National Institute for Health and Care Excellence

Draft for consultation

Cerebral palsy in adults

[A1] Management of abnormal muscle tone: pharmacological treatments for spasticity

NICE guideline tbc

Evidence reviews

July 2018

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Management of abnormal muscle tone in adults aged 19 and over with cerebral palsy, including spasticity and associated movement disorders such as dystonia

Review question

A1 Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

Introduction

Spasticity is a dynamic increase in the tone of muscles, causing muscles to spasm, or to be tight, and is experienced by some adults with cerebral palsy. Spasticity can limit a person's movement, function and quality of life. When factors that aggravate spasticity have been removed, enteral or intramuscular agents are available to treat the remaining spasticity. The aim of this review is to evaluate the effectiveness of pharmacological treatments for spasticity.

PICO table

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults aged 19 years and over with cerebral palsy and spasticity (at least 50% of study population should be 18 years or older)
Intervention	Enteral • Baclofen • Dantrolene • Tizanidine • Diazepam • Gapapentin/pregabalin • Cannabinoids • Botulinum toxin injections
Comparison	• Each other • Placebo/no treatment

Outcome	**Critical**
	• Motor function
	  ○ Swallowing problems
	  ○ Goal Attainment Scale (GAS)
	  ○ Functional Independence Measure (FIM)
	• Muscle tone
	• Health-related quality of life
	• Treatment related adverse events
	  ○ Swallowing problems
	  ○ Seizure threshold

	○ Undue weakness/loss of function – use of spasticity positively ○ Drowsiness and cognitive change ○ Specific problems in people with low proximal tone and high peripheral tone **Important** • Patient or carer reported satisfaction • Participation

For full details see the review protocol in appendix A

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A and for a full description of the methods see supplementary document C.

Declaration of interests were recorded according to NICE's 2014 conflicts of interest policy from May 2016 until April 2018. From April 2018 onwards they were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Interests Register).

Clinical evidence

Included studies

Three studies (N=139) were included in this systematic review (Griffiths 1964, Maanum 2011 and Marchiori 2014).

Griffiths 1964 was a randomised, double-blind crossover study evaluating the spasmolytic effect of oral diazepam compared to placebo in people with severe forms of cerebral palsy.

The other 2 studies examined the effectiveness of botulinum toxin compared to placebo or standard care. Maanum 2011 was a single centre, double-blind, placebo controlled randomised clinical trial assessing the short term effects of botulinum toxin A in ambulant adults with cerebral palsy and spasticity.

Marchiori 2014 was a before-and-after study evaluating the effects of a single multi-site botulinum toxin injection on spatiotemporal and kinematic parameters of adults with cerebral palsy. In addition, this study evaluated if the Gait Deviation Index (GDI) can be used to detect global changes in gait following the administration of botulinum toxin.

The clinical studies included in this evidence review are summarised in Table 2 and evidence from these is summarised in the clinical evidence profiles below (Table 3 and

Table 4).

See also the literature search strategy in appendix B, study selection flow chart in appendix C, forest plots in appendix E and study evidence tables in appendix D.

Excluded studies

Studies excluded from this systematic review, with reasons for their exclusion, are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies.

Table 2: Summary of included studies

Study	Design	Participants	Comparisons	Outcomes
Griffiths 1964	Randomised, crossover study	50 people with severe forms of cerebral palsy (age 12 to 73 years; mean 32 years). United Kingdom	Oral diazepam versus placebo	• Muscle tone • Treatment related adverse effects
Maanum 2011	Randomised controlled trial	66 ambulant adults with cerebral palsy and spasticity (age 18 to 65 years; mean 37 years). Norway	Botulinum toxin A injection versus placebo	• Motor function • Muscle tone • Health-related quality of life • Patient or carer reported satisfaction
Marchiori 2014	Observational before-and-after study	23 ambulant adults with cerebral palsy and spasticity (age 18 to 36 years; mean 25 years). France	Single multi-site botulinum toxin injection versus pre-injection.	• Motor function

See appendix D for full evidence tables.

Quality assessment of clinical outcomes included in the evidence review

The clinical evidence profiles for this review question are presented in Table 3 and Table 4.

Table 3: Summary clinical evidence profile: Comparison 1: Botulinum toxin A versus no treatment or placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participant (studies)	Quality of the evidence (GRADE)
	Assumed risk: no treatment/placebo	Corresponding risk: botulinum toxin A			
Motor function 6 Minute Walk Test Follow up: 8 weeks	The mean change from baseline in the control group was 11.0 metres higher	The adjusted mean change from baseline in the intervention group was 7.9 metres higher (8.3 lower to 24.1 higher)	-	65 (1 RCT)	Low[1, 2]
Motor function Timed Up and Go Follow up: 8 weeks	The mean change from baseline in the control group was 0.14 min lower	The adjusted mean change from baseline in the intervention group was 0.21 min lower (0.6 lower to 0.2 higher)	-	65 (1 RCT)	Low[1, 2]

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participant (studies)	Quality of the evidence (GRADE)
	Assumed risk: no treatment/placebo	Corresponding risk: botulinum toxin A			
Motor function Gait Deviation Index Follow up: 1 month	The authors observed a mean reduction of 3.2 points (p = 0.02; which did not meet the MID of 4 points) between pre- and post-assessment. The 95% CI were not reported			23 (1 observational study)	Very low[2,3,4]
Muscle tone – Muscle stiffness/spasticity visual analogue scale. Follow up: 8 weeks	The mean change from baseline in the control group was 5.1 lower	The adjusted mean difference in the intervention group was 9.6 lower (18.7 lower to 1.2 lower)	-	65 (1 RCT)	Low[1, 2]
Health related quality of life – Short Form 36 (SF-36) – mental health dimension Follow up: 8 weeks	Mean change from baseline in the control group was 1.6 higher	The adjusted mean difference in the intervention group was 1.4 higher (4.4 lower to 7.2 higher)	-	65 (1 RCT)	Low[1, 2]
Health related quality of life – SF-36 – vitality dimension Follow up: 8 weeks	Mean change from baseline in the control group was 5.0 higher	The adjusted mean difference in the intervention group was 0.27 lower (7.8 lower to 7.7 higher)	-	65 (1 RCT)	Low[1, 2]
Health related quality of life – SF-36 – bodily pain dimension Follow up: 8 weeks	Mean change from baseline in the control group was 8.1 higher	The adjusted mean difference in the intervention group was 4.4 lower (12.9 lower to 4.2 higher)	-	65 (1 study)	Low[1, 2]
Health related quality of life – SF-36 – general health dimension Follow up: 8 weeks	Mean change from baseline in the control group was 4.2 higher	The adjusted mean difference in the intervention group was 4.7 lower (11.8 lower to 2.4 higher)	-	65 (1 RCT)	Low[1, 2]
Health related quality of life –	Mean change from baseline	The adjusted mean	-	65 (1 RCT)	Low[1, 2]

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participant (studies)	Quality of the evidence (GRADE)
	Assumed risk: no treatment/placebo	Corresponding risk: botulinum toxin A			
SF-36 – social function dimension Follow up: 8 weeks	in the control group was 0.8 higher	difference in the intervention group was 3.4 higher (4.0 lower to 10.9 higher)			
Health related quality of life – SF-36 – physical function dimension Follow up: 8 weeks	Mean change from baseline in the control group was 3.9 higher	The adjusted mean difference in the intervention group was 1.2 lower (7.6 lower to 5.2 higher)	-	65 (1 RCT)	Low[1, 2]
Health related quality of life – SF-36 – role physical dimension Follow up: 8 weeks	Mean change from baseline in the control group was 9.1 higher	The adjusted mean difference in the intervention group was 11.6 lower (29.1 lower to 5.9 higher)	-	65 (1 RCT)	Low[1, 2]
Health related quality of life – SF-36 – role emotional dimension Follow up: 8 weeks	Mean change from baseline in the control group was 2.0 higher	The adjusted mean difference in the intervention group was 5.7 higher (8.1 lower to 19.5 higher)	-	65 (1 RCT)	Low[1, 2]
Treatment related adverse events – Not reported	-	-	-	-	-
Patient or carer reported satisfaction – Number of patients reporting a positive treatment effect on a three point global verbal scale	273 per 1000	595 per 1000 (316 to 1000)	RR 2.18 (1.16 to 4.07)	65 (1 RCT)	Low[1, 2]

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participant (studies)	Quality of the evidence (GRADE)
	Assumed risk: no treatment/placebo	Corresponding risk: botulinum toxin A			
Follow up: 8 weeks					
Participation – Not reported	-	-	-	-	-

CI: confidence interval; MID, minimally important difference; RR: risk ratio; SF-36: 36 item short form survey.
1 Downgraded for serious indirectness as the participants were highly functioning adults with cerebral palsy. Patients with cognitive impairment were excluded from this study
2 Downgraded for serious imprecision due to sample size < 400 or number of events < 300
3 Downgraded for serious risk of bias due to the risk of selective reporting identified in this study
4 Downgraded for serious indirectness as the control participants in this before and after study were healthy participants

Table 4: Summary clinical evidence profile: Comparison 2: oral diazepam versus no treatment or placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)
	Assumed risk: no treatment/placebo	Corresponding risk: diazepam			
Motor function – Not reported	-	-	-	-	-
Muscle tone – Number of participants identified as becoming 'slightly better' during a clinical assessment using a standardised form Follow up: 6 weeks	The authors identified one participant who became slightly better after receiving diazepam, and one participant who became slightly better after receiving the control (inactive) tablet			50 (1 study)	Very low[1, 2]
Health related quality of life – Not reported	-	-	-	-	-
Treatment related adverse events – Number of adverse events reported Follow up: 6 weeks	Drowsiness was reported in 13 participants, anorexia in four, slurring of speech in two, depression in one, vomiting in four, abdominal pain in one, aggressive tendencies in two, and a faint localised rash in one. Each patient could have experienced more than one adverse event; however, this was not reported.			50 (1 study)	Very low[2,3]
Patient or carer reported	-	-	-	-	-

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)
	Assumed risk: no treatment/placebo	Corresponding risk: diazepam			
satisfaction – Not reported					
Participation – Not reported	-	-	-	-	-

CI: confidence interval.
1 Downgraded for serious indirectness as the participants were some of the "most severely affected" patients with cerebral palsy
2 Downgraded for serious imprecision due to sample size < 400 or number of events < 300, and the lack of adequate inferential analyses
3 Downgraded for serious indirectness as the participants were some of the "most severely affected" patients with cerebral palsy, and the definition of the outcome does not allow for a comparison between the two treatment periods to be made.

See appendix F for the full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no studies were identified which were applicable to this review question.

Excluded studies

No studies were identified which were applicable to this review question.

Summary of studies included in the economic evidence review

No economic evaluations were included in this review.

Economic model

This question was not prioritised for economic modelling although the committee considered there may be some resource impact associated with botulinum toxin injections. Therefore a cost description was undertaken to aid considerations of resource impact and cost effectiveness.

Resource impact

The Committee advised that all pharmacological treatments for spasticity (oral or intravenous) should be initiated by a specialist clinic neurologist/rehabilitation medicine consultant, specialist nurse or specialist prescribing physiotherapist. According to NHS Reference Costs 2015/16 the first attendance for a pre-assessment would cost £217 (currency code WF01B, service code 400, non-admitted face-to-face attendance, first, neurology). However, GPs who have experience in managing spasticity may prescribe pharmacological treatments without an onward referral. According to the unit costs of health and social care, one attendance with a GP would cost £36 (PSSRU 2016 including indirect care staff costs and qualifications, per patient contact lasting 9.22 minutes) whilst a prescription would cost an additional £28 (PSSRU 2016). The resource and costs following an "eligible" assessment, for all pharmacological interventions for which evidence was searched, are described below.

Oral pharmacological treatments

Drug acquisition costs in Table 5 are taken from the NHS Electronic Drug Tariff July 2018. Dosage in the BNF 75 were verified with the committee to ensure the dosages were appropriate for this patient group.

