10,000 U)	OR 0.68 95% CI 0.25 to 1.84	↔	Not significant
[23] Systematic review	92 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, TWSTRS-total score >20 and TWSTRS-severity >10 Data from 1 RCT	<b>Improvement of at least 20% in TWSTRS-total score , 16 weeks</b> 7/62 (11%) with botulinum B toxin (2500–5000 U) 5/30 (17%) with botulinum B toxin (10,000 U)	OR 0.63 95% CI 0.17 to 2.27	↔	Not significant

### Quality of life

No data from the following reference on this outcome. [23]

### Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[23] Systematic review	308 adults with cervical dystonia for at least 1 year and previously treated with botulinum A toxin, Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-total score >20 and TWSTRS-severity >10 2 RCTs in this analysis	<b>Dry mouth</b> 9/98 (9%) with botulinum B toxin (2500–5000 U) 27/69 (39%) with botulinum B toxin (10,000 U)	OR 0.19 95% CI 0.09 to 0.40 P = 0.00002	● ○ ○	low-dose botulinum B toxin

**Botulinum A toxin versus trihexyphenidyl in cervical dystonia in adults:**

We found one systematic review (search date 2003). <sup>[28]</sup>

**Neurological disability**

*Botulinum A toxin compared with trihexyphenidyl* Botulinum A toxin may be more effective at 12 weeks than trihexyphenidyl at improving Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-disability scores, Tsui Scale, and General Health Perception subscale ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Neurological disability</b>					
[28] Systematic review	66 adults with cervical dystonia; see further information on studies  Data from 1 RCT	<b>Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-disability score , 12 weeks</b>  with botulinum A toxin plus placebo tablets  with trihexyphenidyl plus placebo injection  Absolute results not reported	WMD 2.50 95% CI 0.68 to 4.32 P = 0.0097		botulinum A toxin
[28] Systematic review	66 adults with cervical dystonia; see further information on studies  Data from 1 RCT	<b>Tsui Scale score , 12 weeks</b>  with botulinum A toxin plus placebo tablets  with trihexyphenidyl plus placebo injection  Absolute results not reported	WMD 4.60 95% CI 2.14 to 7.06 P = 0.0009		botulinum A toxin
[28] Systematic review	66 adults with cervical dystonia; see further information on studies  Data from 1 RCT	<b>Mean difference in General Health Perception subscale score</b>  with botulinum A toxin plus placebo tablets  with trihexyphenidyl plus placebo injection  Absolute results not reported	Mean score difference 6 95% CI 4 to 12 P = 0.0023		botulinum A toxin
[28] Systematic review	66 adults with cervical dystonia; see further information on studies  Data from 1 RCT	<b>Proportion of people with at least 3-point improvement on Tsui Scale</b>  with botulinum A toxin plus placebo tablets  with trihexyphenidyl plus placebo injection  Absolute results not reported	OR 3.92 95% CI 1.48 to 10.40		botulinum A toxin
[28] Systematic review	66 adults with cervical dystonia; see further information on studies  Data from 1 RCT	<b>Proportion of people with at least 3-point improvement on TWSTRS scale</b>  with botulinum A toxin plus placebo tablets  with trihexyphenidyl plus placebo injection  Absolute results not reported	OR 3.14 95% CI 1.10 to 8.97 P = 0.059		botulinum A toxin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[28] Systematic review	66 adults with cervical dystonia; see further information on studies Data from 1 RCT	<b>Median improvement in TWSTRS-pain score</b> 3 with botulinum A toxin plus placebo tablets 1 with trihexyphenidyl plus placebo injection	Reported this difference did not reach statistical significance, no further details reported	↔	Not significant

### Quality of life

No data from the following reference on this outcome. [28]

### Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[28] Systematic review	66 adults Data from 1 RCT	<b>Number of adverse effects in each group</b> 31 in 32 people with botulinum A toxin plus placebo tablets 76 in 32 people with trihexyphenidyl plus placebo	P = 0.0001	○○○	botulinum A toxin
[28] Systematic review	66 adults Data from 1 RCT	<b>Dry mouth</b> with botulinum A toxin plus placebo with trihexyphenidyl plus placebo Absolute results not reported	OR 7.22 95% CI 2.72 to 19.12	●●●	botulinum A toxin
[28] Systematic review	66 adults Data from 1 RCT	<b>Forgetfulness</b> with botulinum A toxin plus placebo with trihexyphenidyl plus placebo Absolute results not reported	OR 3.51 95% CI 1.25 to 9.89	●●○	botulinum A toxin
[28] Systematic review	66 adults Data from 1 RCT	<b>Fatigue</b> with botulinum A toxin plus placebo with trihexyphenidyl plus placebo Absolute results not reported	OR 9.12 95% CI 1.92 to 43.40 The extremely wide confidence intervals make the clinical relevance of this result questionable	●●○	botulinum A toxin

### Botulinum B toxin in botulinum A toxin-resistant adults versus respondent adults:

We found one systematic review (search date 2003). [23]

### Neurological disability

*Botulinum B toxin in botulinum A-resistant adults compared with botulinum B toxin in botulinum A responders* We don't know whether botulinum B toxin in botulinum A-resistant adults is more effective at 4 weeks at improving Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-total scores (*low-quality evidence*).



Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Neurological disability</b>					
[23] Systematic review	92 adults Data from 1 RCT	<b>Improvement of at least 20% in Toronto Western Spasmodic Torticollis Rating Scale (TW-STRS)-total score , 4 weeks</b>  with botulinum B toxin in people resistant to botulinum A toxin  with botulinum B toxin in people responsive to botulinum A toxin  Absolute results not reported	P value not reported Reported as not significant	↔	Not significant

### Quality of life

No data from the following reference on this outcome. [23]

### Adverse effects

No data from the following reference on this outcome. [23]

### Botulinum A toxin versus placebo in people with blepharospasm (eyelid closure):

We found one systematic review (search date 2003), which found no RCTs. [30] We found no additional or subsequent RCTs satisfying *Clinical Evidence* inclusion criteria.

