ClinicalEvidence

Dystonia

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Ailsa Snaith and Derick Wade

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 European Ashkenazi Jewish 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 for generalised dystonia? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2011 (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 15 systematic reviews, RCTs, or observational 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: acetylcholine release inhibitors (botulinum toxin), acupuncture, anticholinergic/antihistaminic drugs, anticonvulsants, atypical antipsychotic drugs, benzodiazepines, biofeedback, chiropractic manipulation, deep brain stimulation of thalamus and globus pallidus, dopaminergic agonists and antagonists, gamma-aminobutyric acid (GABA) analogues, microvascular decompression, muscle relaxants, myectomy, occupational therapy, osteopathy, pallidotomy, physiotherapy, selective peripheral denervation, serotonergic agonists and antagonists, speech therapy, and thalamotomy.

QUESTIONS

INTERVENTIONS

DRUG TREATMENTS FOR FOCAL DYSTONIA

Beneficial

Unknown effectiveness

DRUG TREATMENTS FOR GENERALISED DYSTONIA

Unknown effectiveness

SURGICAL TREATMENTS FOR FOCAL DYSTONIA

Unknown effectiveness

SURGICAL TREATMENTS FOR GENERALISED DYSTONIA

Unknown effectiveness

Key points

- Dystonia is characterised by involuntary muscle contractions, resulting in abnormal postures and twisting of body parts.

  It 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 European Ashkenazi Jewish descent.
- Botulinum toxin is effective at relieving cervical dystonia symptoms in adults.

  Botulinum A toxin and botulinum B toxin are both effective.
- 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 (benzodiazepines, GABA analogues, atypical antipsychotics, anticonvulsants, anticholinergic/antihistaminic drugs, dopaminergic agonists and antagonists, serotonergic agonists and antagonists, and muscle relaxants) are effective for either focal or generalised dystonia.
- We don't know whether any surgical interventions (thalamotomy, pallidotomy, deep brain stimulation of thalamus and globus pallidus, selective peripheral denervation, or myectomy) are effective for either focal or generalised 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 treatment (acupuncture, biofeedback, chiropractic manipulation, occupational therapy, osteopathy, 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. [1] 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 or use of drugs (e.g., neuroleptic drugs and metoclopramide). [2] 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 pianists and flautists). [3] **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.

INCIDENCE/ PREVALENCE

Dystonia occurs worldwide, with prevalence estimates varying widely depending on study methodology. In the US, the prevalence of focal dystonia has been reported as 30/100,000 people. [4] Cervical dystonia (torticollis or "wry neck") is the most common adult form of focal dystonia, with a prevalence in Europe of 5.7/100,000. [5] Other frequently occurring focal dystonias are blepharospasm (forceful eyelid closures), which affects 3.6/100,000 people, and limb dystonias (e.g., writer's cramp), which affect 1.4/100,000. [5] In the US, the prevalence of generalised dystonia has been reported as 0.2–6.7/100,000 population; [4] generalised dystonia affects more people of European Ashkenazi Jewish descent. [6] In Europe, the prevalence of primary dystonia has been estimated at 15.2/100,000. [7] Studies identified to have rigorous methodology estimated the prevalence of early-onset (at <20 years of age) dystonia to be 11.1/100,000 for dystonia in Ashkenazi Jews from the New York area, 60/100,000 for late-onset (at >20 years of age) dystonia in the overall population of Northern England, and 300/100,000 for late-onset dystonia in the Italian population (aged 50 years or older). [2] Dystonia occurs more frequently in women.

AETIOLOGY/ RISK FACTORS

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. [8] Focal dystonias have been associated with loss of inhibition, [9] abnormal plasticity in the motor cortex, [10] and impairments in partial and temporal discrimination. [11] 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. [12] Currently, 19 types of dystonia can be distinguished on a genetic basis, 6 of which are primary dystonias (*DYT1*, *2*, *4*, *6*, *7*, and *13*). [13] The remainder are secondary dystonia, dystonia-plus syndromes, and paroxysmal dystonias.

PROGNOSIS

Dystonia is usually a lifelong disorder, 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.

AIMS OF INTERVENTION

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.

OUTCOMES

Neurological disability: In dystonia clinical trials, outcome is usually measured using disease-specific rating scales: Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), [14] Tsui scale, [15] Cervical Dystonia Severity Scale (CDSS), [16] Jankovic Rating Scale (JRS), [17] and Blepharospasm Disability Index (BSDI; [18] see table 1, p 43). **Quality of life**; **adverse effects of treatment**.

METHODS

Clinical Evidence search and appraisal February 2011. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2011, Embase 1980 to February 2011, and The Cochrane Database of Systematic Reviews, February 2011 [online] (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, including open studies, containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. We also searched for

controlled clinical trials (non-randomised) for physical therapies. 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 44). 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).