Table 5: Drug acquisition cost for oral pharmacological treatments

Treatment	Pack size	Basic price	Price per unit
Enteral baclofen [a]			
Baclofen 10mg tablets	84	£1.08	£0.01
Baclofen 5mg/5ml oral solution sugar free	300ml	£2.76	£0.05/ 5ml
Dantrolene [b]			
Dantrolene 100mg capsules	100	£43.07	£0.43
Dantrolene 25mg capsules	100	£16.87	£0.17
Tizanidine [c]			
Tizanidine 2mg tablets	120	£3.21	£0.03
Tizanidine 4mg tablets	120	£39.70	£0.33
Diazepam [d]			
Diazepam 10mg tablets	28	£0.53	£0.02
Diazepam 10mg/2.5ml rectal solution tube	5	£7.35	£3.68/ 2.5ml
Diazepam 10mg/2ml solution for injection ampoules	10	£5.50	£1.10/ 2ml
Diazepam 2mg tablets	28	£0.45	£0.02
Diazepam 2mg/5ml oral solution sugar free	100ml	£31.75	£1.59/ 5ml
Diazepam 2mg/5ml oral suspension	100ml	£31.75	£1.59/ 5ml
Diazepam 5mg tablets	28	£0.48	£0.02
Diazepam 5mg/2.5ml rectal solution tube	5	£5.85	£1.17/ 2.5ml
Gabapentin [e]			
Gabapentin 100mg capsules	100	£1.87	£0.02
Gabapentin 300mg capsules	100	£4.82	£0.05
Gabapentin 400mg capsules	100	£4.96	£0.05
Gabapentin 50mg/ml oral solution sugar free	150ml	£68.24	£0.46/ 1ml
Gabapentin 600mg tablets	100	£6.14	£0.06
Gabapentin 800mg tablets	100	£26.59	£0.27
Pregabalin [f]			
Pregabalin 100mg capsules	84	£5.56	£0.07
Pregabalin 150mg capsules	56	£4.01	£0.07
Pregabalin 200mg capsules	84	£5.55	£0.07
Pregabalin 20mg/ml oral solution sugar free	473ml	£99.48	£0.21/ 1ml
Pregabalin 225mg capsules	56	£3.95	£0.07
Pregabalin 25mg capsules	56	£4.15	£0.07
Pregabalin 300mg capsules	56	£4.11	£0.07
Pregabalin 50mg capsules	84	£5.34	£0.06
Pregabalin 75mg capsules	56	£3.87	£0.07
Cannabinoids [g]			
Sativex oromucosal spray (Bayer Plc) Cannabidiol 2.5 mg per 1 dose Dronabinol 2.7 mg per 1 dose	270	£375.00[h]	£1.39[h]

(a) Enteral baclofen. BNF: Chronic severe spasticity resulting from disorders such as multiple sclerosis or traumatic partial section of spinal cord. By mouth, adult: initially 5 mg 3 times a day, gradually increased;

maintenance up to 60 mg daily in divided doses, review treatment if no benefit within 6 weeks of achieving maximum dose: maximum 100 mg per day.

(b) Dantrolene. BNF: Chronic severe spasticity of voluntary muscle. By mouth, adult: initially 25 mg daily, then increased up to 100 mg 4 times a day, dose increased at weekly intervals; usual dose 75 mg 3 times a day. GC advised a maximum of 100 mg 4 times per day.

(c) Tizanidine. BNF: Spasticity associated with multiple sclerosis or spinal cord injury or disease. By mouth, adult: initially 2 mg daily, then increased in steps of 2 mg daily in divided doses, increased at intervals of at least 3-4 days and adjust according to response; usual dose up to 24 mg daily in 3-4 divided doses; maximum 36 mg per day.

(d) Diazepam. Committee advise 2 mg once daily to a maximum of 10 mg 3 times per days.

(e) Gabapentin is not currently licensed for use in cerebral palsy. The committee advise dosage for that of focal seizures. BNF: Monotherapy for focal seizures with or without secondary generalisation. By mouth, adult: initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2-3 days in 3 divided doses, adjusted according to response; usual dose 0.9-3.6 g daily in 3 divided doses.

(f) Pregabalin is not currently licensed for use in cerebral palsy. The committee advise dosage for that of focal seizures. BNF: Adjunctive therapy for focal seizures with or without secondary generalisation. By mouth, adult: initially 25 mg twice daily, then increased in steps of 50 mg daily, dose to be increased at 7 day intervals, increased to 300 mg daily in 2-3 divided doses for 7 days, then increased if necessary up to 600 mg daily in 2-3 divided doses.

(g) Sativex is not currently licensed for use in cerebral palsy. GC advise 1-12 sprays daily.

(h) Not available in drug tariff so price taken from BNF 75

The oral treatments under consideration would not incur administration costs as they would be administered at home, without healthcare professional assistance.

Enteral baclofen, diazepam, gabapentin and pregabalin would be monitored by the patient's GP and by the community team at routine visits. For tizanidine this would also include liver function tests because hepatic dysfunction has been reported in association with tizanidine but rarely at daily doses up to 12mg, it is recommended that liver function tests should be monitored monthly for the first four months in patients receiving doses of 12mg and higher and in patients who develop clinical symptoms suggestive of hepatic dysfunction, such as unexplained nausea, anorexia or tiredness (see Summary of Products Characteristics).

Cannabinoids on the other hand, should be monitored at least every 6 months by a specialist in secondary or tertiary care, because of their expertise and selection criteria. According to NHS Reference Costs 2015/16, a follow-up visit would cost £161 (currency code WF01A, service code 400, non-admitted face-to-face attendance follow-up, neurology).

Botulinum toxin injections

The acquisition cost of botulinum toxin is reproduced from the BNF in Table 6.

Table 6: Drug acquisition cost for botulinum toxin

Treatment	Pack size	Basic price	Price per unit
Botulinum toxin type A			
Botox 50 unit powder for solution for injection vials (Allergan Ltd)	1	£77.50	£77.50
Xeomin 50 unit powder for solution for injection vials (Merz Pharma UK Ltd)	1	£72.00	£72.00
Botox 100 unit powder for solution for injection vials (Allergan Ltd)	1	£138.20	£138.20
Xeomin 100 unit powder for solution for injection vials (Merz Pharma UK Ltd)	1	£129.90	£129.90
Botox 200 unit powder for solution for injection vials (Allergan Ltd)	1	£276.40	£276.40
Xeomin 200 unit powder for solution for injection vials (Merz Pharma UK Ltd)	1	£259.80	£259.80

Treatment	Pack size	Basic price	Price per unit
Dysport 300 unit powder for solution for injection vials (Ipsen Ltd)	1	£92.40	£92.40
Dysport 500 unit powder for solution for injection vials (Ipsen Ltd)	2	£308.00	£154.00

The administration of botulinum toxin involves a day-case admission performed by a neurologist, or a specially trained physiotherapist or nurse in a specialist clinic. Adults with cerebral palsy are unlikely to be sedated, but ultrasound or electromyography may be used for guidance.

The appointment for the injection of botulinum toxin has a NHS reference cost assigned – Torsion dystonia and other involuntary movements drugs band 1 (code XD09Z). This reference cost (£324) will include all costs related to the procedure, the day case admission, drug costs and staff costs.

Following an injection, patients would be monitored every 3 to 4 months by the specialist clinic at a cost of £161 (NHS Reference Costs 2015/16, currency code WF01A, service code 400, non-admitted face-to-face attendance follow-up, neurology) to assess their response and need for repeat injections.

Evidence statements

Comparison 1: Botulinum toxin A versus no treatment or placebo

Critical outcomes

Motor function

- Low quality evidence from one randomised trial including 65 people showed no clinically important difference between intramuscular injections of botulinum toxin A and placebo for motor function (as measured by the 6 Minute Walk index).
- Low quality evidence from one randomised trial including 65 people showed no clinically important difference between intramuscular injections of botulinum toxin A and placebo for motor function (as measured by the ‘Timed Up and Go’ index).
- Very low quality evidence from one observational study including 23 people showed no clinically important improvement in motor function (as measured by the Gait Deviation Index) following a single multi-site botulinum toxin injection.

Muscle tone

- Low quality evidence from one randomised trial including 65 people showed a clinically important beneficial effect of intramuscular injections of botulinum toxin A compared with placebo for muscle tone.

Health related quality of life

- Low quality evidence from one randomised trial including 65 people showed no clinically important difference between intramuscular injections of botulinum toxin A and placebo for quality of life for any of the dimensions of the SF-36 survey.

Treatment related adverse events

- No evidence was found for this outcome.

Important Outcomes

Patient or carer reported satisfaction

- Low quality evidence from one randomised trial including 65 people showed a clinically important beneficial effect of intramuscular injections of botulinum toxin A compared to placebo in terms of self-reported positive treatment effect.

Participation

- No evidence was found for this outcome.

Comparison 2: Oral diazepam versus no treatment or placebo

Critical Outcomes

Motor function

- No evidence was found for this outcome.

Muscle tone

- Very low quality evidence from one randomised study including 50 people showed no clinically important difference between oral diazepam and placebo in terms of muscle tone.

Health related quality of life

- No evidence was found for this outcome.

Treatment related adverse events

- Very low quality evidence from one randomised study including 50 people about rates of adverse events was not reported in a way that allowed a comparison between diazepam and placebo.

Important Outcomes

Patient or carer reported satisfaction

- No evidence was found for this outcome.

Participation

- No evidence was found for this outcome.

Recommendations

A1.1 When considering any treatments for spasticity or dystonia, discuss with the adult with cerebral palsy (and their families and carers, if agreed):

- treatment goals (and document them) **and**
- the benefits and risks of treatments (for example, the risk of deterioration in function) as part of their multidisciplinary treatment strategy.

For further information on supporting people to actively participate in their care and shared decision-making see NICE's guideline on patient experience in adult NHS services.

A1.2 Be aware that adults with cerebral palsy may have both spasticity and dystonia. The severity of symptoms for both conditions may fluctuate in response to health, social and environmental factors.

A1.3 At every review, discuss with the person with cerebral palsy (and their families and carers, if agreed) factors that may exacerbate their spasticity or dystonia, such as:

- bladder problems (for example, urinary tract infection or bladder stones)
- constipation
- emotional distress
- pain
- posture
- pressure sores
- changes in home or work environments, including seating
- medication changes and side effects.

A1.4 Address any modifiable factors identified that may be exacerbating spasticity or dystonia before discussing further management options with the adult with cerebral palsy.

A1.5 Discuss with the person with cerebral palsy (and their families and carers, if agreed) the balance between benefits and harms of treating spasticity and dystonia. In particular, explain that some people use their spasticity or dystonia to help their posture and ability to stand, walk or transfer, and that treatment may affect this.

A1.6 Consider enteral[a] baclofen as the first-line drug treatment for adults with cerebral palsy and generalised spasticity causing:

- functional impairment **or**
- pain **or**
- spasms.

A1.7 Start enteral baclofen[a] treatment with a low dose and increase the dose gradually over about 4 weeks to achieve the optimum therapeutic effect.

A1.8 If enteral baclofen[a] is ineffective or not tolerated by adults with cerebral palsy and generalised spasticity:

- refer the person to a tone or spasticity management service **or**
- discuss other drug treatment options (including other enteral muscle relaxants) with a tone management specialist.

A1.9 Do not offer diazepam for spasticity in adults with cerebral palsy, except in an acute situation when spasticity is causing severe pain or anxiety.

A1.10 Do not rapidly withdraw muscle relaxant drugs if the adult with cerebral palsy has been taking them for more than a few weeks. Reduce the dose gradually to avoid withdrawal symptoms.

A1.11 Consider referring adults with cerebral palsy for botulinum toxin type A treatment if:

- they have spasticity in a limited number of muscle groups that is:
  - affecting their care (such as hygiene or dressing) **or**
  - causing pain **or**
  - impairing activity and participation, **or**
- a tone management specialist agrees that treatment targeted to focal muscle groups is likely to improve function and symptoms.

[a] At the time of consultation (July 2018) oral formulations are usually not licensed to be given via an enteral feeding tube so administration via this route would be off-label. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Research recommendations

Is guided botulinum toxin type A injection using electrical localisation (electrical stimulation or electromyography) of muscles more effective and cost-effective than ultrasound guided or clinical positioning for localisation of injections in treating focal spasticity in adults with cerebral palsy?

Rationale and impact

Why the committee made the recommendations

Initial management of spasticity and dystonia

The committee noted that there is a lack of understanding about the relationship between spasticity and dystonia. Based on their experience, they agreed that a better understanding of these conditions and the factors that affect them is likely to lead to more effective decisions about management. They discussed factors that commonly trigger or worsen symptoms of both spasticity and dystonia, and their concerns that these may sometimes go unrecognised.

The committee also discussed the balance of benefits and risks of treatment to reduce spasticity and dystonia. In particular, some people with cerebral palsy make functional use of their increased muscle tone from spasticity and dystonia, for example to help them walk or transfer independently. For these people a reduction in spasticity or dystonia could have a negative impact on function. To ensure informed decision-making, the risks and benefits of treatment should be discussed with each person and specific treatment goals should be agreed.

There was limited evidence on treatments for spasticity and dystonia in adults with cerebral palsy, but based on their experience and expertise the committee agreed on a stepwise approach to treatment dependant on tolerability and effectiveness. This is from the least invasive to the most invasive treatment option, which is reflected in the order of recommendations in the individual sections:

- first identifying and managing any factors that might be exacerbating their symptoms and considering a physical management programme
- next considering enteral (oral or via a feeding tube) drug treatment and referral
- then considering more invasive options.

Drug treatment for spasticity

Enteral muscle relaxant drug treatments

No evidence was identified on using enteral baclofen for treating spasticity in adults with cerebral palsy. However, the committee discussed the evidence reviewed for NICE's guideline on spasticity in under 19s, and agreed that this could be extrapolated to the adult population. There was limited evidence of effectiveness in children and young people, but the committee agreed that it was sufficient, supported by their experience, for enteral baclofen to be considered as a first-line treatment for generalised spasticity causing functional impairment, pain or spasms.

The evidence on enteral diazepam showed no improvement in muscle tone, and side effects such as drowsiness, vomiting and abdominal pain were recorded. The committee agreed that it should not be offered routinely to treat spasticity because of the risk of adverse events and also of dependency. However, evidence from NICE's guideline on spasticity in children and

young people and the committee's experience suggested that diazepam can be beneficial in the short-term management of pain and anxiety in acute situations.

There was no evidence for any other medicines. However, based on their experience in current practice, the committee acknowledged that alternative drug treatments are available that might be beneficial for some people if enteral baclofen is ineffective or not tolerated. The committee agreed that in these situations specialist advice or referral to specialist services is warranted to consider further treatment options.