### Botulinum A toxin versus placebo in people with spasmodic dysphonia (laryngeal dystonia):

We found one systematic review (search date 2005). [31] The review identified one RCT that did not meet *Clinical Evidence* inclusion criteria (RCT included only 13 people), and so the results are not discussed further. [31]

### Botulinum A toxin versus placebo in people with writer's cramp:

We found one RCT, which compared botulinum A versus placebo. [32]

### Neurological disability

*Botulinum A toxin compared with placebo in people with writer's cramp* Botulinum A toxin may be more effective at 8 weeks at improving symptom severity scores, writer's cramp rating scales, handwriting, and writing speed; however, we don't know whether it improves overall functional status (*low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Neurological disability</b>					
[32] RCT	40 treatment-naive people with symptoms of idiopathic writer's cramp for at least 1 year	<b>Mean improvement in symptom severity scale</b> -3.60 with botulinum A -1.16 with placebo	P = 0.02	○○○	botulinum A toxin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Assessed using symptom severity scale, reduction in score indicates improvement			
[32] RCT	40 treatment-naive people with symptoms of idiopathic writer's cramp for at least 1 year	<b>Mean improvement in writer's cramp scale</b> -2.30 with botulinum A -0.79 with placebo	P < 0.01	○○○	botulinum A toxin
[32] RCT	40 treatment-naive people with symptoms of idiopathic writer's cramp for at least 1 year	<b>Mean improvement in handwriting</b> 1.85 with botulinum A 0.53 with placebo Assessed using a visual analogue scale from 0 cm to 10 cm	P = 0.01	○○○	botulinum A toxin
[32] RCT	40 treatment-naive people with symptoms of idiopathic writer's cramp for at least 1 year	<b>Mean change in writing speed</b> 1.41 with botulinum A 0.27 with placebo Mean change in writing speed = number of lines written in 2 minutes	P = 0.04	○○○	botulinum A toxin
[32] RCT	40 treatment-naive people with symptoms of idiopathic writer's cramp for at least 1 year	<b>Mean improvement in functional status</b> +0.65 with botulinum A -1.42 with placebo Assessed using a 12-item disability scale	P = 0.10	↔	Not significant

### Quality of life

No data from the following reference on this outcome. [32]

### Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[32] RCT	40 treatment-naive people with symptoms of idiopathic writer's cramp for at least 1 year	<b>Weakness in the hand</b> 18/20 (90%) with botulinum A 2/19 (11%) with placebo	P value not reported		
[32] RCT	40 treatment-naive people with symptoms of idiopathic writer's cramp for at least 1 year	<b>Pain at injection site</b> 1/20 (5%) with botulinum A 3/19 (16%) with placebo	P value not reported		

**Further information on studies**

- [19] The quality of the 13 trials was assessed by Jadad's Scale as good. However, all trials were of short duration, and examined the effects of only one injection cycle.
- [22] This was a two-phase trial. In phase 1, all participants were given onabotulinumtoxinA treatment and in the second phase, only those participants that 'responded' to this initial treatment were eligible for randomisation, to either onabotulinumtoxinA or placebo. 'Response' was considered adequate for inclusion in phase 2 if the Cervical Dystonia Severity Scale (CDSS) had improved so that it reached a score of 4 or higher. The results from phase 2 are reported because they meet the inclusion criteria for this *Clinical Evidence* review.
- [23] Of the three RCTs included in the systematic review, one RCT included both people responsive and resistant to botulinum A toxin, one RCT included only people resistant to botulinum A toxin, and one RCT included only people responsive to botulinum A toxin. The quality of the three RCTs was assessed as good by Jadad's Scale.
- [28] The systematic review commented on some limitations of the RCT. [33] It found there were significantly fewer people with history of progressive disease in the botulinum A toxin group than in the trihexyphenidyl group (9/33 [27%] with botulinum A toxin v 21/33 [64%] with trihexyphenidyl;  $P = 0.003$ ); the short duration of the RCT may not favour trihexyphenidyl; and people were injected with botulinum A toxin at baseline and 8 weeks later, which is a shorter interval than the 12- to 16-week interval between injections that would generally be used in clinical practice.
- [32] To optimise treatment effect, people were treated in two sessions: initially after baseline assessment and then 1 month later. People expressing satisfaction with their improvement after one treatment did not receive a second injection. However, if people showed no response to treatment after one session, the dose was doubled for the second session. The primary outcome assessed was the person's response to a question on whether they wished to continue with treatment (assessed at 12 weeks). This is not one of our outcomes of interest, and so the results are not discussed further. Clinical rating scales were measured as secondary outcomes.

**Comment:****Clinical guide:**

Botulinum toxin injections are the mainstay of management of cervical dystonia, and have replaced most treatments used in previous decades. They are sometimes used for other focal dystonias, but with caution, because some focal dystonias (e.g., 'functional dystonias') may have a primarily psychological origin. The evidence supporting botulinum toxin in focal dystonias is strong, partly because there is a strong commercial imperative to show effectiveness, but also because treatment can be localised, and because botulinum toxin is effective at reducing neuromuscular transmission. Its main limitation is that the effect wears off after 12 to 16 weeks, but repeated injections are usually equally effective. Invasive local surgical procedures have largely been displaced by local botulinum toxin injections.

Clinical data from several studies indicate that up to 10% of people treated with botulinum toxin are at risk of developing neutralising antibodies. Presence of antibodies may lead to decreased/no response to further treatment and may necessitate stopping treatment. The risk of formation of antibodies seems to be higher when botulinum toxin is given at frequent intervals at high doses; it has been suggested that the potential for developing antibodies may be ameliorated by using the lowest effective dosing regimen and increasing the time interval between doses. [34] [35]

**Different formulations of botulinum A toxin versus each other in people with blepharospasm (eyelid closure):**

We found one RCT that compared two different formulations of botulinum A toxin with each other — one formulation (Xeomin), a freeze-dried botulinum A toxin, free from complexing proteins, versus another established commercially available formulation of botulinum A toxin (Botox). The RCT found no significant difference between formulations in improvement in blepharospasm symptoms. It found similar rates of adverse effects (ptosis, abnormal vision, back pain, or xerophthalmia) with both treatments. [36]

We found one subsequent RCT involving 65 patients, which compared two different formulations of botulinum A toxin versus each other — one formulation (Xeomin), a freeze-dried botulinum A toxin, free from complexing proteins, versus another established commercially available formulation of botulinum A toxin (Botox). The RCT found no significant difference between formulations in scores on the Blepharospasm Disability Index, Jankovic Rating Scale, or Patient Global Assessment Scale at 4 or 8 weeks. [37]

**Dosage:**

The three commercially available formulations of botulinum A toxin — Dysport, Botox, and Xeomin — differ in potency, and so are not interchangeable. [38] One crossover RCT suggested

a conversion of 3 U of Dysport to 1 U of Botox, although there were differences in both beneficial outcomes and in adverse effects.<sup>[39]</sup> The adverse effects unequivocally associated with botulinum toxin injection are those expected from its local action, and they are more common with higher doses — as would be expected from local spread from the injected muscle. The differences in beneficial and adverse effects reflect relative differences in dosage, not intrinsic differences between preparations.

#### OPTION AMANTADINE FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about amantadine in the treatment of people with focal dystonia.