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

OPTION ACETYLCHOLINE RELEASE INHIBITORS FOR FOCAL DYSTONIA (E.G., BOTULINUM A TOXIN, BOTULINUM B TOXIN)

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- 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 acetylcholine release inhibitors, 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) [19] and one subsequent RCT. [20]

Neurological disability

Compared with placebo Botulinum A toxin is more effective at improving cervical dystonia at up to 16 weeks, as assessed by an improvement in Tsui scale, Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), physician- and patient-rated scores, and the number of people reporting pain relief (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Neurological disability					
[19] Systematic review	113 adults with cervical dystonia 3 RCTs in this analysis	**Improvement of at least 3 points on Tsui scale , 3 to 6 weeks** 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
[19] Systematic review	353 adults with cervical dystonia 6 RCTs in this analysis	**Any improvement in Tsui or Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) , 0 to 12 weeks** 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
[19] Systematic review	510 adults with cervical dystonia 11 RCTs in this analysis	**Any improvement in subjective patient-related scales , 0 to 16 weeks**	OR 6.58 95% CI 4.55 to 9.54 P = 0.00001	●●●	botulinum A toxin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		161/273 (59%) with botulinum A toxin 46/237 (19%) with placebo	NNT 3 95% CI 3 to 3		
[19] Systematic review	350 adults with cervical dystonia 4 RCTs in this analysis	**Physicians reporting improvement , 0 to 16 weeks** 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	**Proportion of people reporting pain relief , time frame not reported** 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	**Mean change in TWSTRS-Total score from baseline , at week 4** –15.6 with botulinum A toxin –6.7 with placebo	P <0.001 Intention-to-treat analysis	○○○	botulinum A toxin

Quality of life

No data from the following reference on this outcome. [19] [20]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] Systematic review	421 adults with cervical dystonia 6 RCTs in this analysis	**Proportion of people with any adverse effect (neck weakness, dysphagia, voice changes/hoarseness, dry mouth/sore throat)** 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	**Proportion of people with neck weakness** 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	**Proportion of people with voice changes/hoarseness** 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	**Proportion of people with dry mouth/sore throat** 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

Botulinum B toxin versus placebo in cervical dystonia in adults:

We found one systematic review (search date 2003). [21]

Neurological disability

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
Neurological disability					
[21] 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	**Improvement of at least 20% of TWSTRS-Total score , 4 weeks** 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
[21] 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	**Improvement of at least 20% of TWSTRS-Total score , 8 weeks** 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
[21] 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	**Improvement of at least 20% of TWSTRS-Total score , 12 weeks** 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
[21] 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	**Improvement of at least 20% of TWSTRS-Total score , 16 weeks** 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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Data from 1 RCT				
[21] 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	**Patient global assessment of change in symptoms , 0 to 4 weeks** 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
[21] 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	**Patient global assessment of change in symptoms , 0 to 4 weeks** 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
[21] 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	**Principal investigator global assessment of change in symptoms , 0 to 4 weeks** 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
[21] 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	**Principal investigator global assessment of change in symptoms , 0 to 4 weeks** 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
[21] 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	**Patient analogue pain assessment , 0 to 4 weeks** 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
[21] 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	**Patient analogue pain assessment , 0 to 4 weeks** 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. [21]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] Systematic review	307 adults with cervical dystonia 3 RCTs in this analysis	**Dry mouth** 45/203 (22%) with botulinum B toxin 3/104 (3%) with placebo	OR 5.19 95% CI 2.69 to 10.03 P <0.00001 NNH 6 95% CI 6 to 8	●●●	placebo
[21] Systematic review	307 adults with cervical dystonia 3 RCTs in this analysis	**Dysphagia** 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. [22] We found three subsequent RCTs. [23] [24] [25]