Severe symptoms, such as life-threatening seizures, are associated with rapid withdrawal of enteral muscle relaxants, so the committee highlighted the importance of gradual withdrawal of these treatments.

Botulinum toxin type A injections

There was some evidence that botulinum toxin type A injections improved muscle tone in adults with cerebral palsy and spasticity. However, the evidence was limited, and this treatment is more invasive and costly than alternative muscle relaxant drug treatment. For these reasons, the committee agreed that it should only be considered for people with focal spasticity and difficulties with their symptoms, who might gain the most benefit from the treatment, or if a specialist agrees that it is likely to be of benefit.

The committee discussed that botulinum toxin type A injections should be given by an experienced specialist. This is important because the injections need to be accurately placed for successful treatment and to avoid side effects. They acknowledged that some healthcare professionals use ultrasound, electrical stimulation or electromyography to help guide the injections, but noted that the benefits and cost effectiveness of these techniques are uncertain. Additional resources are associated with these techniques; for equipment and training, and for an ultrasonographer or radiologist for ultrasound-guided injections. Therefore, the committee developed a research recommendation to help determine the most effective method for ensuring accurate positioning of these injections.

Impact of the recommendations on practice

Overall, the recommendations reflect current good practice and will help to eliminate variation, particularly in referrals to tone or spasticity management services.

The recommendation to consider enteral baclofen as a first-line option to manage spasticity should not lead to a large increase in costs as enteral baclofen is relatively cheap and is already widely used as a first-line option. Despite this, the committee were unable to make a stronger recommendation because there was no comparative clinical evidence that baclofen was the most effective option.

There was clinical evidence to suggest the cost of botulinum toxin could be outweighed by its benefits when treating focal spasticity. The focus on referral for focal spasticity that is causing pain, impacting care, or impairing activity is likely to reduce the number of inappropriate referrals.

Any additional costs of specialist input is expected to be balanced by a reduction in potentially inappropriate treatment and related adverse effects. There may be a change to practice because enteral diazepam will no longer be prescribed routinely, and this may result in a small cost saving.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Spasticity is characterised by stiffness and a wide range of involuntary muscle spasms (sustained muscle contractions or sudden movements). The committee therefore prioritised outcomes related to motor function (such as gross motor function, muscle tone) they also agreed that this would have an impact on health-related quality of life as would any treatment related adverse events. Therefore all of these outcomes were critical when comparing pharmacological treatments for spasticity. The committee agreed that treatments should be satisfactory to patients and that it may also improve participation. These were considered as important outcomes.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. The identified evidence related only to oral diazepam and botulinum toxin A injections. For the botulinum toxin compared to placebo evidence reported outcomes related to motor function, muscle tone, health related quality of life and patient satisfaction. Only patient satisfaction was improved by botulinum toxin A treatment. The quality of evidence for all outcomes was affected by imprecision around the effect sizes which was due to the low sample size. The evidence was therefore very low to low quality according to GRADE criteria. In the comparison between diazepam and placebo only two outcomes were reported (muscle tone and treatment related adverse events). However, both outcomes were poorly reported (one on a non-validated scale' and in the other it was unclear whether there were people with more than one adverse event). It was impossible to calculate an effect size and evidence could only be reported narratively. This evidence was therefore rated as very low quality. This made interpretation of all evidence uncertain. No evidence about enteral baclofen, dantrolene, tizanidine, gabapentin/pregabalin and cannabinoid treatment was identified.

The committee noted that studies used selective populations. Committee members noted that one study comparing botulinum toxin A with placebo excluded adults with cognitive impairments whereas another study comparing oral diazepam with placebo only included adults with severe cerebral palsy. They therefore decided that it would be difficult to extrapolate findings from this evidence.

Only one study was a parallel arm randomised controlled trial. The before and after study and the cross-over trial had inherent study limitations that made the committee less confident in the findings.

Due to the low quality of the evidence, the committee based their recommendations mainly on their expertise and experience.

Benefits and harms

The committee agreed, based on their knowledge, that the risks and benefits of any treatments should be discussed with each person before treatment is initiated and specific treatment goals are agreed. In relation to potentially positive or negative effects of increased tone, the committee highlighted that goals need to be clearly set out and that this should also feature in multidisciplinary team discussions to assess potential changes in function. This would also lead to better shared decision making and would inform the assessment of whether or not treatments are effective.

Based on their experience the committee discussed that the relationship between spasticity and dystonia is not always clear to healthcare professionals and that better knowledge of this would lead to more effective shared decision. To highlight the complexity of conditions of

abnormal muscle tone they therefore decided to describe that adults with cerebral palsy can have both spasticity as well as dystonia, and that symptom severity may vary.

The committee, based on their experience and expertise, agreed that there are a number of factors that can contribute to, or exacerbate, both spasticity and dystonia. They highlighted those factors that are most commonly associated with spasticity or dystonia and that are not always recognised as such. Identifying and addressing these improves the effectiveness of any multidisciplinary spasticity treatment strategy by focusing the management plan (for example if spasticity is exacerbated by pressure sores or constipation, then a treatment plan should address these factors first).

Based on their experience and expertise, the committee considered that treatment of both spasticity and dystonia can reduce pain and improve sleep, has an impact on motor function and can improve quality of life. The difference between spasticity, voluntary resistance and contractures requires careful assessment and it may not be possible to tell them apart in one assessment, or until treatment is initiated where movement is severely restricted. The committee discussed that spasticity as well as dystonia can have a positive impact on motor function. Some people with cerebral palsy make functional use of their increased muscle tone from spasticity and dystonia, for example to help them walk. For these people reduction in spasticity or dystonia could have a negative impact on certain motor functions, for example loss of their ability to transfer independently. However, severe spasticity can also have a negative impact on motor function as increased muscle tone can limit function.

The committee, based on their experience, recommended a stepwise approach to interventions for spasticity, dependant on tolerability and effectiveness.

As described above this should start with non-pharmacological interventions that address the contributing or exacerbating factors and include a physical management programme (covered in evidence review document D2 on physical function).

For prescribing enteral (oral or tube) baclofen in primary/community care, the committee acknowledged that, even though no direct evidence in adults was identified, there was evidence for the effectiveness of enteral baclofen in children and young people. For example, there was evidence from randomised controlled trials in children receiving enteral baclofen which showed that there were improvements in muscle spasms (reductions in tone in lower-extremity as well as upper muscle groups - see NICE guideline Spasticity in under 19s, CG145, 2016). They were aware of potential adverse effects of oral baclofen including nausea and drowsiness, however these were usually tolerable. The committee decided that these findings could be extrapolated to adults with cerebral palsy since the pharmacokinetic and pharmacodynamic properties would be similar in adults. They therefore agreed that this would be the least invasive effective option for adults. However, since there was a lack of direct evidence, they decided to make a weak recommendation for the enteral use of this intervention.

The committee considered the weak evidence related to the use of diazepam to treat spasticity in adults with cerebral palsy. There was very low quality evidence of a number of adverse events (for instance drowsiness, vomiting and abdominal pain) that were reported by people who received diazepam. Even though they did not have much confidence in the evidence, the committee agreed that such adverse events related to diazepam were consistent with their clinical experience along with the known problems of tolerance and dependency. They therefore decided not to recommend diazepam to treat spasticity in adults with cerebral palsy. Based on their experience and expertise and evidence of some benefit in children and young people (in the Spasticity in under 19s: management NICE guideline), it was also discussed that diazepam can have a short term benefit related to the management of pain and anxiety particularly in acute situations, where the side effects on the level of consciousness and breathing can be monitored in vulnerable patients, or at the end of life. The committee agreed that the routine long-term use of diazepam in the management of

spasticity should be discouraged, but that there are exceptional circumstances where it could have a short-term benefit.

The committee was aware of severe symptoms, such as life-threatening seizures, confusion and hallucinations associated with rapid withdrawal of enteral muscle relaxants and so recommended tapered withdrawal to minimise this risk.

Regarding referral to, or discussion with, a tone or spasticity management service for further pharmacological options, there was no evidence for the effectiveness and safety of other enteral pharmacological options. Therefore, the committee decided that adults with cerebral palsy and spasticity who do not tolerate enteral baclofen, or for whom it is ineffective, should be referred to a tone management service. The committee recommended that decisions about any further pharmacological treatments should only be made after referral to such specialist tone management services because of the number of treatment related adverse events.

Based on their expertise and experience, they recommended that botulinum toxin A should only be used for focal spasticity in a limited number of muscles to ensure effectiveness and minimise side effects as it is a neurotoxic substance. The committee agreed that healthcare professionals in such services can tailor, using their clinical judgement, other options (potential non-pharmacological options – see evidence review document A2) taking into account the risks and benefits in relation to the needs and goals of the individual adult with cerebral palsy and spasticity.

Due to the limited evidence, the committee made a research recommendation about how to inject botulinum toxin A. This is important because accurate placement of intramuscular botulinum toxin A is needed for efficacy and to avoid side effects. Localisation of muscles to be injected can be achieved with muscle stimulation, electromyography (EMG) signal or ultrasound to support anatomical knowledge. These techniques require equipment and training in the use of equipment and interpretation of results. Use of ultrasound may require the presence of an ultrasonographer or radiologist in addition to the clinician giving the injection. Further research could therefore provide important information on the comparative effectiveness of these techniques.

Cost effectiveness and resource use

The committee noted that no relevant published economic evaluations had been identified for this topic.

The committee recognised that if spasticity is exacerbated by factors such as pain and emotional distress that are not identified and managed appropriately, they can negatively impact on participation and quality of life. Therefore, knowing what factors can exacerbate spasticity may lead to increased vigilance and thus more timely management which would be cost neutral or cost saving.

The recommendation to offer enteral baclofen as a first line option to manage spasticity should not lead to a large increase in costs as enteral baclofen is relatively cheap with a maintenance dose of 60mg a day (in divided doses) costing £0.12 (NHS Electronic Drug Tariff May 2017: 1x10mg tablet, £0.02) and is already widely used in current clinical practice as a first line option. Despite this, the committee were unable to make a stronger recommendation as there was no comparative clinical evidence that baclofen was the most effective option.

The committee referred to the evidence that diazepam provided no additional benefit compared to placebo and agreed that relatively cheap treatments should not be recommended if they are ineffective. The committee also noted that adults with cerebral palsy are frequently prescribed diazepam in primary care when alternative options should be

explored. For this reason, the committee made a recommendation to not routinely prescribe diazepam to stop the use of limited resources on ineffective practices.

The committee noted that general practitioners in primary care prescribe treatments for spasticity, but agreed they should refer to, or discuss with, healthcare professionals who have experience in tonal disorders, when spasticity is causing problems with pain or impaired function, to ensure the assessment and subsequent management is appropriate for each individual. The committee agreed that the cost of specialist input would be offset by the downstream costs from potentially inappropriate management and the missed adverse effects of treatment.

The committee noted that no one should remain on cheap treatments that are ineffective, as the burden of treatment and long-term cost, including the cost to manage their potential adverse events could be substantial. However, it is important to note that muscle relaxants should be discontinued gradually, to minimise withdrawal symptoms such as anxiety and distress, as those symptoms would offset the cost of immediate discontinuation.

If baclofen is ineffective or not tolerated, the committee stated that alternative pharmacological treatments such as tizanidine, dantrolene or gabapentin would be considered for generalised spasticity. However, there was no evidence for the effectiveness of these and all of them are associated with a number of possible adverse effects. The committee recommended that decisions about any further pharmacological treatments should only be made after referral to specialist tone management services. The cost of these drugs can then be offset by the benefits of an approach tailored to the individual needs of the adult with cerebral palsy. When spasticity is focal, the committee agreed there was clinical evidence to suggest the cost of botulinum toxin could be outweighed by its benefits. Combined with the committee's clinical experience and expertise, the committee focussed their recommendation to consider referral for botulinum toxin for focal spasticity that is causing pain, impacting care, or impairing activity, to reduce the number of inappropriate referrals.

Injecting botulinum toxin is complex and should be assessed and administered by specialists who are competent in its management, to minimise the risks the injection can entail. The committee referred to Spasticity in under 19s: management CG145 which considers the role of EMG or ultrasound to guide botulinum toxin treatment and considered these to be appropriate in an adult population as well, though they also recognised potential cost implications associated with this. Therefore the committee made a research recommendation to assess if guided botulinum toxin treatment using EMG or ultrasound is cost effective.