#### Benefits and harms

##### Amantadine:

We found no systematic review or RCTs of amantadine in people with focal dystonia.

**Comment:** None.

#### OPTION BACLOFEN FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about baclofen in the treatment of people with focal dystonia.

#### Benefits and harms

##### Baclofen:

We found no systematic review or RCTs of baclofen in people with focal dystonia.

**Comment:** None.

#### OPTION BENZATROPINE FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We don't know whether benztropine is effective for focal dystonia.

#### Benefits and harms

##### Benzatropine:

We found no systematic review or RCTs of benztropine in people with focal dystonia.

**Comment:** None.

#### OPTION BROMOCRIPTINE FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .

- We found no direct information from RCTs about bromocriptine in the treatment of people with focal dystonia.

#### Benefits and harms

##### Bromocriptine:

We found no systematic review or RCTs of bromocriptine in people with focal dystonia.

**Comment:** None.

#### OPTION CARBAMAZEPINE FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about carbamazepine in the treatment of people with focal dystonia.

#### Benefits and harms

##### Carbamazepine:

We found no systematic review or RCTs of carbamazepine in people with focal dystonia.

**Comment:** None.

#### OPTION CARBIDOPA/LEVODOPA FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about carbidopa/levodopa in the treatment of people with focal dystonia.

#### Benefits and harms

##### Carbidopa/levodopa:

We found no systematic review or RCTs of carbidopa/levodopa in people with focal dystonia.

**Comment:** None.

#### OPTION CLONAZEPAM FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about clonazepam in the treatment of people with focal dystonia.

#### Benefits and harms

##### Clonazepam:

We found no systematic review or RCTs of clonazepam in people with focal dystonia.

**Comment:** None.

#### OPTION CLOZAPINE FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about clozapine in the treatment of people with focal dystonia.

#### Benefits and harms

##### Clozapine:

We found no systematic review or RCTs of clozapine in people with focal dystonia.

**Comment:** None.

#### OPTION DIAZEPAM FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about diazepam in the treatment of people with focal dystonia.

#### Benefits and harms

##### Diazepam:

We found no systematic review or RCTs of diazepam in people with focal dystonia.

**Comment:** None.

#### OPTION GABAPENTIN FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We don't know whether gabapentin is effective for focal dystonia.

#### Benefits and harms

##### Gabapentin:

We found no systematic review or RCTs of gabapentin in people with focal dystonia.

**Comment:** None.

#### OPTION HALOPERIDOL FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about haloperidol in the treatment of people with focal dystonia.

**Benefits and harms****Haloperidol:**

We found no systematic review or RCTs of haloperidol in people with focal dystonia.

**Comment:** None.

**OPTION LORAZEPAM FOR FOCAL DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about lorazepam in the treatment of people with focal dystonia.

**Benefits and harms****Lorazepam:**

We found no systematic review or RCTs of lorazepam in people with focal dystonia.

**Comment:** None.

**OPTION ONDANSETRON FOR FOCAL DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about ondansetron in the treatment of people with focal dystonia.

**Benefits and harms****Ondansetron:**

We found no systematic review or RCTs of ondansetron in people with focal dystonia.

**Comment:** None.

**OPTION PREGABALIN FOR FOCAL DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We don't know whether pregabalin is effective for focal dystonia.

**Benefits and harms****Pregabalin:**

We found no systematic review or RCTs of pregabalin in people with focal dystonia.

**Comment:** None.

#### OPTION PROCYCLIDINE FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We don't know whether procyclidine is effective for focal dystonia.

#### Benefits and harms

##### Procyclidine:

We found no systematic review or RCTs of procyclidine in people with focal dystonia.

**Comment:** None.

#### OPTION TIZANIDINE FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about tizanidine in the treatment of people with focal dystonia.

#### Benefits and harms

##### Tizanidine:

We found no systematic review or RCTs of tizanidine in people with focal dystonia.

**Comment:** None.

#### OPTION TRAZODONE HYDROCHLORIDE FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about trazodone hydrochloride in the treatment of people with focal dystonia.

#### Benefits and harms

##### Trazodone hydrochloride:

We found no systematic review or RCTs of trazodone hydrochloride in people with focal dystonia.

**Comment:** None.

#### OPTION TRIHEXYPHENIDYL FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We don't know whether trihexyphenidyl is effective for focal dystonia.



**Benefits and harms****Trihexyphenidyl versus botulinum A toxin in cervical dystonia:**

See botulinum A toxin versus trihexyphenidyl in cervical dystonia, p 4 .

**Comment:****Clinical guide:**

Trihexyphenidyl is rarely used in cervical dystonia, given the effectiveness of local botulinum toxin injection, and the perception and risk of more general adverse effects from using an oral drug. There are reports of trihexyphenidyl being administered off-licence for other focal dystonias at doses above the recommended maximum, but this is best considered within specialised services with suitable experience.

**QUESTION**

**What are the effects of surgical treatments for focal dystonia?**

**OPTION**

**DEEP BRAIN STIMULATION OF THALAMUS AND GLOBUS PALLIDUS FOR FOCAL DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about deep brain stimulation of the thalamus in people with only focal dystonia. Evidence in a mixed population of people with focal or generalised dystonia suggests that it may improve function at 3 months.

**Benefits and harms****Deep brain stimulation versus sham treatment:**

We found no systematic review or RCT of deep brain stimulation of the thalamus, solely or predominantly in people with focal dystonia. We found one RCT in a mixed population of people with local and generalised dystonia; however, most people (24/40 [60%]) had generalised dystonia.<sup>[40] [41]</sup> For details [see option on Deep brain stimulation in people with generalised dystonia, p 37](#) .

**Comment:****Clinical guide:**

RCTs with longer follow-ups are required ([see Comment in deep brain stimulation of thalamus and globus pallidus in people with generalised dystonia, p 37](#) ).

**OPTION**

**MYECTOMY FOR FOCAL DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about myectomy in the treatment of people with focal dystonia.

**Benefits and harms****Myectomy:**

We found no systematic review or RCTs of myectomy in people with focal dystonia.

**Comment:****Clinical guide:**

Destructive procedures that mechanically prevent the dystonic posture (e.g., myectomy, thalamotomy, pallidotomy, and selective peripheral denervation) were once used (without supporting evi-

dence), but their apparent ineffectiveness, coupled with the effectiveness of botulinum toxin, has led to their demise.

**OPTION SELECTIVE PERIPHERAL DENERVATION FOR FOCAL DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- We found no direct information from RCTs about selective peripheral denervation in the treatment of people with focal dystonia.

**Benefits and harms**

**Selective peripheral denervation:**

We found no systematic review or RCTs of selective peripheral denervation in people with focal dystonia.