Neurological disability

Botulinum A compared with botulinum B 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
Neurological disability					
[23] RCT	139 adults who previously responded to botulinum A toxin	**Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-Total score , 0 to 4 weeks** 10.2 with botulinum A toxin (up to 250 U Botox) 9.3 with botulinum B toxin (up to 10,000 U Myobloc)	P = 0.75	⟷	Not significant
[23] RCT	139 adults who previously responded to botulinum A toxin	**TWSTRS-Severity score , 4 weeks** 3.7 with botulinum A toxin (up to 250 U Botox) 3.7 with botulinum B toxin (up to 10,000 U Myobloc)	Reported as not significant RR not reported 95% CI not reported P = 0.90	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[23] RCT	139 adults who previously responded to botulinum A toxin	**TWSTRS-Disability score , 0 to 4 weeks** 2.4 with botulinum A toxin (up to 250 U Botox) 2.5 with botulinum B toxin (up to 10,000 U Myobloc)	Reported as not significant RR not reported P = 0.71	⟷	Not significant
[23] RCT	139 adults who previously responded to botulinum A toxin	**TWSTRS-Pain score , 0 to 4 weeks** 3.2 with botulinum A toxin (up to 250 U Botox) 4.0 with botulinum B toxin (up to 10,000 U Myobloc)	Reported as not significant RR not reported P = 0.24	⟷	Not significant
[23] RCT	139 adults who previously responded to botulinum A toxin	**Median duration of effect of treatment** 13 weeks with botulinum A toxin (up to 250 U Botox) 11.7 weeks with botulinum B toxin (up to 10,000 U Myobloc)	Reported as not significant RR not reported P = 0.095	⟷	Not significant
[24] RCT	20 adults who responded to botulinum A toxin within the previous year	**TWSTRS-Severity score , 2 weeks** 14 with botulinum A toxin 15 with botulinum B toxin Doses not reported	Reported as not significant RR not reported	⟷	Not significant
[24] RCT	20 adults who responded to botulinum A toxin within the previous year	**TWSTRS-Pain score , 2 weeks** 6 with botulinum A toxin 4 with botulinum B toxin Doses not reported	Reported as not significant RR not reported	⟷	Not significant
[24] RCT	20 adults who responded to botulinum A toxin within the previous year	**TWSTRS-Disability score , 2 weeks** 10 with botulinum A toxin 12 with botulinum B toxin Doses not reported	Reported as not significant RR not reported	⟷	Not significant
[25] RCT	111 adults with cervical dystonia, not previously treated with botulinum toxin (toxin naive), 93/111 (84%) included in analysis	**Improvement in TWSTRS-Total score , 4 weeks** 8.8 with botulinum A toxin (150 U/2 mL) 11.0 with botulinum B toxin (10,000 U/2 mL)	Difference –2.2 95% CI –5.4 to +1.1 Not intention-to-treat analysis	⟷	Not significant
[25] RCT	111 adults with cervical dystonia, not previously treated with botulinum toxin (toxin naive), 93/111 (84%) included in analysis	**Improvement in TWSTRS-Severity score , 4 weeks** 4.7 with botulinum A toxin (150 U/2 mL) 5.4 with botulinum B toxin (10,000 U/2 mL)	Difference –0.7 95% CI –2.2 to +0.8 Not intention-to-treat analysis	⟷	Not significant
[25] RCT	111 adults with cervical dystonia, not previously treated with botulinum toxin (toxin naive), 93/111 (84%) included in analysis	**Improvement in TWSTRS-Disability score , 4 weeks** 2.5 with botulinum A toxin (150 U/2 mL) 2.9 with botulinum B toxin (10,000 U/2 mL)	Difference –0.5 95% CI –2.0 to +1.0 Not intention-to-treat analysis	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[25] RCT	111 adults with cervical dystonia, not previously treated with botulinum toxin (toxin naive), 93/111 (84%) included in analysis	**Improvement in TWSTRS-Pain score , 4 weeks** 1.7 with botulinum A toxin (150 U/2 mL) 2.7 with botulinum B toxin (10,000 U/2 mL)	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. [23] [24] [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] RCT	139 adults who previously responded to botulinum A toxin	**Dysphagia , 4 weeks** 19% with botulinum A toxin 48% with botulinum B toxin Absolute numbers not reported	P = 0.0005	○○○	botulinum A toxin
[23] RCT	139 adults who previously responded to botulinum A toxin	**Dry mouth , 4 weeks** 41% with botulinum A toxin 80% with botulinum B toxin Absolute numbers not reported	P <0.0001	○○○	botulinum A toxin
[24] RCT	20 adults who responded to botulinum A toxin within the previous year	**Dysphagia** 18% with botulinum A toxin 55% with botulinum B toxin Absolute numbers not reported	P = 0.081	⟷	Not significant
[24] RCT	20 adults who responded to botulinum A toxin within the previous year	**Constipation** 0/11 (0%) with botulinum A toxin 3/9 (33%) with botulinum B toxin	P = 0.037	○○○	placebo
[25] RCT	111 adults, not previously treated with botulinum toxin (toxin naive)	**Dysphagia** 8/55 (15%) with botulinum A toxin 9/56 (16%) with botulinum B toxin	P = 1	⟷	Not significant
[25] RCT	111 adults with cervical dystonia, not previously treated with botulinum toxin (toxin naive)	**Dry mouth** 4/55 (7%) with botulinum A toxin 22/56 (39%) with botulinum B toxin	P = 0.0001	○○○	botulinum A toxin
[25] RCT	111 adults with cervical dystonia, not previously treated with botulinum toxin (toxin naive)	**Injection site pain** 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. [26] We found one additional RCT. [27]

Neurological disability

Low-dose compared with high-dose botulinum A We don't know whether high-dose botulinum A toxin is more effective 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
Neurological disability					
[27] RCT	31 adults	**Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-Severity score , 4 weeks** 0.27 with botulinum A toxin 125 U/mL 1.07 with botulinum A toxin 500 U/mL	P = 0.19	⟷	Not significant
[27] RCT	31 adults	**TWSTRS-Disability score , 4 weeks** 2.6 with botulinum A toxin 125 U/mL 1.2 with botulinum A toxin 500 U/mL	P = 0.26	⟷	Not significant
[27] RCT	31 adults	**TWSTRS-Total score , 4 weeks** 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. [27]

Adverse effects

No data from the following reference on this outcome. [27]

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). [21]

Neurological disability

Low-dose compared with high-dose botulinum B 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
Neurological disability					
[21] 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	**Improvement in TWSTRS-Pain subscale , 4 weeks** 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
[21] 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	**Improvement of at least 20% in TWSTRS-Total score , 4 weeks** 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
[21] 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	**Improvement of at least 20% in TWSTRS-Total score , 8 weeks** 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
[21] 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	**Improvement of at least 20% in TWSTRS-Total score , 12 weeks** 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
[21] 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	**Improvement of at least 20% in TWSTRS-Total score , 16 weeks** 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. [21]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] 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	**Dry mouth** 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 anticholinergic drugs (trihexyphenidyl) in cervical dystonia in adults:
We found one systematic review (search date 2003). [26]