References

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Griffiths APW, Sylvester PE (1964). Clinical trial of diazepam in adult cerebral palsy. Annals of physical medicine; Suppl:25-9

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Appendices

Appendix A – Review protocols

Review protocol for review question A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

Table 7: Review protocol for pharmacological treatments for spasticity

Field (based on PRISMA-P)	Content
Review question	Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?
Type of review question	Intervention review
Objective of the review	The aim of this review is to determine the relative effectiveness of pharmacological treatments for spasticity in adults with cerebral palsy
Eligibility criteria – population/disease/condition/issue/domain	Adults aged 19 years and over with cerebral palsy and spasticity (at least 50% of the study population should be 18 years or older).
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Enteral: • baclofen • dantrolene • tizanidine • diazepam • gabapentin/pregabalin • cannabinoids • botulinum toxin injections

Field (based on PRISMA-P)	Content
Eligibility criteria – comparator(s)/control or reference (gold) standard	Each other or placebo/no treatment

Outcomes and prioritisation	**Critical outcomes**
	• Motor function
	  ○ Swallowing problems
	  ○ Goal Attainment Scale (GAS)
	  ○ Functional Independence Measure (FIM)
	• Muscle tone
	• Health-related quality of life
	• Treatment related adverse events
	  ○ Swallowing problems
	  ○ Seizure threshold
	  ○ Undue weakness/loss of function – use of spasticity positively
	  ○ Drowsiness and cognitive change
	  ○ Specific problems in people with low proximal tone and high peripheral tone
	Important outcomes
	• Patient or carer reported satisfaction
	• Participation
	
	Minimally important differences:
	• Goal Attainment Scale: 7 units
	• Modified Ashworth Scale: 1 unit
	• Quality of Upper Extremities Test: 5 units
	• ICF – Measure of Participation and Activities Screener: 2 units
	• Community Balance and Mobility Scale: 10 units
	• Canadian Occupational Performance Measure: 2 units
	• Five Times Sit to Stand Test: 2.5 seconds

Field (based on PRISMA-P)	Content
	• Seated Shot-Put: 40 cm • Timed Up and Go: 5 seconds • Australian Therapy Outcome Measures for Occupational Therapy: 0.5 units • Assessment of Life Habits: use minimal detectable change for each subdomain reported on rehabmeasures.org • Other dichotomous outcomes will use default MIDs [RR thresholds of 0.80 and 1.2] • Other continuous outcomes will use default MIDs [0.5 times the SD of the control group]
Eligibility criteria – study design	Only published full-text papers of the following types of studies: systematic reviews of RCTs; RCTs; comparative cohort studies (only if RCTs unavailable or limited data to inform decision making); crossover trials; and before-and-after studies Conference abstracts will only be considered if they are related to an RCT
Other inclusion exclusion criteria	None
Proposed sensitivity/sub-group analysis, or meta-regression	Population subgroups: • GMFCS Level I to III vs. GMFCS Level IV to V • Limb (arm vs. leg related to BTx) • Full-time wheelchair users and part-time wheelchair users Intervention subgroups: • Dosage (for Botulinum toxin injections) Important confounders (when comparative observational studies are included for interventional reviews): • Presence of dystonia • Degree of pain/severity • Adjunct medication

Field (based on PRISMA-P)	Content
Selection process – duplicate screening/selection/analysis	A random sample of the references identified in the search will be sifted by a second reviewer. This sample size will be 10% of the total, or 100 studies if the search identified fewer than 1000 studies. All disagreements in study inclusion will be discussed and resolved between the two reviewers. The senior systematic reviewer or guideline lead will be involved if discrepancies cannot be resolved between the two reviewers
Data management (software)	STAR was used to sift through the references identified by the search, and for data extraction Pairwise meta-analyses and production of forest plots was done using Cochrane Review Manager (RevMan5). 'GRADEpro' was used to assess the quality of evidence for each outcome.
Information sources – databases and dates	Database(s): Embase 1974 to Present, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Cochrane Library; WEB OF SCIENCE
Identify if an update	Not an update
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/.
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual 2014

Field (based on PRISMA-P)	Content
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods and process section of the main file
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Alliance (NGA) and chaired by Dr Paul Eunson in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods see supplementary document C.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for those working in the NHS, public health and social care in England
PROSPERO registration number	Not applicable

Btx: botulinum toxin; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; FIM: Functional Independence Measure; GAS: Goal Attainment Scale; GRADE: Grading of Recommendations Assessment, Development and Evaluation; GMFCS, gross motor function classification system; HTA: Health Technology Assessment; ICF: International Classification of Functioning, Disability and Health; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategies for review question A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

This appendix is a combined search strategy and will be the same for all the evidence reviews for the A review questions as listed below:

A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

A2: Are neurosurgical procedures (intrathecal baclofen pump and selective dorsal rhizotomy) effective in adults aged 19 and over with cerebral palsy to reduce spasticity and or dystonia?

A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB)) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

Database: Medline & Embase (Multifile)

Database(s): Embase 1974 to 2018 March 22, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Table 8: Last searched on 22 March 2018

#	Searches
1	exp Cerebral Palsy/ use prmz
2	exp cerebral palsy/ use oemezd
3	((cerebral or brain or central) adj2 (pal* or paralys#s or pares#s)).tw.
4	cerebral palsy.ti,ab.
5	little? disease.tw.
6	((hemipleg* or dipleg* or tripleg* or quadripleg* or unilateral*) adj5 spastic*).tw.
7	((hemipleg* or dipleg* or tripleg* or quadripleg* or unilateral*) adj3 ataxi*).tw.
8	or/1-6
9	limit 8 to english language
10	limit 9 to (adult <18 to 64 years> or aged <65+ years>) use oemezd [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]
11	limit 9 to "all adult (19 plus years)" [Limit not valid in Embase; records were retained]
12	11 use prmz
13	or/10,12
14	exp Muscle Spasticity/ use prmz
15	exp spasticity/ use oemezd
16	spastic*.tw.
17	exp Dystonia/
18	dystoni*.ti,ab.
19	abnormal muscle tone.ti,ab.
20	14 or 15 or 16 or 17 or 18 or 19

#	Searches
21	exp Muscle Spasticity/ or exp Dystonia/ or exp Infusion Pumps, Implantable/ or exp Physical Therapy Modalities/ or exp Rhizotomy/ or exp Splints/ or exp Orthotic Devices/ or exp Deep Brain Stimulation/ or exp Baclofen/ad, ae, tu or exp Botulinum Toxins/ad, ae, tu or exp Diazepam/ad, ae, tu or exp Cannabinoids/ad, ae, tu or exp Acetylcholine Release Inhibitors/ad, ae, tu or exp Muscle Relaxants, Central/ad, ae, tu or exp Levodopa/ad, ae, tu or exp Dantrolene/ad, ae, tu or exp Clonazepam/ad, ae, tu or exp Pregabalin/ad, ae, tu or exp Clonidine/ad, ae, tu or exp Trihexyphenidyl/ad, ae, tu or exp Tetrabenazine/ad, ae, tu or exp Anti-Dyskinesia Agents/ad, ae, tu
22	21 use prmz
23	exp implantable infusion pump/ or exp physiotherapy/ or exp dorsal rhizotomy/ or exp splint/ or exp orthosis/ or exp brain depth stimulation/ or exp baclofen/ae, ad, cb, dt or exp botulinum toxin/ae, ad, cb, dt or exp diazepam/ae, ad, cb, dt or exp cannabinoid/ae, ad, cb, dt or exp acetylcholine release inhibitor/ae, ad, cb, dt or exp central muscle relaxant/ae, ad, cb, dt or exp levodopa/ae, ad, cb, dt or exp tizanidine/ae, ad, cb, dt or exp gabapentin/ae, ad, cb, dt or exp dantrolene/ae, ad, cb, dt or exp clonazepam/ae, ad, cb, dt or exp pregabalin/ae, ad, cb, dt or exp clonidine/ae, ad, cb, dt or exp trihexyphenidyl/ae, ad, cb, dt or exp tetrabenazine/ae, ad, cb, dt
24	23 use oemezd
25	(physiotherap* or botulinum or baclofen or tizanidine or intrathecal baclofen pump or gabapentin or levodopa or dantrolene or clonazepam or pregabalin or clonidine or dorsal rhizotomy or tetrabenazine or trihexyphenidyl or lycra or DBS or deep brain stimulat* or splint* or serial cast*).ti,ab.
26	22 or 24 or 25
27	13 and 20
28	13 and 26
29	27 or 28
30	conference abstract.pt. use oemezd
31	letter.pt. or LETTER/ use oemezd
32	Letter/ use prmz
33	EDITORIAL/ use prmz
34	editorial.pt. use oemezd
35	NEWS/ use prmz
36	exp HISTORICAL ARTICLE/ use prmz
37	note.pt. use oemezd
38	ANECDOTES AS TOPIC/ use prmz
39	COMMENT/ use prmz
40	CASE REPORT/ use prmz
41	CASE REPORT/ use oemezd
42	CASE STUDY/ use oemezd
43	(letter or comment* or abstracts).ti.
44	or/30-43
45	RANDOMIZED CONTROLLED TRIAL/ use prmz
46	RANDOMIZED CONTROLLED TRIAL/ use oemezd
47	random*.ti,ab.
48	or/45-47
49	44 not 48
50	ANIMALS/ not HUMANS/ use prmz
51	ANIMAL/ not HUMAN/ use oemezd
52	exp ANIMALS, LABORATORY/ use prmz

#	Searches
53	exp ANIMAL EXPERIMENTATION/ use prmz
54	exp MODELS, ANIMAL/ use prmz
55	exp RODENTIA/ use prmz
56	NONHUMAN/ use oemezd
57	exp ANIMAL EXPERIMENT/ use oemezd
58	exp EXPERIMENTAL ANIMAL/ use oemezd
59	ANIMAL MODEL/ use oemezd
60	exp RODENT/ use oemezd
61	(rat or rats or mouse or mice).ti.
62	or/49-61
63	29 not 62
64	remove duplicates from 63

Database: Cochrane Library

Table 9: Last searched on 22 March 2018

#1	MeSH descriptor: [Cerebral Palsy] explode all trees
#2	((cerebral or brain or central) N2 (pal* or paralys?s or pare?s))
#3	((hemipleg* or dipleg* or tripleg* or quadripleg* or unilateral*) N5 spastic*)
#4	((hemipleg* or dipleg* or tripleg* or quadripleg* or unilateral*) N3 ataxi*)
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Muscle Spasticity] explode all trees
#7	MeSH descriptor: [Dystonia] explode all trees
#8	Dystoni* or spastic*
#9	#6 or #7 or #8
#10	MeSH descriptor: [Baclofen] explode all trees
#11	MeSH descriptor: [Botulinum Toxins] explode all trees
#12	MeSH descriptor: [Diazepam] explode all trees
#13	MeSH descriptor: [Cannabinoids] explode all trees
#14	MeSH descriptor: [Acetylcholine Release Inhibitors] explode all trees
#15	MeSH descriptor: [Muscle Relaxants, Central] explode all trees
#16	MeSH descriptor: [Infusion Pumps, Implantable] explode all trees
#17	MeSH descriptor: [Levodopa] explode all trees
#18	MeSH descriptor: [Physical Therapy Modalities] explode all trees
#19	physiotherap* or Botulinum or baclofen or tizanidine or intrathecal pump or gabapentin or levodopa
#20	MeSH descriptor: [Dantrolene] explode all trees
#21	MeSH descriptor: [Clonazepam] explode all trees
#22	MeSH descriptor: [Pregabalin] explode all trees
#23	MeSH descriptor: [Clonidine] explode all trees
#24	MeSH descriptor: [Trihexyphenidyl] explode all trees
#25	MeSH descriptor: [Rhizotomy] explode all trees
#26	MeSH descriptor: [Splints] explode all trees
#27	MeSH descriptor: [Orthotic Devices] explode all trees
#28	MeSH descriptor: [Deep Brain Stimulation] explode all trees
#29	MeSH descriptor: [Tetrabenazine] explode all trees

#1	MeSH descriptor: [Cerebral Palsy] explode all trees
#30	Tetrabenazine or Deep Brain Stimulation or DBS or Splint* or orthotic* or dorsal Rhizotomy or Trihexyphenidyl or Clonidine or Pregabalin or Clonazepam or Dantrolene or serial cast* or lycra or splint cast*
#31	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#32	#5 and #31
#33	#5 and #9
#34	#32 or #33

Database: Web of Science

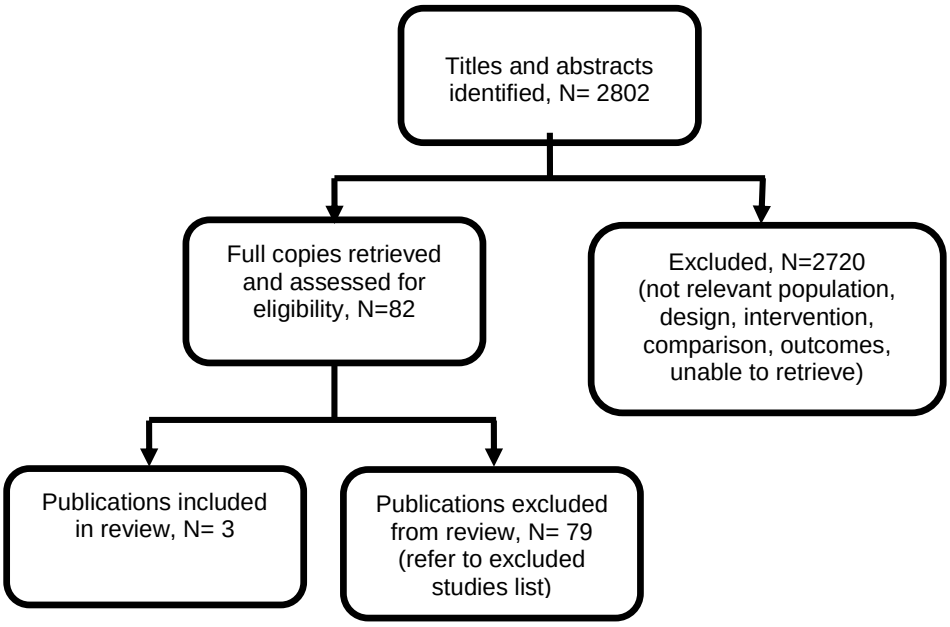
Table 10: Last searched on 27 March 2018