**Comment:** See Comment on myectomy under surgical treatments for focal dystonia, p 25 .

**QUESTION What are the effects of physical treatments for focal dystonia?**

**OPTION PHYSIOTHERAPY FOR FOCAL DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- Most people will see a physiotherapist after diagnosis, but there is no consistent approach to treatment.

**Benefits and harms**

**Physiotherapy in children with developmental or early congenital cervical dystonia:**

We found no systematic review or RCTs (see Comment).

**Physiotherapy versus drug treatment:**

We found no systematic review or RCTs.

**Physiotherapy plus biofeedback plus drug treatment versus drug treatment alone:**

We found one crossover RCT, which examined the effect of physical therapy (physiotherapy plus biofeedback) plus botulinum A toxin compared with botulinum A toxin alone. <sup>[42]</sup>

**Neurological disability**

*Physiotherapy plus biofeedback plus drug treatment compared with drug treatment alone* Physical therapy plus botulinum A toxin may be more effective at improving pain and activities of daily living scores, but we don't know whether it is more effective at improving cervical dystonia, as assessed by an improvement in Tsui Scale and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) (*very low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Neurological disability</b>					
<sup>[42]</sup> RCT Crossover design	40 people with idiopathic cervical dystonia for at least 3 years, and who	<b>Improvement in Tsui Scale score, end of observation period</b> -8.1 with botulinum A toxin alone	Reported as no significant difference	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	previously responded to at least 2 botulinum A toxin injections	<p>-7.2 with botulinum A toxin plus physical therapy (physiotherapy plus biofeedback)</p> <p>People crossed over to the alternative treatment arm after 45–120 days, depending on duration of subjective clinical benefits, confirmed by EMG evaluation</p> <p>Physical therapy involved daily sessions lasting 60–90 minutes, for 2 weeks</p>			
[42] RCT Crossover design	40 people with idiopathic cervical dystonia for at least 3 years, and who previously responded to at least 2 botulinum A toxin injections	<p><b>Improvement in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) score , end of observation period</b></p> <p>-9.1 with botulinum A toxin alone</p> <p>-10.2 with botulinum A toxin plus physical therapy (physiotherapy plus biofeedback)</p> <p>People crossed over to the alternative treatment arm after 45–120 days, depending on duration of subjective clinical benefits, confirmed by EMG evaluation</p> <p>Physical therapy involved daily sessions lasting 60–90 minutes, for 2 weeks</p>	Reported as no significant difference	↔	Not significant
[42] RCT Crossover design	40 people with idiopathic cervical dystonia for at least 3 years, and who previously responded to at least 2 botulinum A toxin injections	<p><b>Improvement in activities of daily living , end of observation period</b></p> <p>-5.3 with botulinum A toxin alone</p> <p>-9.8 with botulinum A toxin plus physical therapy (physiotherapy plus biofeedback)</p> <p>People crossed over to the alternative treatment arm after 45–120 days, depending on duration of subjective clinical benefits, confirmed by EMG evaluation</p> <p>Physical therapy involved daily sessions lasting 60–90 minutes, for 2 weeks</p>	P <0.05	○○○	botulinum toxin A plus physical therapy
[42] RCT Crossover design	40 people with idiopathic cervical dystonia for at least 3 years, and who previously responded to at least 2 botulinum A toxin injections	<p><b>Total pain score , end of observation period</b></p> <p>-7.1 with botulinum A toxin alone</p> <p>-13.0 with botulinum A toxin plus physical therapy (physiotherapy plus biofeedback)</p> <p>People crossed over to the alternative treatment arm after 45–120 days, depending on duration of subjective clinical benefits, confirmed by EMG evaluation</p> <p>Physical therapy involved daily sessions lasting 60–90 minutes, for 2 weeks</p>	P <0.001	○○○	botulinum toxin A plus physical therapy

### Quality of life

No data from the following reference on this outcome. <sup>[42]</sup>

### Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
<sup>[42]</sup> RCT Crossover design	40 people with idiopathic cervical dystonia for at least 3 years, and who previously responded to at least 2 botulinum A toxin injections	<b>Adverse effects , end of observation period</b> with botulinum A toxin alone with botulinum A toxin plus physical therapy (physiotherapy plus biofeedback) Absolute results not reported Adverse effects were described as infrequent and mild (transient dry mouth and neck muscle weakness) in both groups			

### Physiotherapy versus surgery:

We found no systematic review or RCTs.

### Physiotherapy plus relaxation versus no physiotherapy plus relaxation:

We found one RCT, which compared an active exercise programme plus relaxation versus relaxation alone. <sup>[43]</sup> The active exercise programme comprised individually designed programmes that involved neck exercises to activate and strengthen the neck muscles and whole body relaxation. The RCT initially excluded people having botulinum toxin as part of their management. After nine people were enrolled, this criteria was removed, and further recruitment included participants having botulinum toxin. Hence, some participants also had botulinum toxin and some did not.

### Neurological disability

*Physiotherapy plus relaxation versus no physiotherapy plus relaxation* We don't know whether an active exercise programme (individually designed programmes that involved neck exercises to activate and strengthen the neck muscles and whole body relaxation) plus relaxation is more effective than relaxation alone at reducing neurological disability in adults with cervical dystonia ([low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Neurological disability</b>					
<sup>[43]</sup> RCT	20 adults with cervical dystonia	<b>Mean change from baseline in Toronto Western Spasmodic Torticollis Rating Scale (TW-STRS) , at week 12</b> -3.9 with exercise programme plus relaxation -1.5 with relaxation only	Mean difference -1.9 95% CI -9.0 to +5.2 Intention-to-treat analysis Difference between groups was adjusted for baseline (week 0) score based on ANCOVA	↔	Not significant
<sup>[43]</sup> RCT	20 adults with cervical dystonia	<b>Change from baseline in TW-STRS , at week 16</b> -3.0 with exercise programme plus relaxation -0.6 with relaxation only	Mean difference -2.5 95% CI -8.9 to +3.9 Intention-to-treat analysis Difference between groups was adjusted for baseline (week 0) score based on ANCOVA	↔	Not significant

**Quality of life**

*Physiotherapy plus relaxation versus no physiotherapy plus relaxation* We don't know whether an active exercise programme plus relaxation is more effective than relaxation alone in improving quality of life in adults with cervical dystonia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Quality of life</b>					
[43] RCT	20 adults with cervical dystonia	<b>Mean change from baseline in Craniocervical Dystonia Questionnaire 24 , at week 12</b> -6.3 with exercise programme plus relaxation -7.0 with relaxation only	Mean difference -0.2 95% CI -11.6 to +11.1 Intention-to-treat analysis Difference between groups was adjusted for baseline (week 0) score based on ANCOVA	↔	Not significant
[43] RCT	20 adults with cervical dystonia	<b>Mean change from baseline in Craniocervical Dystonia Questionnaire 24 , at week 16</b> -2.6 with exercise programme plus relaxation -7.0 with relaxation only	Mean difference +4.4 95% CI -7.3 to +16.1 Intention-to-treat analysis Difference between groups was adjusted for baseline (week 0) score based on ANCOVA	↔	Not significant

**Adverse effects**

No data from the following reference on this outcome. [43]

**Further information on studies**

[42] The RCT also found that when physical therapy plus botulinum A toxin was given as the first treatment, this resulted in longer duration of clinical benefit before people needed to cross over to the alternative treatment, and that a lower dose of botulinum toxin was required at the next injection, compared with when botulinum A toxin alone was used as the first treatment.