Neurological disability

Compared with anticholinergic drugs 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
Neurological disability					
[26] Systematic review	66 adults with cervical dystonia, see further information on studies Data from 1 RCT	**Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-Disability score , 12 weeks** with botulinum A toxin (Dysport, 292 U in first session, 262 U in second session, under EMG guidance) plus placebo tablets with trihexyphenidyl (mean dose 16.25 mg) plus placebo injection Absolute results not reported	WMD 2.50 95% CI 0.68 to 4.32 P = 0.0097	○○○	botulinum A toxin
[26] Systematic review	66 adults with cervical dystonia, see further information on studies Data from 1 RCT	**Tsui score , 12 weeks** with botulinum A toxin (Dysport, 292 U in first session, 262 U in second session, under EMG guidance) plus placebo tablets with trihexyphenidyl (mean dose 16.25 mg) plus placebo injection Absolute results not reported	WMD 4.60 95% CI 2.14 to 7.06 P = 0.0009	○○○	botulinum A toxin
[26] Systematic review	66 adults with cervical dystonia, see further information on studies Data from 1 RCT	**Mean difference in General Health Perception subscale score** with botulinum A toxin (Dysport, 292 U in first session, 262 U in second session, under EMG guidance) plus placebo tablets	Mean score difference 6 95% CI 4 to 12 P = 0.0023	○○○	botulinum A toxin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with trihexyphenidyl (mean dose 16.25 mg) plus placebo injection Absolute results not reported			
[26] Systematic review	66 adults with cervical dystonia, see further information on studies Data from 1 RCT	**Proportion of people with at least 3-point improvement on Tsui scale** with botulinum A toxin (Dysport, 292 U in first session, 262 U in second session, under EMG guidance) plus placebo tablets with trihexyphenidyl (mean dose 16.25 mg) plus placebo injection Absolute results not reported	OR 3.92 95% CI 1.48 to 10.40	●●○	botulinum A toxin
[26] Systematic review	66 adults with cervical dystonia, see further information on studies Data from 1 RCT	**Proportion of people with at least 3-point improvement on TWSTRS scale** with botulinum A toxin (Dysport, 292 U in first session, 262 U in second session, under EMG guidance) plus placebo tablets with trihexyphenidyl (mean dose 16.25 mg) plus placebo injection Absolute results not reported	OR 3.14 95% CI 1.10 to 8.97 P = 0.059	●●○	botulinum A toxin
[26] Systematic review	66 adults with cervical dystonia, see further information on studies Data from 1 RCT	**Median improvement in TWSTRS-Pain score** 3 with botulinum A toxin (Dysport, 292 U in first session, 262 U in second session, under EMG guidance) plus placebo tablets 1 with trihexyphenidyl (mean dose 16.25 mg) 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. [26]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[26] Systematic review	66 adults Data from 1 RCT	**Number of adverse effects in each group** 31 in 32 people with botulinum A toxin (Dysport, 292 U in first session, 262 U in second session, under EMG guidance) plus placebo tablets 76 in 32 people with trihexyphenidyl plus placebo	P = 0.0001	○○○	botulinum A toxin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[26] Systematic review	66 adults Data from 1 RCT	**Dry mouth** 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
[26] Systematic review	66 adults Data from 1 RCT	**Forgetfulness** 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
[26] Systematic review	66 adults Data from 1 RCT	**Fatigue** 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 versus respondent adults:

We found one systematic review (search date 2003). [21]

Neurological disability

Botulinum B in botulinum A-resistant adults compared with botulinum B 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
Neurological disability					
[21] Systematic review	92 adults Data from 1 RCT	**Improvement of at least 20% in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-Total score , 4 weeks** 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. [21]

Adverse effects

No data from the following reference on this outcome. [21]

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

We found one systematic review (search date 2003), which found no RCTs. [28] 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). [29] 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. [29]

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

We found one RCT, which compared botulinum A versus placebo. [30]

Neurological disability

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
Neurological disability					
[30] RCT	40 treatment-naive people with symptoms of idiopathic writer's cramp for at least 1 year	**Mean improvement in symptom severity scale** –3.60 with botulinum A –1.16 with placebo Assessed using symptom severity scale, reduction in score indicates improvement	P = 0.02	○○○	botulinum A toxin
[30] RCT	40 treatment-naive people with symptoms of idiopathic writer's cramp for at least 1 year	**Mean improvement in writer's cramp scale** –2.30 with botulinum A –0.79 with placebo	P <0.01	○○○	botulinum A toxin
[30] RCT	40 treatment-naive people with symptoms of idiopathic writer's cramp for at least 1 year	**Mean improvement in handwriting** 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
[30] RCT	40 treatment-naive people with symptoms of idiopathic writer's cramp for at least 1 year	**Mean change in writing speed** 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
[30] RCT	40 treatment-naive people with symptoms of idiopathic writer's cramp for at least 1 year	**Mean improvement in functional status** +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. [30]

Adverse effects

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

[21] 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.

[30] 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.

[26] The systematic review commented on some limitations of the RCT. [31] 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.

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 many focal 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 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. [32] [33]

Different formulations of botulinum A toxin versus each other in people with blepharospasm (eyelid closure):
We found one RCT which 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. [34]

Dosage:
The three commercially available formulations of botulinum A toxin — Dysport, Botox, and Xeomin — differ in potency, and so are not interchangeable. [35] 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. [36] 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. Notably, use of Xeomin has not been associated with development of neutralising antibodies.

OPTION ANTICHOLINERGIC DRUGS/ANTIHISTAMINE DRUGS FOR FOCAL DYSTONIA (E.G., TRIHEXYPHENIDYL, ORPHENADRINE, BENZATROPINE, PROCYCLIDINE, PROFENAMINE [ETHOPROPAZINE], DIPHENHYDRAMINE)

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We don't know whether anticholinergic/antihistaminic drugs are effective for focal dystonia.