#6	#5 OR #3
#5	#4 AND #1
#4	ts=spasticity or ts=spastic* or ts=dystonia or ts=dystoni*
#3	#2 AND #1
#2	ts=physiotherap* or ts=Botulinum or ts=baclofen or ts=tizanidine or ts=intrathecal pump or ts=gabapentin or ts=levodopa or ts=Muscle Relaxant* or ts=Acetylcholine Release Inhibitor* or ts=Cannabinoid* or ts=Diazepam or ts=Tetrabenazine or ts=Deep Brain Stimulation or ts=DBS or ts=Splint* or ts=orthotic* or ts=dorsal Rhizotomy or ts=Trihexyphenidyl or ts=Clonidine or ts=Pregabalin or ts=Clonazepam or ts=Dantrolene or ts=serial cast* or ts=lycra or ts=splint cast*
#1	ts=Cerebral Palsy

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

Figure 1: Flow diagram of clinical article selection for pharmacological treatments for spasticity review



Appendix D – Clinical evidence tables

Clinical evidence tables for review question A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

Table 11: Studies included in the evidence review for pharmacological treatments for spasticity

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation: Griffiths, A. P., Sylvester, P. E., Clinical trial of diazepam in adult cerebral palsy, Annals of Physical Medicine, Suppl, 25-9, 1964 Ref Id 342472 **Country/ies where the study was carried out**: United Kingdom **Study type**: Randomised, double-blind crossover study **Aim of the study**: To evaluate the spasmolytic effect of diazepam on a group of patients suffering from severe forms of cerebral palsy **Study dates**: not reported	**Sample size:** 50 Characteristics • 32 women & 18 men • Mean age: 37 years (SD not reported) • Age range: 12 - 73 years • Range of IQ scores: 76 or less **Inclusion criteria:** not specified **Exclusion criteria:** not specified	**Interventions** Diazepam: • Duration: 6 weeks • Initial dose: 6 mg • Increase: 6 mg every week for four weeks • Dose maintained at 24 mg for the remaining two weeks Control (inactive) tablets: administered for 6 weeks	**Details**: Random allocation sequence only known to the pharmacist. Assessments were carried out by medical and nursing staff at the following time points: baseline, at the conclusion of the first course, and at the conclusion of the second course. Assessments were conducted using a form with the following code: 0 - worse than on entry on trial; 1 - same as on entry on trial; 2 - slightly better than on entry to trial; 3 - much better than on entry to trial	**Results**: Muscle tone (considered as sitffness): • Number of patients becoming slightly better: 1 after diazepam, and 1 after inactive control • Number of patients becoming worse: 1 after diazepam Adverse events (more than one event was possible in each patient): • Drowsiness: 13 patients • Anorexia: 4 patients • Slurring in speech: 2 patients • Depression: 1 patient • Vomiting: 1 patient	**Limitations**: Definition of muscle tone as stiffness might not be appropriate Other information: additional information sought by outcome assessors included involuntary movements, walking, feeding, speech and swallowing, dressing, sphincter control, and behaviour

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding: not declared				• Faint localised rash: 1 patient • Vomiting: 3 patients • Aggressive tendencies: 2 patients Number of patients withdrawn from the study due to adverse events: 8	
Full citation: Maanum,G., Jahnsen,R., Stanghelle,J.K., Sandvik,L., Keller,A., Effects of botulinum toxin A in ambulant adults with spastic cerebral palsy: a randomized double-blind placebo controlled-trial, Journal of Rehabilitation Medicine, 43, 338-347, 2011 Ref Id 132702 **Country/ies where the study was carried out**: Norway **Study type:** single-centre, double-blind, placebo-controlled, randomised clinical trial	**Sample size**: 66 (33 received injections of Botulinum toxin A; 33 received placebo) **Characteristics:** Men/Women: Placebo – 16/17; BoNT-A 14/19 Mean age (SD): Placebo – 38.4(12.1); BoNT-A 36.2(10.6) CP Unilateral/Bilateral: Placebo – 14/19; BoNT-A – 16/17 GMFCS Level I (Present/adolescence): Placebo – 4/15; BoNT-A – 5/15 GMFCS Level II – (Present/adolescence): 24/17; 24/18 GMFCS Level III – (Present/adolescence): Placebo – 5/1; BoNT-A – 4/0	**Interventions** • Intervention: a dilution of 50 U/ml of Botox® (Purified Neurotoxin Complex, Allergan, Inc., Irvine, CA, USA). • Placebo: 0.9% saline Both treatments were prepared by a nurse and a pharmacists in 2 ml syringes All injections were performed by the same physician using electromiography and electrical stimulation to confirm the presence of abnormal muscle activity and to guide the injections Dosing was based on 2002 Guidelines	**Details**: Potential participants were assessed by a multidisciplinary team through standardised clinical history-taking, clinical examination, and visual observation of gait Those eligible to participate, and who completed the informed consent form, underwent baseline assessment (where treatment goals were defined) Intramuscular injections were administered within a week of the baseline assessment	**Results**: Outcomes were measured at baseline, week 8 and week 16. However, data for week 16 were not reported by the authors Domains of the Norwegian version of the Short Form 36 (Mean(SD)): Mental health: Placebo: 77.7(16.8) baseline; 79.3(15.9) week 8 BoNT-A: 74.4(14.6) baseline; 78.5(15.0) week 8 Vitality: Placebo: 51.5(22.8) baseline; 56.5(22.6) week 8	**Limitations:** Power calculation was based on assumptions of kinematic SDs in previous publications on BoNT-A interventions in children with cerebral palsy. Relatively wide confidence intervals for the SF-36

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study: To assess the short-term effects of botulinum toxin A in ambulant adults with spastic cerebral palsy **Study dates**: November 2006 - January 2009 **Source of funding:** East Regional Health Administration and Sunnaas Rehabilitation Hospital (grant number 206 24 503)	**Inclusion criteria** • Spastic cerebral palsy (unilateral or bilateral) • Hypertonicity in lower-extremity muscle group(s) • Age between 18 and 65 years • Gross Motor Function Classification System (GMFCS) levels I - III • Decreased walking compared with adolescence • Walking without aids for a minimum of 20 minutes • Gait characterised by functional equinus and/or pathological knee extension or flexion strategy • No changes in other treatments during the study period **Exclusion criteria** • Cognitive impairment • Pregnancy or planning pregnancy • Botulinum Toxin A treatment in the last 6 months • Orthopaedic surgery in the last 18 months		Post-treatment was conducted 8 weeks after the injections	BoNT-A: 45.2(15.5) baseline; 51.2(21.9) week 8 Bodily pain: Placebo: 64.8(22.1) baseline; 72.9(24.1) week 8 BoNT-A: 54.4(24.7) baseline; 61.0(23.6) week 8 General health: Placebo: 63.5(18.9) baseline; 67.6(19.2) week 8 BoNT-A: 59.8(22.9) baseline; 60.3(22.8) week 8 Social function: Placebo: 83.3(17.9) baseline; 84.1(20.8) week 8 BoNT-A: 80.1(18.7) baseline; 85.6(15.9) week 8 Physical function: Placebo: 64.9(17.8) baseline; 68.8(20.0) week 8 BoNT-A: 67.8(20.7) baseline; 69.7(17.5) week 8 Role physical: Placebo: 54.6(42.1) baseline; 63.6(39.6) week 8	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Musculoskeletal pathology with no indication for Botulinum Toxin A treatment • Other diseases that can affect the level of physical function (rheumatoid, neurological, psychological) • New treatment in the past 4 weeks which affects the musculoskeletal system (pain-killers, acupuncture, physical therapy, fitness training)			BoNT-A: 43.8(39.1) baseline; 46.9(40.0) week 8 Role emotional: Placebo: 77.8(36.0) baseline; 79.8(33.3) week 8 BoNT-A: 69.8(39.1) baseline; 82.3(29.3) week 8 Muscle stiffness/spasticity (muscle tone measured through a 0 -100 mm visual analogue scale): Placebo: 45.8(22.7) baseline; 40.7(21.0) week 8 BoNT-A: 41.5(24.9) baseline; 28.6(21.6) week 8 6-minute walk test (motor function): Placebo: 493.4(74.7) baseline; 504.4(69.2) week 8 BoNT-A: 495.1(92.1) baseline; 514.5(94.8) week 8 Timed Up and Go (motor function:	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Placebo: 7.4(2.6) baseline; 7.3(2.6) week 8 BoNT-A: 7.3(1.9) baseline; 6.9(2.0) week 8 Number of participants perceiving a positive treatment effect on a three-point verbal Global Scale: Placebo: 9 participants BoNT-A: 19 participants	
Full citation: Marchiori, C., Roche, N., Vuillerme, N., Zory, R., Pradon, D., Effect of multisite botulinum toxin injections on gait quality in adults with cerebral palsy, Disability & Rehabilitation, 36, 1971-4, 2014 **Ref Id** 342716 **Country/ies where the study was carried out:** France	**Sample size:** 23 **Characteristics** • Men/women: 10/13 • Mean age (SD): 24.6 (7) • Age range: 18 - 36 years • Mean height: 163.8 cm • Mean weight: 57.1	**Interventions** Botox® (Purified Neurotoxin Complex, Allergan, Inc., Irvine, CA): 50 U/ml Injections were carried out under guidance of electrical stimulation Between 2 and 10 different muscles were injected in each participant	**Details** Study protocol involved three visits: • Baseline • Administration of botulinum toxin injections • Follow-up one month after injection	**Results** Mean Gait Deviation Index (GDI) score: 65.2 pre-treatment; 62.0 post treatment (the SD was not reported by the authors)	**Limitations**: The control group consisted of healthy individuals Other information: kinematics (angle joints) were also assessed in this study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type: Controlled before and after study (control was a group of healthy individuals). **Aim of the study**: To evaluate the effects of a single multi-site botulinum toxin injections on spatiotemporal parameters and kinematic parameters of adults with cerebral palsy. To determine if the Gait Deviation Index can be used to detect global changes in gait following this therapeutic approach. **Study dates**: not reported **Source of funding:** not declared					

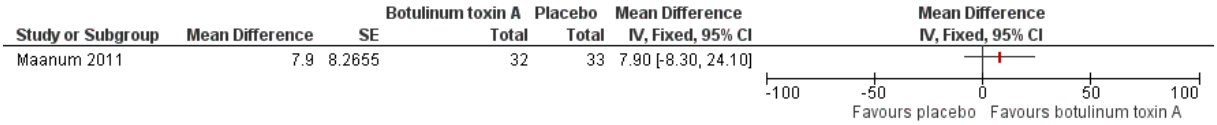
BoNT-A: botulinum toxin A; GDI: gait deviation index; GMFCS: Gross Motor Function Classification System; IQ: intelligence quotient; SD: standard deviation

Appendix E – Forest plots

Forest plots for review question A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

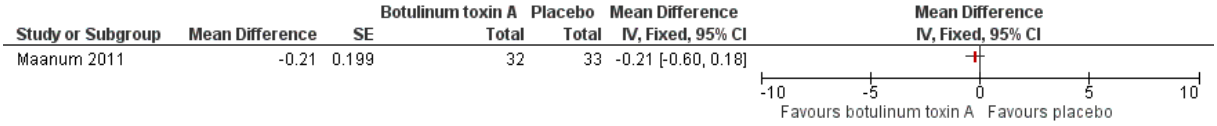
Comparison 1: Botulinum toxin A versus no treatment or placebo

Figure 2: Motor function: 6 minute Walk Test



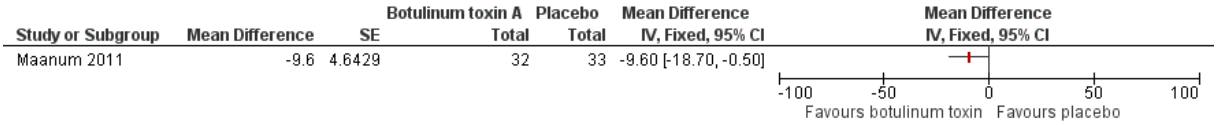
CI: confidence interval; IV: inverse variance; SD: standard deviation; SE: standard error