**Comment:****Physiotherapy in children with developmental cervical dystonia:**

We found one case series (23 children, mean age 3.8 months [range 3 weeks–10.5 months] diagnosed with developmental cervical dystonia), which examined the effect of passive cervical stretching by positioning and active strengthening of identified weak muscles. [44] The average number of treatments was 3.8 (range 1.0–10.0) provided over mean treatment duration of 2.9 months. At follow-up (mean age at follow-up: 18 months, range 5–49 months), the case series found that a similar number of parents reported 'good' or 'excellent' outcomes in their children (excellent = symmetrical head features, symmetrical facial features, passive cervical rotation of at least 75° bilaterally, passive cervical lateral flexion of at least 40° bilaterally, complete head righting, and lack of resting head tilt; good = 4–5 of these outcomes; fair = 3 of these outcomes; poor = 1–2 of the outcomes: 11/23 [48%] excellent v 11/23 [48%] good v 1/23 [4%] fair v 0/23 [0%] poor).

**Physiotherapy in children with early congenital cervical dystonia**

We found one case series (126 children with mild to severe congenital cervical dystonia seen over 30 years), which examined the effect of passive stretching exercises (PSE). [45] Subjective physician measurement of PSE showed that PSE for early congenital cervical dystonia (<3 months) produced excellent results in 52/81 (64%) of cases at an average follow-up of 9 months (excellent = full rotation and no asymmetry; good = full rotation and mild asymmetry or mild limitation of rotation and no asymmetry; fair = mild limitation of rotation and mild asymmetry; poor = no improvement: 65% excellent v 27% good v 8% fair v 0% poor).

Case series should be carefully interpreted, because: (1) the intervention will vary over time; (2) a number of outcomes are subjective; and (3) it is hard to determine whether the specified physiotherapy actually took place in the home setting. Also, the outcome was probably assessed by someone who was not blinded to the treatment — even by the treating therapist.

**Clinical guide:**

Most people will see a physiotherapist at some point after diagnosis, but there is no consistent approach to treatment, and practice can vary from place to place with no consensus on best practice. At present, physiotherapy cannot be recommended positively and clinicians should consider whether raising unrealistic expectations may be more harmful than any potential and unproven benefit.

**OPTION ACUPUNCTURE FOR FOCAL DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from systematic reviews or RCTs about the effects of acupuncture in the treatment of people with focal dystonia.

**Benefits and harms**

**Acupuncture:**

We found no systematic review or RCTs of acupuncture in people with focal dystonia.

**Comment:** None.

**OPTION BIOFEEDBACK FOR FOCAL DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found insufficient information from systematic reviews or RCTs to judge the effects of biofeedback in the treatment of people with focal dystonia.

**Benefits and harms**

**Biofeedback for cervical dystonia:**

We found no systematic review or RCTs (see Comment).

**Physiotherapy plus biofeedback plus drug treatment versus drug treatment alone:**

See option on physiotherapy, p 26 .

**Comment:**

**Biofeedback for cervical dystonia:**

We found one case series (80 adults, 69 with spasmodic cervical dystonia and 11 with focal dystonia) examining auditory and visual EMG biofeedback.<sup>[46]</sup> It found that clinically significant improvement of dystonia was achieved by 45/80 (56%) people at 8 to 12 weeks with biofeedback. The improvements ranged from a sustained response (as measured by EMG activity and degree of functional deficiency) after feedback was withdrawn, to the person being able to maintain control of head movements for extended periods without feedback. Changes were seen in range of motion, control of oscillation, and activities of daily living.

**Clinical guide:**

The aim of biofeedback is to re-establish a more normal posture and pattern of muscular activity. While it seems a reasonable approach, it needs to be tested using well-designed RCTs. Enthusiasm

for recommending this treatment should be balanced by concerns about raising expectations that are unfulfilled.

**OPTION OCCUPATIONAL THERAPY FOR FOCAL DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- We found no direct information from systematic reviews or RCTs about occupational therapy in the treatment of people with focal dystonia.

**Benefits and harms**

**Occupational therapy:**

We found no systematic review or RCTs of occupational therapy in people with focal dystonia.

**Comment:** None.

**OPTION SPEECH THERAPY FOR FOCAL DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- Evidence for benefit of voice therapy plus botulinum toxin versus sham voice therapy plus botulinum toxin versus botulinum toxin-only is unclear.

**Benefits and harms**

**Voice therapy plus botulinum A toxin versus sham voice therapy plus botulinum A toxin versus botulinum A toxin-only for laryngeal dystonia (adductor spasmodic dysphonia):**

We found one small RCT, which compared voice therapy plus botulinum toxin versus sham voice therapy plus botulinum toxin versus botulinum toxin-only for laryngeal dystonia. [47] Participants were compensated for their participation in the RCT, and excluded if they were unwilling to be allocated to the voice therapy or sham therapy arms. In addition, the botulinum injection was left to the complete discretion of the physician regarding dosage or administration.

**Neurological disability**

No data from the following reference on this outcome. [47]

**Quality of life**

*Voice therapy plus botulinum A toxin versus sham voice therapy plus botulinum A toxin versus botulinum A toxin-only for laryngeal dystonia* We don't know how effective voice therapy plus botulinum A toxin, sham voice therapy plus botulinum A toxin, and botulinum A toxin alone are, compared with each other, in improving quality of life in people with adductor spasmodic dysphonia (very-low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Quality of life</b>					
[47] RCT	31 adults with adductor spasmodic dysphonia	<b>Voice-related quality of life</b> with voice therapy plus botulinum A toxin with sham voice therapy plus botulinum A toxin with botulinum A toxin-only Absolute results not reported	Reported as not significant P value not provided Statistical analysis not clear	↔	Not significant

**Adverse effects**

No data from the following reference on this outcome. <sup>[47]</sup>

**Comment:** None.

**QUESTION** What are the effects of drug treatments for generalised dystonia?

**OPTION** AMANTADINE FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about amantadine in the treatment of people with generalised dystonia.