Benefits and harms

Anticholinergic drugs versus botulinum A toxin in cervical dystonia:
See botulinum A toxin versus anticholinergic drugs (trihexyphenidyl) in cervical dystonia, p 4 .

Further information on studies

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. High doses of the anticholinergic drug trihexyphenidyl (up to 80–160 mg/day) are sometimes used for other focal dystonias, but the evidence is limited, probably because the condition is relatively rare and not life threatening.

OPTION ANTICONVULSANTS FOR FOCAL DYSTONIA (E.G., CARBAMAZEPINE, GABAPENTIN, PREGABALIN)

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about anticonvulsants in the treatment of people with focal dystonia.

Benefits and harms

Anticonvulsants:
We found no systematic review or RCTs of anticonvulsants in people with focal dystonia.

Further information on studies

Comment: None.

OPTION ATYPICAL ANTIPSYCHOTIC DRUGS FOR FOCAL DYSTONIA (E.G., CLOZAPINE)

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about atypical antipsychotic drugs in the treatment of people with focal dystonia.

Benefits and harms

Atypical antipsychotic drugs:

We found no systematic review or RCTs of atypical antipsychotic drugs in people with focal dystonia.

Further information on studies

Comment: None.

OPTION BENZODIAZEPINES FOR FOCAL DYSTONIA (E.G., CLONAZEPAM, DIAZEPAM, LORAZEPAM, ALPRAZOLAM)

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about benzodiazepines in the treatment of people with focal dystonia.

Benefits and harms

Benzodiazepines:

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

Further information on studies

Comment: None.

OPTION DOPAMINERGIC AGONISTS FOR FOCAL DYSTONIA (E.G., CARBIDOPA/LEVODOPA, BROMOCRIPTINE, AMANTADINE)

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about dopaminergic agonists in the treatment of people with focal dystonia.

Benefits and harms

Dopaminergic agonists:

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

Further information on studies

Comment: None.

OPTION DOPAMINERGIC ANTAGONISTS FOR FOCAL DYSTONIA (E.G., HALOPERIDOL, PIMOZIDE)

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about dopaminergic antagonists in the treatment of people with focal dystonia.

Benefits and harms

Dopaminergic antagonists:

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

Further information on studies

Comment: None.

OPTION GABA ANALOGUES FOR FOCAL DYSTONIA (E.G., BACLOFEN)

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about GABA analogues in the treatment of people with focal dystonia.

Benefits and harms

GABA analogues:

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

Further information on studies

Comment: None.

OPTION SEROTONERGIC AGONISTS FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .

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

Benefits and harms

Serotonergic agonists for focal dystonia:

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

Further information on studies

Comment: None.

OPTION SEROTONERGIC ANTAGONISTS FOR FOCAL DYSTONIA (E.G., SPIPERONE, METHIOTHEPIN, ERGOTAMINE, YOHIMBINE, METERGOLINE, NEFAZODONE, TRAZODONE, MIRTAZAPINE, KETANSERIN, CYPROHEPTADINE, PIZOTIFEN, LYSERGIDE [LSD], METOCLOPRAMIDE, RENZAPRIDE, TEGASEROD)

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about serotonergic antagonists in the treatment of people with focal dystonia.

Benefits and harms

Serotonergic antagonists:

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

Further information on studies

Comment: None.

OPTION MUSCLE RELAXANTS (E.G., TIZANIDINE, CYCLOBENZAPRINE) FOR FOCAL DYSTONIA N e w

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about muscle relaxants in the treatment of people with focal dystonia.

Benefits and harms

Muscle relaxants:

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

Further information on studies

Comment: None.

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

OPTION **ACETYLCHOLINE RELEASE INHIBITORS FOR GENERALISED DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about acetylcholine release inhibitors in the treatment of people with generalised dystonia.

Benefits and harms

Acetylcholine release inhibitors:

We found no systematic review or RCTs of acetylcholine release inhibitors in people with generalised dystonia.

Further information on studies

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. Relatively high doses (up to 80 mg/day) of the anticholinergic drug trihexyphenidyl are possibly effective. 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 **ANTICHOLINERGIC/ANTIHISTAMINIC DRUGS FOR GENERALISED DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about anticholinergic/antihistaminic drugs in the treatment of people with generalised dystonia.

Benefits and harms

Anticholinergic/antihistaminic drugs:

We found no systematic review or RCTs of anticholinergic/antihistaminic drugs in people with generalised dystonia.

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION **ANTICONVULSANTS FOR GENERALISED DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about anticonvulsants in the treatment of people with generalised dystonia.

Benefits and harms

Anticonvulsants:

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

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION ATYPICAL ANTIPSYCHOTIC DRUGS FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about atypical antipsychotic drugs in the treatment of people with generalised dystonia.

Benefits and harms

Atypical antipsychotic drugs:

We found no systematic review or RCTs of atypical antipsychotic drugs in people with generalised dystonia.

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION BENZODIAZEPINES FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about benzodiazepines in the treatment of people with generalised dystonia.

Benefits and harms

Benzodiazepines:

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

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION DOPAMINERGIC AGONISTS FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about dopaminergic agonists in the treatment of people with generalised dystonia.