Figure 3: Motor function: Timed Up and Go



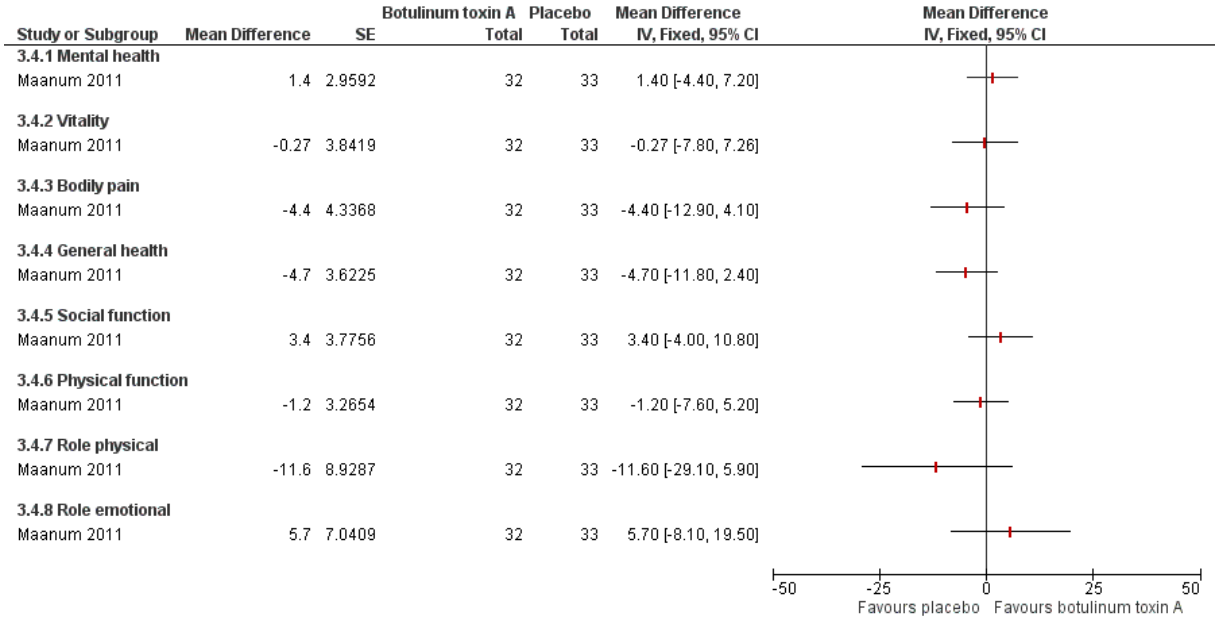
CI: confidence interval; IV: inverse variance; SD: standard deviation; SE: standard error

Figure 4: Muscle tone



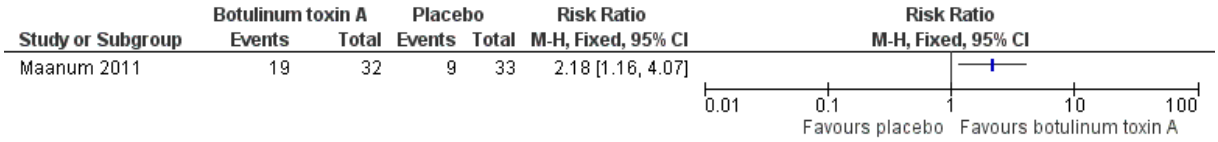
CI: confidence interval; IV: inverse variance; SD: standard deviation; SE: standard error

Figure 5: Health related quality of life (SF-36)



CI: confidence interval; IV: inverse variance; SD: standard deviation; SE: standard error; SF-36: 36-Item Short Form Health Survey

Figure 6: Patient reported satisfaction



CI: confidence interval; M-H: Mantel-Haenszel

Appendix F – GRADE tables

GRADE tables for review question A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

Table 12: Clinical evidence profile: Comparison 1: Botulinum toxin A injection versus no treatment or placebo

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Botulinum toxin	Standard care or placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Motor function (follow up: 8 weeks; assessed with: 6 Minute Walk Test)												
1	Randomised trials	Not serious	Not serious	Serious[1]	Serious[2]	None	32	33	-	MD 7.9 m higher (8.3 lower to 24.1 higher)	LOW	CRITICAL
Motor function (follow up: 8 weeks; assessed with: Timed Up and Go)												
1	Randomised trials	Not serious	Not serious	Serious[1]	Serious[2]	None	32	33	-	MD 0.21 min lower (0.6 lower to 0.2 higher)	LOW	CRITICAL
Motor function (follow up: 1 month; assessed with: Gait Deviation Index												
1	Observational studies	Serious[3]	Not serious	Serious[4]	Serious[2]	None	The authors observed a mean reduction of 3.2 points (p = 0.02) in the Gait Deviation Index (which did not meet the minimally clinical important difference of 4 points)				VERY LOW	CRITICAL

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Botulinum toxin	Standard care or placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
							between pre- and post-assessment. The 95% CI were not reported					
Muscle tone (follow up: 8 weeks; assessed with: muscle stiffness-spasticity visual analogue scale)												
1	Randomised trials	Not serious	Not serious	Serious[1]	Serious[2]	None	32	33	-	MD 9.6 lower (18.7 lower to 1.2 lower)	LOW	CRITICAL
Health related quality of life (follow up: 8 weeks; assessed with: Short Form 36 – mental health dimension)												
1	Randomised trials	Not serious	Not serious	Serious[1]	Serious[2]	None	32	33	-	MD 1.4 higher (4.4. lower to 7.2 higher)	LOW	CRITICAL
Health related quality of life (follow up: 8 weeks; assessed with: Short Form 36 – vitality dimension)												
1	Randomised trials	Not serious	Not serious	Serious[1]	Serious[2]	None	32	33	-	MD 0.27 lower (7.8 lower to 7.7 higher)	LOW	CRITICAL
Health related quality of life (follow up: 8 weeks; assessed with: Short Form 36 – bodily pain dimension)												
1	Randomised trials	Not serious	Not serious	Serious[1]	Serious[2]	None	32	33	-	MD 4.4 lower (12.9 lower to	LOW	CRITICAL

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Botulinum toxin	Standard care or placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
										4.2 higher)		
Health related quality of life (follow up: 8 weeks; assessed with: Short Form 36 – general health dimension)												
1	Randomised trials	Not serious	Not serious	Serious[1]	Serious[2]	None	32	33	-	MD 4.7 lower (11.8 lower to 2.4 higher)	LOW	CRITICAL
Health related quality of life (follow up: 8 weeks; assessed with: Short Form 36 – social function dimension)												
1	Randomised trials	Not serious	Not serious	Serious[1]	Serious[2]	None	32	33	- -	MD 3.4 higher (4.0 lower to 10.9 higher)	LOW	CRITICAL
Health related quality of life (follow up: 8 weeks; assessed with: Short Form 36 – physical function dimension)												
1	Randomised trials	Not serious	Not serious	Serious[1]	Serious[2]	None	32	33	- -	MD 1.2 lower (7.6 lower to 5.2 higher)	LOW	CRITICAL
Health related quality of life (follow up: 8 weeks; assessed with: Short Form 36 – role physical dimension)												
1	Randomised trials	Not serious	Not serious	Serious[1]	Serious[2]	None	32	33	-	MD 11.6 lower (29.1 lower to	LOW	CRITICAL

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Botulinum toxin	Standard care or placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
										5.9 higher)		
Health related quality of life (follow up: 8 weeks; assessed with: Short Form 36 – role emotional dimension)												
1	Randomised trials	Not serious	Not serious	Serious[1]	Serious[2]	None	32	33	-	MD 5.7 higher (8.1 lower to 19.5 higher)	LOW	CRITICAL
Treatment related adverse events – Not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Patient or carer reported satisfaction (follow up: 8 weeks; assessed with: number of patients reporting a positive treatment effect on a three point global verbal scale)												
1	Randomised trials	Not serious	Not serious	Serious[1]	Serious[2]	None	19/32 (59.4%)	9/33 (27.3%)	RR 2.18 (1.16 to 4.07)	322 more per 1,000 (from 44 more to 837 more)	LOW	IMPORTANT
Participation – Not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: confidence interval; MD: mean difference; RR: relative risk.

1. *Downgraded for serious indirectness as the participants were highly functioning adults with cerebral palsy. Patients with cognitive impairment were excluded from this study*
2. *Downgraded for serious imprecision due to sample size < 400 or number of events < 300*
3. *Downgraded for serious risk of bias due to the risk of selective reporting identified in this study*
4. *Downgraded for serious indirectness as the control participants in this before and after study were healthy participants*

Table 13: Clinical evidence profile: Comparison 2: oral diazepam versus placebo

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Diazepam	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Motor function – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Muscle tone (follow up: 6 weeks; assessed with: the number of participants identified as becoming slightly better during a clinical assessment conducted using a standardised assessment form)												
1	Observational studies	Not serious	Not serious	Serious[1]	Serious[2]	None	The authors identified 1 participant who became slightly better after receiving Diazepam, and 1 participant who became slightly better after receiving the control (inactive) tablet				VERY LOW	CRITICAL
Health related quality of life – Not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Treatment related adverse events (follow up: 6 weeks; assessed with: number of adverse events reported during the administration of diazepam)												
1	Observational studies	Not serious	Not serious	Serious[1]	Serious[2]	None	Drowsiness was reported in 13 patients, anorexia in 4, slurring of speech in 2, depression in 1, vomiting in 4, abdominal pain in 1, aggressive tendencies in 2, and a faint localised rash in 1. Each patient could have experienced more than one adverse event (however, this was not reported)				VERY LOW	CRITICAL
Patient or carer reported satisfaction – Not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Participation – Not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: confidence interval.

1. *Downgraded for serious indirectness as the authors recruited some of the "most severely affected" patients for this study*

2. Downgraded for serious imprecision due to small sample size < 400 or number of events < 300 and the authors not implementing appropriate inferential statistical tests

Appendix G – Economic evidence study selection

Economic evidence study selection for review question A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

No economic evidence was identified for this review.

Appendix H – Economic evidence tables

Economic evidence tables for review question A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

No economic evidence was identified for this review.

Appendix I – Health economic evidence profiles

Health economic evidence profiles for review question A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

No economic evidence was identified for this review.

Appendix J – Health economic analysis

Health economic analysis for review question A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

No economic analysis was included in this review.

Appendix K – Excluded studies

Clinical and economic lists of excluded studies for review question A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

Clinical studies

Table 14: Excluded clinical studies for pharmacological treatments for spasticity

Excluded studies – A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?	
Study	**Reason for Exclusion**
Ade-Hall, Ruth, Moore, Peter, Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy, Cochrane Database of Systematic Reviews, 2000	The age range of participants included in this systematic review was 0 to 19 years old. Objective of the systematic review (as stated in the full-text report): "To determine whether BtA is an effective and safe treatment for lower limb spasticity in children with cerebral palsy." Type of participants considered for inclusion (as stated in the full text report): "Eligible trials must have involved children (defined, for the purposes of this review, as individuals between the ages of 0 and 19 years old) with CP who had been treated for lower limb spasticity. Trials may be subdivided according to type of CP, distribution of spasticity, severity, dose of BtA, age at which BtA administered."
Agarwal S, Patel T, Shah N, et al (2017). Comparative study of therapeutic response to baclofen vs tolperisone in spasticity. Biomedicine & Pharmacotherapy; 87: 628 - 635	32 participants out of 150 reported in the full text (101 participants according to an email received from the

Excluded studies – A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?	
Study	**Reason for Exclusion**
	contact author) had cerebral palsy (as opposed to post-stroke spasticity). Of these, only 7 were 19 years of age or older
Alahmar-Bianchin, M., Saraiva-Storti, H. C., Fornari-Chueire, R., Lucato, R., Prevalence of hand dysfunction in cerebral palsy following botulinum toxin therapy, Revista De Neurologia, 45, 334-337, 2007	Cross sectional study. Mean age of participants 15.4 years.
Awaad, Y. M., High dose of botulinum toxin type-A (BTX/A): Safety and efficacy in patients with cerebral palsy, Movement Disorders, 21, S422-S422, 2006	Fewer than 50% of participants were adults (4 adults out of 22 participants - 18%). In addition, this was a case series.
Baker, R, Jasinski, M, Maciag-Tymecka, I, Michalowska-Mrozek, J, Bonikowski, M, Carr, L, MacLean, J, Lin, Jp, Lynch, B, Theologis, T, Wendorff, J, Eunson, P, Cosgrove, A, Botulinum toxin treatment of spasticity in diplegic cerebral palsy: a randomized, double-blind, placebo-controlled, dose-ranging study, Developmental Medicine and Child Neurology, 44, 666-75, 2002	Age range of participants was 2 to 9 years.
Baricich,A., Carda,S., Bertoni,M., Maderna,L., Cisari,C., A single-blinded, randomized pilot study of botulinum toxin type A combined with non-pharmacological treatment for spastic foot, Journal of Rehabilitation Medicine, 40, 870-872, 2008	Participants were post-stroke survivors.
Barnes, M., Schnitzler, A., Medeiros, L., Aguilar, M., Lehnert-Batar, A., Minnasch, P., Efficacy and safety of NT 201 for upper limb spasticity of various etiologies - A randomized parallel-group study, Acta Neurologica Scandinavica, 122, 295-302, 2010	The proportion of participants with spasticity due to cerebral palsy was below 50% (3.1% in one arm of the study and 0% in the other)
Beecham, E., Candy, B., Howard, R., McCulloch, R., Laddie, J., Rees, H., Vickerstaff, V., Bluebond-Langner, M., Jones, L., Pharmacological interventions for pain in children and adolescents with life-limiting conditions, Cochrane Database of Systematic Reviews, 3, CD010750, 2015	Age range of participants was 0 to 18 years.
Bergfeldt, U., Borg, K., Kullander, K., Julin, P., Focal spasticity therapy with botulinum toxin: effects on function, activities of daily living and pain in 100 adult patients, Journal of Rehabilitation Medicine, 38, 166-71, 2006	Proportion of participants with cerebral palsy below 50% (41 out of 100 participants). In addition, the reporting of outcomes is inconsistent: total number of participants changes with each