**Benefits and harms****Amantadine:**

We found no systematic review or RCTs of amantadine in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

**OPTION** BACLOFEN FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about baclofen in the treatment of people with generalised dystonia.

**Benefits and harms****Baclofen:**

We found no systematic review or RCTs of baclofen in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

**OPTION** BENZATROPINE FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about benztropine in the treatment of people with generalised dystonia.

**Benefits and harms****Benzatropine:**

We found no systematic review or RCTs of benztropine in people with generalised dystonia.



**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

#### OPTION BOTULINUM TOXINS FOR GENERALISED DYSTONIA (E.G., BOTULINUM A TOXIN, BOTULINUM B TOXIN)

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about botulinum toxins in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Botulinum toxins:

We found no systematic review or RCTs of botulinum toxins in people with generalised dystonia.

#### Comment: Clinical guide:

As with focal dystonia, the evidence supporting treatments for generalised dystonia is limited. Generalised dystonia is a relatively rare condition (small commercial incentive for research) that is variable both within and between people with the condition, and the effect is not easily measured. There are reports of trihexyphenidyl being administered off-licence at doses above the recommended maximum, but this is best considered within specialised services with suitable experience. People may often see a physiotherapist after diagnosis, but no specific therapeutic manoeuvres are known. Beliefs about the usefulness of physiotherapy vary. Surgical treatments are also used, although there is little long-term evidence of either benefits or risks from surgery.

#### OPTION BROMOCRIPTINE FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about bromocriptine in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Bromocriptine:

We found no systematic review or RCTs of bromocriptine in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

#### OPTION CARBAMAZEPINE FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about carbamazepine in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Carbamazepine:

We found no systematic review or RCTs of carbamazepine in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

#### OPTION CARBIDOPA/LEVODOPA FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- We found no direct information from RCTs about carbidopa/levodopa in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Carbidopa/levodopa:

We found no systematic review or RCTs of carbidopa/levodopa in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

#### OPTION CLONAZEPAM FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- We found no direct information from RCTs about clonazepam in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Clonazepam:

We found no systematic review or RCTs of clonazepam in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

#### OPTION CLOZAPINE FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- We found no direct information from RCTs about clozapine in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Clozapine:

We found no systematic review or RCTs of clozapine in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

**OPTION DIAZEPAM FOR GENERALISED DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about diazepam in the treatment of people with generalised dystonia.

**Benefits and harms****Diazepam:**

We found no systematic review or RCTs of diazepam in people with generalised dystonia.

**Comment:** [See Comment on botulinum toxins for generalised dystonia, p 33](#) .

**OPTION GABAPENTIN FOR GENERALISED DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about gabapentin in the treatment of people with generalised dystonia.

**Benefits and harms****Gabapentin:**

We found no systematic review or RCTs of gabapentin in people with generalised dystonia.

**Comment:** [See Comment on botulinum toxins for generalised dystonia, p 33](#) .

**OPTION HALOPERIDOL FOR GENERALISED DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about haloperidol in the treatment of people with generalised dystonia.

**Benefits and harms****Haloperidol:**

We found no systematic review or RCTs of haloperidol in people with generalised dystonia.

**Comment:** [See Comment on botulinum toxins for generalised dystonia, p 33](#) .

**OPTION LORAZEPAM FOR GENERALISED DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about lorazepam in the treatment of people with generalised dystonia.

**Benefits and harms****Lorazepam:**

We found no systematic review or RCTs of lorazepam in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

#### OPTION ONDANSETRON FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- We found no direct information from RCTs about ondansetron in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Ondansetron:

We found no systematic review or RCTs of ondansetron in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

#### OPTION PREGABALIN FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- We found no direct information from RCTs about pregabalin in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Pregabalin:

We found no systematic review or RCTs of pregabalin in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

#### OPTION PROCYCLIDINE FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- We found no direct information from RCTs about procyclidine in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Procyclidine:

We found no systematic review or RCTs of procyclidine in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

**OPTION TIZANIDINE FOR GENERALISED DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about tizanidine in the treatment of people with generalised dystonia.

**Benefits and harms****Tizanidine:**

We found no systematic review or RCTs of tizanidine in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

**OPTION TRAZODONE HYDROCHLORIDE FOR GENERALISED DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about trazodone hydrochloride in the treatment of people with generalised dystonia.

**Benefits and harms****Trazodone hydrochloride:**

We found no systematic review or RCTs of trazodone hydrochloride in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

**OPTION TRIHEXYPHENIDYL FOR GENERALISED DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from RCTs about trihexyphenidyl in the treatment of people with generalised dystonia.

**Benefits and harms****Trihexyphenidyl:**

We found no systematic review or RCTs of trihexyphenidyl in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

**QUESTION What are the effects of surgical treatments for generalised dystonia?****OPTION DEEP BRAIN STIMULATION OF THALAMUS AND GLOBUS PALLIDUS FOR GENERALISED DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .

- We found no direct information from RCTs about deep brain stimulation of the thalamus in only people with generalised dystonia. Evidence in a mixed population of people with focal or generalised dystonia suggests that it may improve function at 3 months.

**Benefits and harms**

**Deep brain stimulation versus sham treatment:**

We found no systematic review or RCTs of deep brain stimulation of the thalamus in people with only generalised dystonia. We found one RCT that compared deep brain stimulation of the internal globus pallidus versus sham stimulation in people with either generalised or focal dystonia. <sup>[40] [41]</sup>

**Neurological disability**

*Deep brain stimulation compared with sham stimulation* Deep brain stimulation of the thalamus and globus pallidus may be more effective at 3 months at improving total movement (with imputation) and disability scores on the Burke-Fahn-Marsden Dystonia (BFMD) Rating Scale in people with primary segmental and generalised dystonia ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Neurological disability</b>					
[40] RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years	<b>Improvement in Burke-Fahn-Marsden Dystonia (BFMD) Rating Scale total movement score , 3 months</b> –15.8 with neurostimulation –1.4 with sham stimulation Change in BFMD score for movement from baseline; possible range of scores of 0–120	P <0.001		neurostimulation
[40] RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years	<b>Improvement in BFMD Rating Scale disability score , 3 months</b> –3.9 with neurostimulation –0.8 with sham stimulation Change in BFMD score for disability from baseline; possible range of scores of 0–30	P <0.001		neurostimulation