Benefits and harms

Dopaminergic agonists:

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

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION DOPAMINERGIC ANTAGONISTS FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about dopaminergic antagonists in the treatment of people with generalised dystonia.

Benefits and harms

Dopaminergic antagonists:

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

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION GABA ANALOGUES FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about GABA analogues in the treatment of people with generalised dystonia.

Benefits and harms

GABA analogues:

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

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION SEROTONERGIC AGONISTS FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about serotonergic agonists in the treatment of people with generalised dystonia.

Benefits and harms

Serotonergic agonists:

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

Further information on studies

Comment: None.

OPTION SEROTONERGIC ANTAGONISTS FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about serotonergic antagonists in the treatment of people with generalised dystonia.

Benefits and harms

Serotonergic antagonists:

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

Further information on studies

Comment: None.

OPTION MUSCLE RELAXANTS FOR GENERALISED DYSTONIA New

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about muscle relaxants in the treatment of people with generalised dystonia.

Benefits and harms

Muscle relaxants:

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

Further information on studies

Comment: None.

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 44 .
- 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 local 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. [37] [38] For details see option on deep brain stimulation in people with generalised dystonia, p 28 .

Further information on studies

Comment: **Clinical guide:**
RCTs with longer follow-up are required (see comment in deep brain stimulation of thalamus and globus pallidus in people with generalised dystonia, p 28).

OPTION **MYECTOMY FOR FOCAL DYSTONIA**

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- 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.

Further information on studies

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 PALLIDOTOMY FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about pallidotomy in the treatment of people with focal dystonia.

Benefits and harms

Pallidotomy:

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

Further information on studies

Comment: See comment on myectomy under surgical treatments for focal dystonia, p 26 .

OPTION SELECTIVE PERIPHERAL DENERVATION FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- 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.

Further information on studies

Comment: See comment on myectomy under surgical treatments for focal dystonia, p 26 .

OPTION THALAMOTOMY FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about thalamotomy in the treatment of people with focal dystonia.

Benefits and harms

Thalamotomy:

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

Further information on studies

Comment: See comment on myectomy under surgical treatments for focal dystonia, p 26 .

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 44 .
- 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. [37] [38]

Neurological disability

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
Neurological disability					
[37] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years	**Improvement in Burke–Fahn–Marsden Dystonia (BFMD) Rating Scale total movement score , 3 months** –15.8 with neurostimulation –1.4 with sham stimulation Change in BFMD score for movement from baseline; possible range of scores of 0 to 120	P <0.001	○○○	neurostimulation
[37] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years	**Improvement in BFMD Rating Scale disability score , 3 months** –3.9 with neurostimulation –0.8 with sham stimulation Change in BFMD score for disability from baseline; possible range of scores of 0 to 30	P <0.001	○○○	neurostimulation

Quality of life

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
Quality of life					
[37] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years	**Improvement in short form (SF)-36 physical component score** 10.1 with neurostimulation 3.8 with sham stimulation Change in SF-36 physical component score; possible range of scores of 0 to 100	P = 0.02 33/40 (82.5%) assessed for this outcome	○○○	neurostimulation
[37] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years	**Improvement in SF-36 mental component score** 5.2 with neurostimulation 0.2 with sham stimulation Change in SF-36 mental component score; possible range of scores of 0 to 100	P = 0.39	⟷	Not significant
[38] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [37]	**Improvement in SF-36 physical function score , 3 months** 27.3 with neurostimulation 3.0 with sham stimulation Change in SF-36 physical function score; possible range of scores of 0 to 100	P = 0.001 36/40 (90%) assessed for this outcome	○○○	neurostimulation
[38] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [37]	**Improvement in SF-36 bodily pain score , 3 months** 22.7 with neurostimulation 9.7 with sham stimulation Change in SF-36 bodily pain score; possible range of scores of 0 to 100	P = 0.04 37/40 (93%) assessed for this outcome	○○○	neurostimulation
[38] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [37]	**Improvement in SF-36 general health score , 3 months** 17.6 with neurostimulation 2.1 with sham stimulation Change in SF-36 general health score; possible range of scores of 0 to 100	P = 0.02 37/40 (93%) assessed for this outcome	○○○	neurostimulation
[38] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [37]	**Improvement in SF-36 vitality score , 3 months** 14.7 with neurostimulation 2.0 with sham stimulation Change in SF-36 vitality score; possible range of scores of 0 to 100	P = 0.047 37/40 (93%) assessed for this outcome	○○○	neurostimulation
[38] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia	**Improvement in SF-36 role physical score , 3 months** 25.0 with neurostimulation 13.2 with sham stimulation	P = 0.20 35/40 (88%) assessed for this outcome	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	(24 people) for a minimum of 5 years Further report of reference [37]	Change in SF-36 role limitations due to physical problems score; possible range of scores of 0 to 100			
[38] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [37]	**Improvement in SF-36 social function score , 3 months** 21.1 with neurostimulation 0.7 with sham stimulation Change in SF-36 social function score; possible range of scores of 0 to 100	P = 0.07 37/40 (93%) assessed for this outcome	⟷	Not significant
[38] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [37]	**Improvement in SF-36 role emotional score , 3 months** 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 to 100	P = 0.43 36/40 (90%) assessed for this outcome	⟷	Not significant
[38] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [37]	**Improvement in SF-36 mental health score , 3 months** 10.7 with neurostimulation 2.0 with sham stimulation Change in SF-36 mental health score; possible range of scores of 0 to 100	P = 0.54 37/40 (93%) assessed for this outcome	⟷	Not significant
[38] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years Further report of reference [37]	**Improvement in Brief Psychiatric Rating Scale , 3 months** –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
Adverse effects					
[37] RCT	40 people aged 14 to 75 years with primary segmental (16 people) or generalised dystonia (24 people) for a minimum of 5 years	**Infection at stimulator site** 1/20 (5%) with neurostimulation 2/20 (10%) with sham treatment	Reported as not significant		

Further information on studies

[37] [38] 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 acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION MYECTOMY FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about myectomy in the treatment of people with generalised dystonia.