Excluded studies – A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?	
Study	**Reason for Exclusion**
	outcome, and it is not clear whether the authors are referring to patients with cerebral palsy or patients with other diagnoses.
Bes,A., Eyssette,M., Pierrot-Deseilligny,E., Rohmer,F., Warter,J.M., A multi-centre, double-blind trial of tizanidine, a new antispastic agent, in spasticity associated with hemiplegia, Current Medical Research and Opinion, 10, 709-718, 1988	Participants presented spasticity following stroke or trauma (no cerebral palsy)
Blaszczyk, I., Foumani, N. P., Ljungberg, C., Wiberg, M., Questionnaire about the adverse events and side effects following botulinum toxin A treatment in patients with cerebral palsy, 7, 4645-4654, 2015	Study describing active surveillance on the incidence of adverse events and side effects in patients with cerebral palsy who were treated for spasticity or dystonia in the upper or upper and lower extremity muscles during February 2010 to May 2011
Bresolin,N., Zucca,C., Pecori,A., Efficacy and tolerability of eperisone in patients with spastic palsy: a cross-over, placebo-controlled dose-ranging trial, European Review for Medical and Pharmacological Sciences, 13, 365-370, 2009	2 out of 18 participants (11%) had spastic palsy due to CP.
Cardoso,E.S., Rodrigues,B.M., Barroso,M., Menezes,C.J., Lucena,R.S., Nora,D.B., Melo,A., Botulinum toxin type A for the treatment of the spastic equinus foot in cerebral palsy, Pediatric Neurology, 34, 106-109, 2006	Age range of participants in the included studies was 2 to 16 years of age.
Carter,C.H., Evaluation of diazepam in skeletal muscle hypertonicity in cerebral palsy, Archives of Physical Medicine and Rehabilitation, 49, 519-523, 1968	Age range of participants 3 to 27 years, and the majority were less than 13 years of age.
Charles,P.D., Gill,C.E., Taylor,H.M., Putman,M.S., Blair,C.R., Roberts,A.G., Ayers,G.D., Konrad,P.E., Spasticity treatment facilitates direct care delivery for adults with profound intellectual disability, Movement Disorders, 25, 466-473, 2010	Before and after study. More than 50% of participants were adults with a diagnosis of cerebral palsy. However, the aim was to identify the healthcare needs of adults with intellectual disabilities, and a key component was to determine care goals.

Excluded studies – A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?	
Study	**Reason for Exclusion**
	Treatment included botulinum toxin and ITB (depending on specialist assessment).
Chua,K.S., Kong,K.H., Lui,Y.C., Botulinum toxin A in the treatment of hemiplegic spastic foot drop--clinical and functional outcomes, Singapore Medical Journal, 41, 209-213, 2000	None of the participants had a diagnosis of cerebral palsy
Chyatte,S.B., Basmajian,J.V., Dantrolene sodium: long-term effects in severe spasticity, Archives of Physical Medicine and Rehabilitation, 54, 311-315, 1973	Less than 50% of participants had a diagnosis of cerebral palsy (5 out of 30 participants - 17%)
Chyatte,S.B., Birdsong,J.H., Bergman,B.A., The effects of dantrolene sodium on spasticity and motor performance in hemiplegia, Southern Medical Journal,South.Med.J., 64, 180-185, 1971	Participants had spasticity of vascular/traumatic origin.
Corry, Is, Cosgrove, Ap, Duffy, Cm, McNeill, S, Taylor, Tc, Graham, Hk, Botulinum toxin A compared with stretching casts in the treatment of spastic equinus: a randomised prospective trial, Journal of pediatric orthopedics, 18, 304-11, 1998	Age range of participants between 2 and 9 years of age.
Corry, Is, Cosgrove, Ap, Duffy, Cm, Taylor, Tc, Graham, Hk, Botulinum toxin A in hamstring spasticity, Gait & PostureGait Posture, 10, 206-10, 1999	Age range of participants was 4 to 11 years of age.
Cucu, T., Nacu, A., Siric, A., First Experience of Using Botulinum Toxin in Treatment of Spastic Cerebral Palsy in the Republic of Moldova, European Journal of Neurology, 18, 146-146, 2011	Participants were children. Publication is a conference abstract, and there is no mention of randomisation.
Delgado, Mr, Tilton, A, Russman, B, Benavides, O, Bonikowski, M, Carranza, J, Dabrowski, E, Dursun, N, Gormley, M, Jozwiak, M, Matthews, D, Maciag-Tymecka, I, Unlu, E, Pham, E, Tse, A, Picaut, P, AbobotulinumtoxinA for Equinus Foot Deformity in Cerebral Palsy: A Randomized Controlled Trial, Pediatrics, 137, e20152830, 2016	Age range of participants was 2 to 17 years of age.
Denhoff, E., Feldman, S., Litchman, H., Efficacy of Dantrolene Sodium Suspension in Spastic Cerebral-Palsy, Developmental Medicine and Child Neurology, 17, 392-393, 1975	Age range of participants was 1.5 and 11 years.
Detrembleur, C, Lejeune, Tm, Renders, A, Bergh, Py, Botulinum toxin and short-term electrical stimulation in the treatment of equinus in cerebral palsy, Movement disorders : official journal of the Movement Disorder Society, 17, 162-9, 2002	Age range of participants 3.5 to 7.5.
Fietzek, U. M., Kossmehl, P., Schelosky, L., Ebersbach, G., Wissel, J., Early botulinum toxin treatment for spastic pes equinovarus - a randomized double-blind placebo-controlled study, European Journal of Neurology, 21, 1089-1095, 2014	Participants presented spasticity due to traumatic brain injury, diï¬use cerebral hypoxia or stroke (no cerebral palsy).

Excluded studies – A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?	
Study	**Reason for Exclusion**
Flett, Pj, Stern, Lm, Waddy, H, Connell, Tm, Seeger, Jd, Gibson, Sk, Botulinum toxin A versus fixed cast stretching for dynamic calf tightness in cerebral palsy, Journal of Paediatrics and Child Health, 35, 71-7, 1999	Age range of participants was 2 to 8 years of age.
Frasson, E, Dall'ora, E, Bordignon, M, Brigo, F, Tocco, P, Primon, D, Didonè, G, Vicentini, S, Fiaschi, A, Bertolasi, L, Spread of botulinum neurotoxin type a at standard doses is inherent to the successful treatment of spastic equinus foot in cerebral palsy: short-term neurophysiological and clinical study, Journal of Child Neurology, 27, 587-93, 2012	Age range of participants was 2.1 to 9.5 years of age.
Goyal, V., Laisram, N., Wadhwa, R. K., Kothari, S. Y., Prospective randomized study of oral Diazepam and Baclofen on spasticity in cerebral palsy, Journal of Clinical and Diagnostic Research, 10, RC01-RC05, 2016	Age range of participants: 2 - 18 years of age.
Graham, K., Safety of Botulinum toxin a in cerebral palsy, Toxicon, 51, 28-28, 2008	Participants were children. Publication is an abstract.
Grigoriu, A. I., Dinomais, M., Remy-Neris, O., Brochard, S., Impact of injection-guiding techniques on the effectiveness of botulinum toxin for the treatment of focal spasticity and dystonia: A systematic review, Annals of Physical and Rehabilitation Medicine, 58, e84, 2015	The studies included in this systematic review did not meet the inclusion criteria for this guideline in relation to the diagnosis of participants or age.
Hazneci, B, Tan, Ak, Guncikan, Mn, Dincer, K, Kalyon, Ta, Comparison of the efficacies of botulinum toxin A and Johnstone pressure splints against hip adductor spasticity among patients with cerebral palsy: a randomized trial, Military medicine, 171, 653-6, 2006	Participants were children: Participants in the Botulinum Toxin A group had a mean age of 8.19 years (SD = 2.49); participants in the Johnstone Pressure Splints had a mean age of 7.61 years (SD = 1.25).
Hefter, H., Rosenthal, D., Improvement of upper trunk posture during walking in hemiplegic patients after injections of botulinum toxin into the arm, Clinical Biomechanics, 43, 15-22, 2017	Post-stroke participants.
Hurst, D. L., Lajara-Nanson, W. A., Schiffer, R. B., Modafinil use in spastic cerebral palsy: A pilot study, Annals of Neurology, 50, S118-S118, 2001	Paediatric population. In addition, publication is an abstract not associated with an RCT.
Ianieri, G., Santamato, A., Saponieri, F., Di Cillo, P., Megna, G., Safety and efficacy of botulinum toxin in cerebral palsy: Four-year study, Movement Disorders, 17, S337-S337, 2002	Before and after study. Full text report is an abstract that is not linked to an RCT. Mean age of participants 9.1 years.

Excluded studies – A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?	
Study	**Reason for Exclusion**
Jianjun, L., Shurong, J., Weihong, W., Yan, Z., Fanyong, Z., Nanling, L., Botulinum toxin-A with and without rehabilitation for the treatment of spastic cerebral palsy, Journal of International Medical Research, 41, 636-41, 2013	Age range of participants 1 to 23. Mean age of participants 6.35 (SD = 2.76).
Kanovsky, P., Bares, M., Severa, S., Benetin, J., Kraus, J., Richardson, A., Lisy, L., Functional benefit of botulinum toxin (Dysport (R)) in the treatment of dynamic equinus cerebral palsy spasticity: a prospective, multicentre, double-blind, placebo-controlled study, Naunyn-Schmiedebergs Archives of Pharmacology, 365, R25-R25, 2002	Age ranges of participants was 2 to 7 years of age.
Karaca, B., Unlu, E., Kose, G., Gonen, E., Cakcl, A., Outcomes of Botulinum Toxin Type A Injection Followed by Rehabilitation in Cases of Cerebral Palsy with Upper Extremity Involvement, 31, 357-363, 2016	Retrospective review of medical records of patients who received botulinum toxin type A followed by a rehabilitation program
Koman, La, Mooney, Jf, Smith, Bp, Goodman, A, Mulvaney, T, Management of spasticity in cerebral palsy with botulinum-A toxin: report of a preliminary, randomized, double-blind trial, Journal of pediatric orthopedics, 14, 299-303, 1994	Age range of participants was 4 to 11 years old.
Koman, La, Mooney, Jf, Smith, Bp, Walker, F, Leon, Jm, Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: a randomized, double-blind, placebo-controlled trial. BOTOX Study Group, Journal of pediatric orthopedics, 20, 108-15, 2000	Age range of participants was 2 to 16 years.
Kwon, Jy, Hwang, Jh, Kim, Js, Botulinum toxin a injection into calf muscles for treatment of spastic equinus in cerebral palsy: a controlled trial comparing sonography and electric stimulation-guided injection techniques: a preliminary report, American journal of physical medicine & rehabilitation, 89, 279-86, 2010	Participants older than 7 years of age were excluded from this trial.
Maanum,G., Jahnsen,R., Stanghelle,J.K., Sandvik,L., Keller,A., A randomized, double-blind, placebo-controlled study on the effects of botulinum toxin A in ambulant adults with spastic cerebral palsy, Developmental Medicine and Child Neurology, 64th Annual Meeting of the American Academy for Cerebral Palsy and Developmental Medicine Washington, DC United States. Conference Start, 43-44, 2010	Conference abstract of an already included study
Manzano, F. S., Granero, L. M., Masiero, D., Santos, M. T. B. R. D., Treatment of muscle spasticity in patients with cerebral palsy using BTX-A: A pilot study, Special Care in Dentistry, 24, 235-239, 2004	Proportion of participants over the age of 19 less than 50%
Maritz, N. G., Muller, F. O., Pompevanmeerdervoort, H. F., Piracetam in Management of Spasticity in Cerebral-Palsy, South African Medical Journal, 53, 889-891, 1978	Age range of participants 3 to 14 years. Cross-over study.
McGinley, J., Dobson, F., Morgan, P., A systematic review of the effect of interventions on gait in adults with cerebral palsy, Developmental Medicine and Child Neurology, 54, 45-46, 2012	Not specific to the treatment of spasticity. In addition, full text

Excluded studies – A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?	
Study	**Reason for Exclusion**
	report is an abstract not linked to an RCT.
Molenaers, G., Desloovere, K., De Cat, J., Jonkers, I., De Borre, L., Pauwels, P., Nijs, J., Fabry, G., De Cock, P., Single event multilevel botulinum toxin type A treatment and surgery: similarities and differences, European Journal of Neurology, 8 Suppl 5, 88-97, 2001	Age range of participants receiving BTX-A was 4 to 10 years.
Molenaers, G., Desloovere, K., Eyssen, M., Decat, J., Jonkers, I., De Cock, P., Botulinum toxin type A treatment of cerebral palsy: An integrated approach, European Journal of Neurology, 6, S51-S57, 1999	Median age of participants was 5.5 years of age.
Mooney, J. F., Koman, L. A., Smith, B. P., Pharmacologic management of spasticity in cerebral palsy, Journal of Pediatric Orthopaedics, 23, 679-686, 2003	Edited article of the current issues on the treatment of spasticity in cerebral palsy (not a study)
Naumann, M., Jankovic, J., Safety of botulinum toxin type A: a systematic review and meta-analysis, Current Medical Research and Opinion, 20, 981-990, 2004	All the studies included in this systematic review were identified through our electronic searches. These studies were excluded from this guideline on the basis of participants' age.
Papadonikolakis, A. S., Vekris, M. D., Korompilias, A. V., Kostas, J. P., Ristanis, S. E., Soucacos, P. N., Botulinum A toxin for treatment of lower limb spasticity in cerebral palsy: gait analysis in 49 patients, Acta Orthopaedica Scandinavica, 74, 749-55, 2003	Age range of participants was 2 to 19 years of age. In addition, this was a before and after study.
Papavasiliou,A.S., Nikaina,I., Foska,K., Bouros,P., Mitsou,G., Filiopoulos,C., Safety of botulinum toxin a in children and adolescents with cerebral palsy in a pragmatic setting, Toxins, 5, 524-536, 2013	The participants evaluated were 18 years old or younger. In addition, this was a retrospective review of cases.
PascualPascual, S. I., deMuniain, P. S., Roche, M. C., PascualCastroviejo, I., Botulinum toxin as treatment of cerebral palsy, Revista De Neurologia, 25, 1369-1375, 1997	Less than 50% of participants were 19 years old or older. Retrospective review of cases.
Patrick, J., Roberts, A., Sewry, C. A., Long term effects of Botulinum toxin treatment on muscle morphology in patients with cerebral palsy, Neuromuscular Disorders, 18, 789-790, 2008	Full text report is an abstract not linked to an RCT (instead, this study compared tissue samples of treated patients with those of untreated patients). In addition, the report mentions adolescents.