**Quality of life**

*Deep brain stimulation compared with sham stimulation* Deep brain stimulation of the thalamus and globus pallidus may be more effective at improving the physical component of quality-of-life scores (assessed using short form [SF]-36 questionnaire) and several subscale scores, including bodily pain score. However, we don't know whether it is more effective at improving the mental component of quality-of-life scores or other subscale scores in people with primary segmental and generalised dystonia ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Quality of life</b>					
[40] RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years	<b>Improvement in short form (SF)-36 physical component score</b> 10.1 with neurostimulation 3.8 with sham stimulation Change in SF-36 physical component score; possible range of scores of 0–100	P = 0.02 33/40 (82.5%) assessed for this outcome		neurostimulation
[40] RCT	40 people aged 14–75 years with primary segmental	<b>Improvement in SF-36 mental component score</b> 5.2 with neurostimulation	P = 0.39		Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	(16 people) or generalised dystonia (24 people) for a minimum of 5 years	0.2 with sham stimulation Change in SF-36 mental component score; possible range of scores of 0–100			
[41] RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [40]	<b>Improvement in SF-36 physical function score , 3 months</b> 27.3 with neurostimulation 3.0 with sham stimulation Change in SF-36 physical function score; possible range of scores of 0–100	P = 0.001 36/40 (90%) assessed for this outcome		neurostimulation
[41] RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [40]	<b>Improvement in SF-36 bodily pain score , 3 months</b> 22.7 with neurostimulation 9.7 with sham stimulation Change in SF-36 bodily pain score; possible range of scores of 0–100	P = 0.04 37/40 (93%) assessed for this outcome		neurostimulation
[41] RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [40]	<b>Improvement in SF-36 general health score , 3 months</b> 17.6 with neurostimulation 2.1 with sham stimulation Change in SF-36 general health score; possible range of scores of 0–100	P = 0.02 37/40 (93%) assessed for this outcome		neurostimulation
[41] RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [40]	<b>Improvement in SF-36 vitality score , 3 months</b> 14.7 with neurostimulation 2.0 with sham stimulation Change in SF-36 vitality score; possible range of scores of 0–100	P = 0.047 37/40 (93%) assessed for this outcome		neurostimulation
[41] RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [40]	<b>Improvement in SF-36 role physical score , 3 months</b> 25.0 with neurostimulation 13.2 with sham stimulation Change in SF-36 role limitations due to physical problems score; possible range of scores of 0–100	P = 0.20 35/40 (88%) assessed for this outcome		Not significant
[41] RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years	<b>Improvement in SF-36 social function score , 3 months</b> 21.1 with neurostimulation 0.7 with sham stimulation Change in SF-36 social function score; possible range of scores of 0–100	P = 0.07 37/40 (93%) assessed for this outcome		Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Further report of reference <sup>[40]</sup>				
<sup>[41]</sup> RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years  Further report of reference <sup>[40]</sup>	<b>Improvement in SF-36 role emotional score , 3 months</b> 24.6 with neurostimulation 13.7 with sham stimulation  Change in SF-36 role limitations due to emotional problems score; possible range of scores of 0–100	P = 0.43 36/40 (90%) assessed for this outcome	↔	Not significant
<sup>[41]</sup> RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years  Further report of reference <sup>[40]</sup>	<b>Improvement in SF-36 mental health score , 3 months</b> 10.7 with neurostimulation 2.0 with sham stimulation  Change in SF-36 mental health score; possible range of scores of 0–100	P = 0.54 37/40 (93%) assessed for this outcome	↔	Not significant
<sup>[41]</sup> RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years  Further report of reference <sup>[40]</sup>	<b>Improvement in Brief Psychiatric Rating Scale , 3 months</b> –5.9 with neurostimulation –3.0 with sham stimulation  Scale range not defined, higher score indicates a greater severity of symptoms	P = 0.09 37/40 (93%) assessed for this outcome	↔	Not significant

### Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
<sup>[40]</sup> RCT	40 people aged 14–75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years	<b>Infection at stimulator site</b> 1/20 (5%) with neurostimulation 2/20 (10%) with sham treatment	Reported as not significant		

### Further information on studies

<sup>[40]</sup> <sup>[44]</sup> The RCT analysed data for all people who underwent randomisation (last observation carried forward). The RCT did not carry out a subgroup analysis of people with generalised dystonia, which may affect the generalisability of the results.



**Comment:** **Clinical guide:** RCTs with longer follow-up are required. The beneficial effects of stimulation may wear off over time, and the long-term risks and adverse effects of implantation into the brain and of brain stimulation itself are not known. We suggest that a minimum of 12 months' controlled observation (i.e., without implantation into the control group) may be required to judge effectiveness, and that a minimum of 5 years of natural history follow-up (i.e., after implantation) may be required to judge safety and long-term risk, and to confirm persistence of any beneficial effect. See also [Comment on botulinum toxins for generalised dystonia, p 33](#) .

#### QUESTION What are the effects of physical treatments for generalised dystonia?

#### OPTION ACUPUNCTURE FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from systematic reviews or RCTs about acupuncture in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Acupuncture:

We found no systematic review or RCTs of acupuncture in people with generalised dystonia.

**Comment:** See [Comment on botulinum toxins for generalised dystonia, p 33](#) .

#### OPTION BIOFEEDBACK FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from systematic reviews or RCTs about biofeedback in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Biofeedback:

We found no systematic review or RCTs of biofeedback in people with generalised dystonia.

**Comment:** See [Comment on botulinum toxins for generalised dystonia, p 33](#) .

#### OPTION OCCUPATIONAL THERAPY FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, [see table, p 46](#) .
- We found no direct information from systematic reviews or RCTs about occupational therapy in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Occupational therapy:

We found no systematic review or RCTs of occupational therapy in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

#### OPTION PHYSIOTHERAPY FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- We found no direct information from systematic reviews or RCTs about physiotherapy in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Physiotherapy:

We found no systematic review or RCTs of physiotherapy in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

#### OPTION SPEECH THERAPY FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 46 .
- We found no direct information from systematic reviews or RCTs about speech therapy in the treatment of people with generalised dystonia.

#### Benefits and harms

##### Speech therapy:

We found no systematic review or RCTs of speech therapy in people with generalised dystonia.

**Comment:** See Comment on botulinum toxins for generalised dystonia, p 33 .

## GLOSSARY

**High-quality evidence** Further research is very unlikely to change our confidence in the estimate of effect.

**Low-quality evidence** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Moderate-quality evidence** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Very low-quality evidence** Any estimate of effect is very uncertain.

## SUBSTANTIVE CHANGES

**Botulinum toxins for focal dystonia** Two RCTs added. <sup>[21]</sup> <sup>[22]</sup> Categorisation of botulinum toxins for focal dystonia unchanged (beneficial).