Benefits and harms

Myectomy:

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

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 and comment on myectomy under surgical treatments for focal dystonia, p 26 .

OPTION PALLIDOTOMY FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about pallidotomy in the treatment of people with generalised dystonia.

Benefits and harms

Pallidotomy:

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

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 and comment on myectomy under surgical treatments for focal dystonia, p 26 .

OPTION SELECTIVE PERIPHERAL DENERVATION FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about selective peripheral denervation in the treatment of people with generalised dystonia.

Benefits and harms

Selective peripheral denervation:

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

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 and comment on myectomy under surgical treatments for focal dystonia, p 26 .

OPTION THALAMOTOMY FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs about thalamotomy in the treatment of people with generalised dystonia.

Benefits and harms

Thalamotomy:

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

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 and comment on myectomy under surgical treatments for focal dystonia, p 26 .

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 44 .
- 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, RCTs, or controlled clinical trials (see comment).

Physiotherapy versus drug treatment:

We found no systematic review, RCTs, or controlled clinical trials.

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. [39]

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
Neurological disability					
[39] 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	**Improvement in Tsui scale score , end of observation period** –8.1 with botulinum A toxin alone –7.2 with botulinum A toxin plus physical therapy (physiotherapy plus biofeedback) People crossed over to the alternative treatment arm after 45 to 120 days, depending on duration of subjective clinical benefits, confirmed by EMG evaluation Physical therapy involved daily sessions lasting 60 to 90 minutes, for 2 weeks	Reported as no significant difference	⟷	Not significant
[39] 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	**Improvement in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) score , end of observation period** –9.1 with botulinum A toxin alone –10.2 with botulinum A toxin plus physical therapy (physiotherapy plus biofeedback) People crossed over to the alternative treatment arm after 45 to 120 days, depending on duration of subjective clinical benefits, confirmed by EMG evaluation Physical therapy involved daily sessions lasting 60 to 90 minutes, for 2 weeks	Reported as no significant difference	⟷	Not significant
[39] 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	**Improvement in activities of daily living , end of observation period** –5.3 with botulinum A toxin alone –9.8 with botulinum A toxin plus physical therapy (physiotherapy plus biofeedback) People crossed over to the alternative treatment arm after 45 to 120 days, depending on duration	P <0.05	○○○	botulinum toxin A plus physical therapy

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		of subjective clinical benefits, confirmed by EMG evaluation Physical therapy involved daily sessions lasting 60 to 90 minutes, for 2 weeks			
[39] 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	**Total pain score , end of observation period** –7.1 with botulinum A toxin alone –13.0 with botulinum A toxin plus physical therapy (physiotherapy plus biofeedback) People crossed over to the alternative treatment arm after 45 to 120 days, depending on duration of subjective clinical benefits, confirmed by EMG evaluation Physical therapy involved daily sessions lasting 60 to 90 minutes, for 2 weeks	P <0.001	○○○	botulinum toxin A plus physical therapy

Quality of life

No data from the following reference on this outcome. [39]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[39] 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	**Adverse effects , end of observation period** 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, RCTs, or controlled clinical trials.

Further information on studies

[39] 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 crossover 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. [40] 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). [41] 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.

OPTION ACUPUNCTURE FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs or controlled clinical trials about the effects of acupuncture in the treatment of people with focal dystonia.

Benefits and harms

Acupuncture:
We found no systematic review, RCTs, or controlled clinical trials of acupuncture in people with focal dystonia.

Further information on studies

Comment: None.

OPTION BIOFEEDBACK FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found insufficient information from RCTs or controlled clinical trials 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, RCTs, or controlled clinical trials (see comment).

Physiotherapy plus biofeedback plus drug treatment versus drug treatment alone:

See benefits and harms of physiotherapy, p 32 .

Further information on studies

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. [42] It found that clinically significant improvement of dystonia was achieved by 45/80 (56%) of 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.

OPTION CHIROPRACTIC MANIPULATION FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs or controlled clinical trials about chiropractic manipulation in the treatment of people with focal dystonia.

Benefits and harms

Chiropractic manipulation:

We found no systematic review, RCTs, or controlled clinical trials of chiropractic manipulation in people with focal dystonia.

Further information on studies

Comment: None.

OPTION OCCUPATIONAL THERAPY FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs or controlled clinical trials about occupational therapy in the treatment of people with focal dystonia.

Benefits and harms

Occupational therapy:

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

Further information on studies

Comment: None.

OPTION OSTEOPATHY FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs or controlled clinical trials about osteopathy in the treatment of people with focal dystonia.

Benefits and harms

Osteopathy:

We found no systematic review, RCTs, or controlled clinical trials of osteopathy in people with focal dystonia.