Excluded studies – A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?	
Study	**Reason for Exclusion**
Phadke, C. P., Balasubramanian, C. K., Holz, A., Davidson, C., Ismail, F., Boulias, C., Adverse Clinical Effects of Botulinum Toxin Intramuscular Injections for Spasticity, Canadian Journal of Neurological Sciences, 43, 298-310, 2016	Review of adverse event reported to Health Canada plus systematic review. In addition, not specific to cerebral palsy. Many of the indications for botulinum toxin were for post-stroke spasticity.
Ploumis, A., Varvarousis, D., Konitsiotis, S., Beris, A., Effectiveness of botulinum toxin injection with and without needle electromyographic guidance for the treatment of spasticity in hemiplegic patients: a randomized controlled trial, Disability and Rehabilitation, 36, 313-318, 2014	Less than 50% of patients had a diagnosis of cerebral palsy (3 out of 27 participants - 11%).
Pradon, D., Hutin, E., Khadir, S., Taiar, R., Genet, F., Roche, N., A pilot study to investigate the combined use of Botulinum toxin type-a and ankle foot orthosis for the treatment of spastic foot in chronic hemiplegic patients, Clinical Biomechanics, 26, 867-872, 2011	Inclusion criteria: hemiplegia due to stroke.
Rodriquez,A.A., McGinn,M., Chappell,R., Botulinum toxin injection of spastic finger flexors in hemiplegic patients, American Journal of Physical Medicine and Rehabilitation, 79, 44-47, 2000	Before and after study. Participants were attending a stroke outpatient clinic.
Rousseau, M. C., Nadji, M., Effective results with botulinum toxin in adults with cerebral palsy, Evaluation de la prise en charge par toxine botulinique des limitations articulaires chez les patients adultes polyhandicapes. [French, English], Annals of Physical and Rehabilitation Medicine, 55, e335+e338, 2012	Full-text report is an abstract of a before and after study (not linked to an RCT).
Ruiz, P. J. G., Pascual, I. P., Bernardos, V. S., Progressive response to Botulinum A toxin in cerebral palsy, European Journal of Neurology, 7, 191-193, 2000	Mean age of participants 4.7 (SD = 2)
Rutz,E., Hofmann,E., Brunner,R., Preoperative botulinum toxin test injections before muscle lengthening in cerebral palsy, Journal of Orthopaedic Science, 15, 647-653, 2010	Case series. Full text report is an abstract not linked to an RCT. Lastly, aim of the study was to determine if pre-operative administration of BTX-A could provide an indication of functional deterioration in patients selected for surgical muscle lengthening.
Saber, N., El Mikawy, D., Efficacy of Multilevel Botulinum Toxin a Treatment of Hemiplegic and Diplegic Spastic Cerebral Palsy: A Clinical and Neurophysiological Study, Muscle & NerveMuscle Nerve, 54, 566-566, 2016	Age range of participants was 5 to 18 years of age.

Excluded studies – A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?	
Study	**Reason for Exclusion**
Sakzewski, L, Ziviani, J, Boyd, Rn, Efficacy of upper limb therapies for unilateral cerebral palsy: a meta-analysis (Provisional abstract), Pediatrics, 133, e175-204, 2014	Studies were included if they evaluated a population of children/adolescents between 0 and 18 years of age.
Schmidt, E., DiMario, F. J., Efficacy profile for anti-spasticity therapies in cerebral palsy, Journal of Investigative Medicine, 47, 165A-165A, 1999	The aim of the study was to "define a patient selection algorithm for the best treatment choice for the individual patient based upon their subjective assessment of benefit." In addition, the full-text report was an abstract not linked to an RCT. Lastly, only paediatric participants were considered.
Schramm, A., Ndayisaba, J. P., Auf dem Brinke, M., Hecht, M., Herrmann, C., Huber, M., Lobsien, E., Mehnert, S., Reuter, I., Stenner, A., van der Ven, C., Winterholler, M., Kupsch, A., Wissel, J., Spasticity treatment with onabotulinumtoxin A: data from a prospective German real-life patient registry, Journal of Neural Transmission, 121, 521-30, 2014	Less than 50% of participants presented spasticity due to cerebral palsy: Of the 508 patients reviewed, 103 (20.3%) were categorised as 'Other', which included cerebral palsy, anoxia, hereditary spastic paralysis and spasticity of unknown origin. The other categories included stroke, ischaemia, bleeding, traumatic brain injury and multiple sclerosis.
Serizawa, E., Galeano, C., Cost-Effectiveness Analysis of Two Forms of Botulinum Toxin Type a in Colombia for the Treatment of Cerebral Palsy, Value in Health, 16, A720-A720, 2013	Abstract of a systematic review to assess the cost-effectiveness of two forms of botulinum toxin in a paediatric population.
Simpson, D. M., Gracies, J. M., Graham, H. K., Miyasaki, J. M., Naumann, M., Russman, B., Simpson, L. L., So, Y., Therapeutics,, Technology Assessment Subcommittee of the American Academy of, Neurology, Assessment: Botulinum neurotoxin for the treatment of spasticity (an evidence-based review): report of the Therapeutics and	Spasticity due to cerebral palsy was only considered in children.

Excluded studies – A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?	
Study	**Reason for Exclusion**
Technology Assessment Subcommittee of the American Academy of Neurology, Neurology, 70, 1691-8, 2008	
Simpson,D.M., Clinical trials of botulinum toxin in the treatment of spasticity, Muscle & nerve, 6, -175, 1997	Review of studies. Those related to cerebral palsy were conducted in paediatric populations.
Singh, B., Shahwan, S. A., Miller, V. S., Riela, A. R., Use of Botulinum Toxin for Adductor Spasticity in Cerebral-Palsy, Annals of Neurology, 36, 513-513, 1994	Abstract describing a before and after study in children aged between 3 and 10 years.
Soboloff, H. R., Dantrolene - Drug for Cerebral-Palsy - 2-Year Study, Developmental Medicine and Child Neurology, 16, 252-252, 1974	Age range of participants was 13 to 17 years.
Steinberg,F.U., Ferguson,K.L., Effect of dantrolene sodium on spasticity associated with hemiplegia, Journal of the American Geriatrics Society, 23, 70-73, 1975	None of the participants had a diagnosis of cerebral palsy.
Suarez, G., Blight, A. R., Rabinowicz, A. L., Carrazana, E., Safety, Tolerability, and Sensorimotor Effects of Extended-release Dalfampridine in Adults With Cerebral Palsy: A Pilot Study, Clinical Therapeutics, 39, 337-346, 2017	Aim of the study was to determine the tolerability and safety profile of Dalfampridine. Not powered for efficacy
Sutherland, D. H., Kaufman, K. R., Wyatt, M. P., Chambers, H. G., Mubarak, S. J., 1998 GCMAS Best Paper Award - Double-blind study of botulinum A toxin injections into the gastrocnemius muscle in patients with cerebral palsy, Gait & PostureGait Posture, 10, 1-9, 1999	Age range of participants was 2 to 16 years of age.
Tanikawa, H., Kagaya, H., Saitoh, E., Ozaki, K., Hirano, S., Itoh, N., Yamada, J., Kanada, Y., Efficacy of Botulinum Toxin A Treatment for Pes Varus during Gait, Journal of Stroke and Cerebrovascular Diseases, 24, 2416-2422, 2015	Spasticity was not due to cerebral palsy.
Ubhi, T, Bhakta, Bb, Ives, Hl, Allgar, V, Roussounis, Sh, Randomised double blind placebo controlled trial of the effect of botulinum toxin on walking in cerebral palsy, Archives of Disease in Childhood, 83, 481-7, 2000	Age range of participants was 2 to 16 years of age.
Unlu,E., Sen,T., Umay,E., Bal,B., Elhan,A., Cakci,A., Botulinum toxin injection of the subscapularis muscle, Journal of Clinical Neuroscience, 17, 1265-1266, 2010	Case series. Participants did not have a diagnosis of cerebral palsy.
Ward, A. B., The use of botulinum toxin type A in spastic diplegia due to cerebral palsy, European Journal of Neurology, 6, S95-S98, 1999	Case series. Participants were adolescents.
Wein, T., Beauchamp, R., Ismail, F., Jog, M., Miller, R., Huang, B., Bhogal, M., Simonyi, S., Resource utilization by patients with adult focal spasticity (AFS) and cerebral palsy (CP) receiving botulinum toxin type a (BOTOX) in a prospective observational cohort study: Mobility study, Neurorehabilitation and Neural Repair, 26 (6), 664-665, 2012	Full text report was an abstract not linked to an RCT. Less than 50% of participants (64 out of 424 - 15%) had a

Excluded studies – A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?	
Study	**Reason for Exclusion**
	diagnosis of cerebral palsy.
Westhoff,B., Seller,K., Wild,A., Jaeger,M., Krauspe,R., Ultrasound-guided botulinum toxin injection technique for the iliopsoas muscle, Developmental Medicine and Child Neurology, 45, 829-832, 2003	Case series. The majority of participants with a diagnosis of cerebral palsy were under 19 years of age.
Wissel,J., Heinen,F., Schenkel,A., Doll,B., Ebersbach,G., Muller,J., Poewe,W., Botulinum toxin A in the management of spastic gait disorders in children and young adults with cerebral palsy: A randomized, double-blind study of 'high-dose' versus 'low-dose' treatment, Neuropediatrics, 30, 120-124, 1999	Mean age of participants was 10 years.
Yagudina, R., Kulikov, A., Ugrekhelidze, D., Budget Impact Analysis of Botulinum Toxin Type A Treatment for Cerebral Palsy In The Russian Federation, Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research, 18, A752, 2015	The full text report is an abstract that describes the development of a budget impact model of spastic cerebral palsy treatment in the Russian federation.

Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

Is guided Botulinum Toxin A injection using electrical localisation (electrical stimulation or electromyography) of muscles more effective and cost-effective than ultrasound guided or clinical positioning for localisation of injections in treating focal spasticity in adults with cerebral palsy?

Table 15: Research recommendation rationale

Research question	**Is guided Botulinum Toxin A injection using electrical localisation (electrical stimulation or electromyography) of muscles more effective and cost-effective than ultrasound guided or clinical positioning for localisation of injections in treating focal spasticity in adults with cerebral palsy?**
Importance to 'patients' or the population	The procedure does cause some discomfort and may be repeated after some months. Injection of the wrong muscle is a significant risk without accurate localisation. It is important that the patient gets maximum benefit from the procedure. It is preferable if this service is available as close to the person's home as possible and skills in localising muscles and equipment may not be readily available in local injecting centres
Relevance to NICE guidance	Ability to advise clinicians and service managers the most effective way to deliver the treatment
Relevance to the NHS	The drug itself is costly. It does have beneficial effect for this patient group. This would allow a more cost effective service to be established
National priorities	Encourage equitable access geographically to an effective service

Research question	Is guided Botulinum Toxin A injection using electrical localisation (electrical stimulation or electromyography) of muscles more effective and cost-effective than ultrasound guided or clinical positioning for localisation of injections in treating focal spasticity in adults with cerebral palsy?
Current evidence base	There is some evidence including a systematic review showing that ultrasound or muscle stimulation is more accurate in placement of injection compared to manual identification of muscle in people with spasticity following stroke. This did not include cost effectiveness Chan 2017 Clinical Rehabilitation. 2017 Jun;31(6):713-721. Does the method of botulinum neurotoxin injection for limb spasticity affect outcomes? A systematic review.
Equality	Applies to all adults with cerebral palsy who have focal spasticity

Table 16: Research recommendation modified PICO table

Criterion	Explanation
Population	Adults with cerebral palsy who would benefit from Botulinum Toxin A Injections for focal spasticity
Intervention	• Muscle stimulation or EMG guided Botulinum Toxin A Injection • Ultrasound guided Botulinum Toxin Injection
Comparator	Clinical positioning for localisation for Botulinum Toxin A injection or each other
Outcome	• Reduction in muscle tone at 8 weeks and 4 months • Side effects using patient/carer questionnaire • Patient acceptability • Goal attainment score • Time to repeat injection or alternative management • Cost per injection episode
Study design	Randomised. Assessor of muscle tone would be blinded to technique. Patient and injector would not be blinded
Timeframe	2 years
Additional information	Could stratify for upper limb (smaller muscles) and lower limb as there would be different functional goals.

EMG: Electromyography