**Physiotherapy for focal dystonia** One RCT added. <sup>[43]</sup> Categorisation of physiotherapy for focal dystonia unchanged (unknown effectiveness).

**Speech therapy for focal dystonia** One RCT added. <sup>[47]</sup> Categorisation of speech therapy for focal dystonia unchanged (unknown effectiveness).

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**TABLE 1** Commonly used rating scales for dystonia. <sup>[14]</sup> <sup>[15]</sup> <sup>[16]</sup> <sup>[17]</sup> <sup>[18]</sup>

Scale	Feature	Interpretation	Range*
Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) <sup>[14]</sup>	Three subscales, assessed by clinician: (1) movement disorder severity (range 0–35) (2) disability (range 0–30) (3) pain (range 0–20)	A decrease in TWSTRS-total or subscale score indicates an improvement in the person's dystonia. Dystonia trials frequently use TWSTRS-total or the individual TWSTRS-severity, TWSTRS-pain, or TWSTRS-disability scales as the primary outcome	0–85
Tsui Scale <sup>[15]</sup>	Clinician-assessed scale of impairment that grades severity of postural deviance (rotatorcollis, antecollis, retrocollis, head tilt, and elevation of shoulder), acknowledges the presence or absence of head tremor, and includes whether the movements are continuous or intermittent		0–25
Cervical Dystonia Severity Scale (CDSS) <sup>[16]</sup>	Uses a protractor and wall chart to rate the severity of the head's deviation from neutral in each of the three planes of motion (rotation, laterocollis, antecollis/retrocollis)		
Jankovic Rating Scale (JRS) <sup>[17]</sup>	Includes two categories: severity and frequency, each with 5 rating classes of 0–4 points		0–8
Blepharospasm Disability Index (BSDI) <sup>[18]</sup>	Disease-specific self-assessment scale consisting of 6 × 5-point items assessing vehicle driving, reading, watching TV, shopping, getting about on foot, and doing everyday activities	0 = no interference in these activities and 30 = severe interference	0–30
Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) <sup>[48]</sup>	Assessment of severity and frequency of dystonia in 9 body areas (including eyes, mouth, speech or swallowing, neck, right and left arms, trunk, and right and left legs)	0 = no dystonia and 120 = maximum severity	0–120
Writer's Cramp Rating Scale (WCERS) <sup>[49]</sup>	Assessment of writing posture (elbow, wrist, and fingers), movements (latency and tremor), and speed of writing	0 = no impairment and 30 = marked impairment	0–30

\*Higher score indicates greater severity in all scales.

**GRADE** Evaluation of interventions for Dystonia.

Important outcomes	Studies (Participants)	Outcome	Comparison	Type of evidence	Neurological disability, Quality of life				GRADE	Comment
					Quality	Consistency	Directness	Effect size		
<i>What are the effects of drug treatments for focal dystonia?</i>										
	at least 14 (at least 1029) [19] [20] [21] [22]	Neurological disability	Botulinum A toxin versus placebo in cervical dystonia in adults	4	0	0	-1	0	Moderate	Directness point deducted for including only people who had previously responded to onabotulinumtoxinA in 1 RCT
	3 (308) [23]	Neurological disability	Botulinum B toxin versus placebo in cervical dystonia in adults	4	0	0	0	0	High	
	3 (252) [25] [26] [27]	Neurological disability	Botulinum A toxin versus botulinum B toxin in cervical dystonia in adults	4	0	0	-2	0	Low	Directness points deducted for not reporting doses in 1 study and population differences between studies in previous experience with botulinum A toxin
	1 (31) [29]	Neurological disability	Low-dose (100 U Botox/250 U Dysport) versus high-dose (>200 U Botox/960 U Dysport) botulinum A toxin in cervical dystonia in adults	4	-2	0	-1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for no direct comparison between groups
	1 (92) [23]	Neurological disability	Low-dose (2500–5000 U) versus high-dose (10,000 U) botulinum B toxin in cervical dystonia in adults	4	-1	-1	0	0	Low	Quality point deducted for sparse data; consistency point deducted for differing results with different outcome measures
	1 (66) [28]	Neurological disability	Botulinum A toxin versus trihexyphenidyl in cervical dystonia in adults	4	-2	0	-2	0	Very low	Quality points deducted for sparse data and incomplete reporting; directness points deducted for differences in disease severity between groups and short cycle intervals between injections affecting generalisability of results
	1 (92) [23]	Neurological disability	Botulinum B toxin in botulinum A toxin-resistant adults versus respondent adults	4	-2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
	1 (40) [32]	Neurological disability	Botulinum A toxin versus placebo in people with writer's cramp	4	-1	-1	0	0	Low	Quality point deducted for sparse data; consistency point deducted for differing results with different outcome measures
<i>What are the effects of physical treatments for focal dystonia?</i>										
	1 (40) [42]	Neurological disability	Physiotherapy plus biofeedback plus drug treatment versus drug treatment alone	4	-2	0	-1	0	Very low	Quality points deducted for sparse data, results after crossover, and unequal observation periods; directness point deducted for including only people who had previously responded to botulinum A toxin
	1 (20) [43]	Neurological disability	Physiotherapy plus relaxation versus no physiotherapy plus relaxation	4	-1	0	-1	0	Low	Quality point deducted for sparse data; directness point deducted for including a subset of participants who were also receiving botulinum toxin

Important outcomes	Neurological disability, Quality of life								GRADE	Comment
	Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size		
1 (20) <sup>[43]</sup>	Quality of life	Physiotherapy plus relaxation versus no physiotherapy plus relaxation	4	-1	0	-1	0	Low	Quality point deducted for sparse data; directness point deducted for including a subset of participants who were also receiving botulinum toxin	
1 (31) <sup>[47]</sup>	Quality of life	Voice therapy plus botulinum A toxin versus sham voice therapy plus botulinum A toxin versus botulinum A toxin-only for laryngeal dystonia (adductor spasmodic dysphonia)	4	-3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, selection bias, and botulinum toxin dose inconsistencies	
<i>What are the effects of surgical treatments for generalised dystonia?</i>										
1 (40) <sup>[40]</sup>	Neurological disability	Deep brain stimulation versus sham treatment	4	-2	0	-1	0	Very low	Quality points deducted for sparse data and no long-term results; directness point deducted for inclusion of mixed population of people with focal and generalised dystonia	
1 (less than 40) <sup>[40] [41]</sup>	Quality of life	Deep brain stimulation versus sham treatment	4	-2	-1	-1	0	Very low	Quality points deducted for sparse data and no long-term results; consistency point deducted for lack of consistent benefit in different elements of quality of life; directness point deducted for inclusion of people with focal dystonia, affecting generalisability of results	

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [ $<200$  people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.