Further information on studies

Comment: None.

OPTION SPEECH THERAPY FOR FOCAL DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs or controlled clinical trials about speech therapy in the treatment of people with focal dystonia.

Benefits and harms

Speech therapy:

We found no systematic review, RCTs, or controlled clinical trials of speech therapy for focal dystonia.

Further information on studies

Comment: None.

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 44 .
- We found no direct information from RCTs or controlled clinical trials about acupuncture in the treatment of people with generalised dystonia.

Benefits and harms

Acupuncture:

We found no systematic review, RCTs, or controlled clinical trials of acupuncture in people with generalised dystonia.

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION BIOFEEDBACK FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs or controlled clinical trials about biofeedback in the treatment of people with generalised dystonia.

Benefits and harms

Biofeedback:

We found no systematic review, RCTs, or controlled clinical trials of biofeedback in people with generalised dystonia.

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION CHIROPRACTIC MANIPULATION FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs or controlled clinical trials about chiropractic manipulation in the treatment of people with generalised dystonia.

Benefits and harms

Chiropractic manipulation:

We found no systematic review, RCTs, or controlled clinical trials of chiropractic manipulation in people with generalised dystonia.

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION OCCUPATIONAL THERAPY FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs or controlled clinical trials about occupational therapy in the treatment of people with generalised dystonia.

Benefits and harms

Occupational therapy:

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

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION OSTEOPATHY FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs or controlled clinical trials about osteopathy in the treatment of people with generalised dystonia.

Benefits and harms

Osteopathy:

We found no systematic review, RCTs, or controlled clinical trials of osteopathy in people with generalised dystonia.

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION PHYSIOTHERAPY FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs or controlled clinical trials about physiotherapy in the treatment of people with generalised dystonia.

Benefits and harms

Physiotherapy:

We found no systematic review, RCTs, or controlled clinical trials of physiotherapy in people with generalised dystonia.

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

OPTION SPEECH THERAPY FOR GENERALISED DYSTONIA

- For GRADE evaluation of interventions for Dystonia, see table, p 44 .
- We found no direct information from RCTs or controlled clinical trials about speech therapy in the treatment of people with generalised dystonia.

Benefits and harms

Speech therapy:

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

Further information on studies

Comment: See comment on acetylcholine release inhibitors for generalised dystonia, p 22 .

GLOSSARY

Chiropractic manipulation This involves manipulation of the spine by a chiropractor. It is based on the theory that manipulating the vertebrae helps normal nervous system functioning and the body's ability to heal itself.

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.

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

SUBSTANTIVE CHANGES

Muscle relaxants for focal dystonia New option added. Categorised as Unknown effectiveness, as we found no RCT evidence to assess the effects of this intervention.

Muscle relaxants for generalised dystonia New option added. Categorised as Unknown effectiveness, as we found no RCT evidence to assess the effects of this intervention.

Biofeedback for focal dystonia New evidence added. [39] Categorisation unchanged (Unknown effectiveness) because evidence remains insufficient to judge the effects of this intervention.

Botulinum toxin for focal dystonia New evidence added. [25] [20] Categorisation unchanged (Beneficial).

Deep brain stimulation for generalised dystonia New evidence added. [38] Categorisation unchanged (Unknown effectiveness), because new evidence was a further report of an already included RCT and evidence remains insufficient to judge the effects of this intervention.

Physiotherapy for focal dystonia New evidence added. [39] Existing evidence re-evaluated in line with new stricter inclusion criteria, and two small case series in children with cervical dystonia (previously supporting a categorisation of Likely to be beneficial) were excluded from the benefits and harms section. Categorisation changed from Likely to be beneficial to Unknown effectiveness, because evidence is insufficient to judge the effects of this intervention.

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Ailsa Snaith
Academic Clinical Fellow
Oxford Radcliffe Hospitals Trust
Oxford
UK

Derick Wade
Consultant and Professor in Neurological Rehabilitation
Oxford Centre for Enablement
Oxford
UK

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

Scale	Feature	Interpretation	Range*
Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [14]	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 [15]	Clinician-assessed scale of impairment that grades severity of postural deviance (rotatocollis, 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) [16]	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, anterocollis/retrocollis)		
Jankovic Rating Scale (JRS) [17]	Includes two categories: severity and frequency, each with 5 rating classes of 0–4 points		0–8
Blepharospasm Disability Index (BSDI) [18]	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) [43]	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 (WCRS) [44]	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				Neurological disability, Quality of life					
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of drug treatments for focal dystonia?									
at least 12 (at least 626) [19] [20]	Neurological disability	Botulinum A toxin versus placebo in cervical dystonia in adults	4	0	0	0	0	High	
3 (308) [21]	Neurological disability	Botulinum B toxin versus placebo in cervical dystonia in adults	4	0	0	0	0	High	
3 (252) [23] [24] [25]	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) [27]	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) [21]	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) [26]	Neurological disability	Botulinum A toxin versus anticholinergic drugs (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) [21]	Neurological disability	Botulinum B toxin in botulinum A toxin-resistant versus respondent adults	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (40) [30]	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
What are the effects of surgical treatments for generalised dystonia?									
1 (40) [37]	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) [37] [38]	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
What are the effects of physical treatments for focal dystonia?									

Important outcomes			Neurological disability, Quality of life						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (40) [39]	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

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.